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STUDIES OF BRØNSTED ACID-BASE EQUILIBRIA IN WATER AND NONAQUEOUS MEDIA

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PRESS

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CONTENTS

LIST OF ORIGINAL PUBLICATIONS

The thesis consists of the seven articles listed below and a review. The articles are referred in the text by Roman numerals I–VII. The review summarizes and supplements the articles.

I. Acidity of Benzoylcarbamates in Dimethyl Sulfoxide. Confirmation of Mixed N/O Alkylation in the Mitsunobu Reaction. Koppel, I.; Koppel, J.; Koppel, I.; Leito, I.; Pihl, V.; Wallin, A.; Grehn, L.; Ragnarsson, U. *J. Chem. Soc., Perkin Trans. 2* **1993**, 655–658.

II. The Acidity of Substituted 1-Hydroxybenzotriazoles in Water and Dimethyl Sulfoxide. Koppel, I.; Koppel, J.; Leito, I.; Pihl, V.; Grehn, L.; Ragnarsson, U.; *J. Chem. Res. (S)* **1993**, 446–447; *J. Chem. Res. (M)* **1993**, 3008–3028.

III. The Acidity of Some Neutral NH-acids in Water and Dimethyl Sulfoxide. Koppel, I.; Koppel, J.; Leito, I.; Pihl, V.; Grehn, L.; Ragnarsson, U. *J. Chem. Res. (S)* **1994**, 212–213; *J. Chem. Res. (M)* **1994**, 1173–1186.

IV. Synthesis and Cathodic Cleavage of a Set of Substituted Benzenesulfonamides Including the Corresponding *tert*-Butyl Sulfonylcarbamates: pK_a of Sulfonamides. Nyasse, B.; Grehn, L.; Ragnarsson, U.; Maia, H. L. S.; Monteiro, L. S.; Leito, I.; Koppel, I.; Koppel, J. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2025–2031.

V. Basicity of 3-Aminopropionamidine Derivatives in Water and Dimethyl Sulphoxide. Implication for a Pivotal Step in the Synthesis of Distamycin A Analogues. Koppel, I.; Koppel, J.; Leito, I.; Grehn, L. *J. Phys. Org. Chem.* **1996**, *9*, 265–268.

VI. Spectrophotometric Acidity Scale of Strong Neutral Brønsted Acids in Acetonitrile. Leito, I.; Kaljurand, I.; Koppel, I. A.; Yagupolskii, L. M.; Vlasov, V. M. *J. Org. Chem.* **1998**, *63*, 000–000, *accepted.*

VII. Acid-Base Equilibria in Nonpolar Media. 1. A Spectrophotometric Method for Acidity Measurements in Heptane. Leito, I.; Rodima, T; Koppel, I. A.; Schwesinger, R.; Vlasov, V. M. *J. Org. Chem.*, **1997**, *62*, 8479–8483.

ABBREVIATIONS

a	Activity
AN	Acceptor Number
AN	Acetonitrile
Boc	–C(=O)O-*t*-Bu
Bz	Benzoyl
Bzl	Benzyl
D	Dielectric constant
DA	Distamycin A
DCC	N,N'-Dicyclohexylcarbodiimide
DME	Dimethoxyethane
DMSO	Dimethyl Sulfoxide
DN	Donor Number
EPA	Electron Pair Acceptor
EPD	Electron Pair Donor
ΔG_{acid}	Gas Phase Acidity
HBA	Hydrogen Bond Acceptor
HBD	Hydrogen Bond Donor
HOAt	1-Hydroxy-7-azabenzotriazole
HOBt	1-Hydroxybenzotriazole
HOObt	3-Hydroxy-4-oxo-3,4-dihydro-1,2,3-benzotriazine
N	Number of points in statistical analysis
NHP	N-Hydroxyphthalimide
NHS	N-Hydroxysuccinimide
NMR	Nuclear Magnetic Resonance
Poc	$-C(=O)-OCH_2-4-C_5H_4N$
r	correlation coefficient in statistical analysis
s	standard deviation in statistical analysis
t-Bu-P_4	3-(tert-Butylimino)-1,1,1,5,5,5-hexakis (dimethylamino)-3-{[tris-(dimethylamino) phosphoranylidene] amino}-$1\lambda^5,3\lambda^5,5\lambda^5$-1,4-triphosphazadiene
Tf	Trifluoromethanesulfonyl
Tos	4-Toluenesulfonyl
Troc	$-C(=O)-OCH_2-CCl_3$
UV	Ultraviolet
VIS	Visible
Z	$-C(=O)-OCH_2-C_6H_5$
Z(NO_2)	$-C(=O)-OCH_2-C_6H_4-NO_2$

INTRODUCTION

Acid-base behavior of molecules is very important in chemistry.[1] It is practically impossible to find a branch of chemistry, which is not in some way involved with acid-base properties of compounds. Molecules of key importance in molecular biology and biochemistry — proteins, nucleic acids — contain acidic and basic centers and their acid-base properties are highly important from the standpoint of their functions. Acids and bases find extensive applications in industrial chemistry[2] and in laboratory synthesis as catalysts[3] and auxiliary reagents[4, 5].

Thousands of studies have been carried out on acid-base properties of molecules. Large collections of pK_a values of different compounds in various solvents have been published. [6–9] Acidity measurements can also be carried out in the gas phase. A truly absolute scale of intrinsic acidity in the gas phase has been established, ranging for almost 90 orders of magnitude.[7, 10]

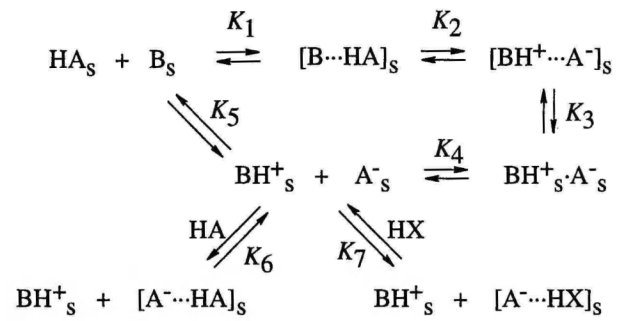
Nevertheless, there are significant gaps in our knowledge in this field. This is particularly true for nonaqueous media, as traditionally most of the studies have been carried out in water. Also many compounds related to newly emerged procedures in biochemistry, molecular biology and organic synthesis, although extensively used, have been insufficiently studied from the standpoint of their acid-base behavior. Although the latter is often of utmost importance in elucidating the mechanisms of the reactions and devising new, more efficient synthetic approaches.

New exciting horizons are emerging in the field of superacids and superbases. New strategies of designing superstrong acids[11, VI] and bases[12, 13] offer promises of new families of compounds with unprecedented catalytic and other properties. Studies of these compounds are still in their initial phase.

The aim of the present work was to contribute to filling some of these gaps.

1. THE MAIN CONCEPTS

The simplified picture of interaction between a proton donor HA and a base B in a solvent S is presented on Scheme 1:



Scheme 1

The interaction involves several reversible steps described by the respective equilibrium constants K_1 ... K_7. The first step is the initial acid-base complex formation (K_1). This complex is usually hydrogen-bonded but when steric restrictions are present and/or the bond H–A in $[B\cdots HA]_S$ is weakly polar, then the complex can be held together by nonspecific van der Waals forces. The next step (K_2) is the proton transfer from HA to B. As a result, a complex between the cation and the anion forms. This step is also called the primary ionization step. This complex is also usually hydrogen-bonded but when steric restrictions are present and/or the charges of the ions in $[BH^+\cdots A^-]_S$ are very delocalized then it can be held together by electrostatic and/or nonspecific van der Waals forces. The complex $[BH^+\cdots A^-]_S$ is also called contact ion pair. The next step is the formation of the solvent-separated ion pair $BH^+_S{\cdot}A^-_S$ which is held together by Coulomb forces. This ion pair can then undergo dissociation into free ions (K_4). If the solvent solvates anions insufficiently then A^- can react with proton donors present in the solution. If the proton donor is the conjugated acid of A^- then the process (K_6) is called homoconjugation.[15] If the proton donor is some other acid HX, then the process (K_7) is called heteroconjugation.[15]

The extent of the interaction between HA and B is determined by the intrinsic strengths of the acid HA and the base B as well as by the properties of the solvent. The following properties are important for the acid-base processes:[16]

1. Ionizing power. It consists of two properties: the EPD ability is important for solvating cations (quantitatively described by the donor number *DN*) and the EPA ability for solvating anions (quantitatively described by the acceptor number *AN*).[16]

2. Dissociating power. This property reflects the ability of the solvent to promote dissociation of ion pairs into free ions. It is quantitatively described by the dielectric constant D of the solvent.
3. Basicity and acidity. These properties set the limits to the strengths of acids and bases, that can be studied in a given solvent. No stronger base can exist in the given solvent than the deprotonated solvent molecule and no stronger acid than the protonated solvent molecule. A combination of these two properties is the autoprotolysis constant of the solvent, which determines the width of the pK_a scale that can be established in the solvent (see below).

The following are very short guidelines for estimating the situation in different solvents.

If the solvent is able to solvate both anions and cations and has $D \geq 40$ (water, formamide) then only the equilibrium described by K_5 is important[16] and the Scheme 1 simplifies to give the Brønsted scheme of interaction:[17]

$$HA_S + B_S \quad \rightleftarrows \quad A^-_S + BH^+_S \qquad (1)$$

In solvents with high *DN* and $D \geq 30$ but low *AN* (dipolar aprotic solvents) the acid-base interaction generally proceeds to the formation of free ions. Some ion-pairing may also occur depending on the solvent. Due to the lack of solvation of anions, the latter tend to undergo homo- and heteroconjugation reactions in these media.

In solvents with $D = 15$ .. 30 (acetone, benzonitrile) very complex picture is usually found, involving various amounts of all the species described on Scheme 1, as well as different higher associates.

In solvents with high *DN* but low D (pyridine, cyclohexanone) the interaction stops at the stage of solvent separated ion pair. The cation is strongly solvated but the solvation of the anion is weak.

In solvents with low D that also lack the ability to solvate ions (hydrocarbons, halohydrocarbons) the interaction stops at the initial hydrogen bond formation or at the contact ion pair stage. The extent of the interaction is dependent on the medium and the HA and B involved (their strength, charge delocalization in the respective ions, etc.). In these solvents numerous other processes, not presented on Scheme 1, can take place. Ions and neutrals can form aggregates of higher order, ion tetra- and hexamers can be formed in addition to the ion pairs.[15] In alkanes — extremely nonpolar solvents — ions are generally present as very large aggregates.

In principle, all the equilibria presented on Scheme 1 can be studied, but in polar solvents the complete acid-base reaction (K_5) is the most popular. When speaking of acidity of an acid in a solvent S, then the base B on Scheme 1 is in fact the solvent molecule S. Acidity of an acid HA generally refers to the following equilibrium:

$$HA + S \quad \rightleftarrows \quad A^- + SH^+ \qquad (2)$$

and is quantitatively expressed as the equilibrium constant of equilibrium 2 (K_a) or (even more frequently) its negative logarithm (pK_a).

$$K_a = \frac{a(SH^+) \cdot a(A^-)}{a(HA)} \tag{3}$$

$$pK_a = -\log(K_a) \tag{4}$$

A special case of acid-base interaction is found, when molecules of solvent — SH in this case — act both as the acid and the base:

$$SH + SH \rightleftarrows S^- + SH_2^+ \tag{5}$$

This process is called autoprotolysis and is described by the autoprotolysis constant K_{auto} of the solvent SH:

$$K_{auto} = a(S^-)\, a(SH_2^+) \tag{6}$$

$$pK_{auto} = -\log(K_{auto}) \tag{7}$$

The pK_{auto} of the solvent determines for how many orders of magnitude can an acidity scale range in the solvent and is one of the most important characteristics of the solvent.

In nonpolar solvents the concentration of free ions is too low to be of use and in these media ion pair acidities according to equilibria 8 and/or 9 are studied instead.

$$HA_S + S \rightleftarrows [A^- \cdot H^+]_S \tag{8}$$

$$HA_S + S \rightleftarrows A^-_S \cdot SH^+_S \tag{9}$$

The ion-pair acidities are generally termed pK_a as well, but it is usually explicitly declared that the pK_a refers to the ion-pair acidity. In addition to the pK_a values, it is necessary to clarify, according to what scheme (equilibria 8 and/or 9 or some higher degree of association) is the reaction proceeding.

2. STUDIES OF NH AND NOH ACIDS

In this part of the work various synthetically important compounds were studied from the standpoint of their acid-base behavior. In many cases the latter has important or even deciding influence on their reactivity.

2.1. Various NH Acids as Novel Gabriel and Mitsunobu Reagents

For the synthesis of primary amines from alkyl halides using the Gabriel reaction[19] or from alcohols using the Mitsunobu reaction[20] phthalimide is generally used. The cleavage of the resulting N-substituted phthalimide to obtain the amine is often problematic, as usually rather harsh conditions have to be used.[21] Therefore other reagents — various imidodicarbonates, acylcarbamates, and tosylcarbamates — have been proposed and used for these reactions.[21] It was found that some of them gave the expected products in high yields, while with others the reaction did not go at all.[22] It was suspected, that the reactivity of these compounds was influenced by their acidity and an acidity study was undertaken to elucidate this.

The results of the study are presented in Table 1.

It is of interest to compare the acidity data obtained in water to the data available in DMSO. The analysis of the data in terms of equation 10 was carried out (see III for details).

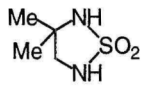
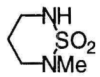
$$pK_a(\text{DMSO}) = m + n\ pK_a(H_2O) \qquad (10)$$

The results are as follows: m=1.52; n=1.36; s=0.92; r^2=0.968; N=20. These results follow the general behavior of neutral acids: the acidity of an acid decreases on transfer from water to DMSO.[8] This is caused mostly by the weak ability of DMSO to solvate anions (see, however, ref. 23). The imides display 1.36 times higher sensitivity towards substitution in DMSO than in water.

The results clearly indicate strong correlation between the yields in Mitsunobu reaction and the acidity of imides (Table 1). The imidodicarbonates are the least acidic and generally give the lowest yield. It can be pointed out, that particularly the acidic tosylcarbamates give high yields in Mitsunobu reaction. The benzoylcarbamates studied in this work are more acidic that imidodicarbonates, but are not very good reagents for Mitsunobu reaction because of the high percentage of O-alkylation.[I] The relationship between the pK_a of the compounds and the yields of the Mitsunobu reaction is not simple, however. There seems to be a pK_a value of approximately 10 in water (14 in

DMSO), which is pivotal from the standpoint of Mitsunobu reaction. Imides with higher pK_a give essentially zero yield.

Table 1. Acidities of various NH-acids in water and DMSO (a fuller version of the table can be found in III).

Acid	pK_a in water[I, III]	pK_a in DMSO[22]	Mitsunobu Yield (%)[22, 26, I]
1. Saccharin	1.6	3.8	ND
2. 4-Me$SO_2C_6H_4SO_2$NHBoc	3.76	7.2	ND
3. TosNHZ(NO_2)	3.8	7.0	93
4. TosNHZ	4.21	7.5	91
5. TosNHBoc	5.05	8.5	93
6. TrocNHBz	9.1	12.3	94
7. ZNHBz	9.4	13.7	98
8. PocNHBz	9.8	12.8	ND
9. TrocNHZ	9.8	12.7	83
10. BocNHBz	10.3	15.0	ND
11. MeOCONHBz	10.3	14.0	ND
12. Z_2NH	10.3	14.2	42
13. 	10.39	16.8	50
14. 	10.78	17.3	ND
15. Boc_2NH	11.0	16.9	<5
16. 	11.2	17.7	~0

It has been shown, that cyclic sulfamides (13, 14, 16) have also widely differing reactivity under Mitsunobu conditions.[24] It may be expected, that the acidity of the compounds has a role in this. From the data in Table 1 it can be seen that the size of the ring is an important factor influencing the acidity of these compounds. The sulfamide 13 differing from 16 only by one methylene fragment has pK_a of 0.8 units lower in water. It is interesting to compare the data for 13 and 16 with those for 1,3-propanesultam (pK_a=11.39[25]) and 1,4-butanesultam (pK_a=12.02[25]). The sultams are about ten times less acidic than the sulfamides. The inductive effect of the NMe fragment thus overplays the resonance effect. The size of the ring has the same effect on sultams as on sulfamides: the ΔpK_a is about 0.6 units.

It has been found, that the sulfamide 13 undergoes Mitsunobu alkylation with the yield 50–60%,[26] while the less acidic sulfamide 16 does not alkylate at all[26] (with sulfamide 14 the reaction follows a different pathway[24]).

2.2. NOH Acids

Compounds containing the NOH moiety are very important to biochemistry. At the early days of peptide synthesis HOBt was introduced as an auxiliary reagent and racemization suppressor[27] in DCC-mediated peptide synthesis. Within a short time DCC-mediated coupling in the presence of HOBt became a standard method for fragment condensation of peptides.[28] Later several other NOH compounds and their derivatives have been proposed (HOObt, HOAt).[29] Chemical literature does not contain much pK_a data on NOH acids in general and on these reagents in particular. Thus the study of their acidity in water was undertaken. The data for DMSO are also available (see II). The results of the pK_a measurements are compiled in Table 1, ref. II.

It is of interest to compare the pK_a values of the NOH acids to those of analogous NH acids. Acidity of a given acid is determined by the following factors: the electronegativity of the first atom of the acidity center, the extent of delocalization of the charge in the anion, inductive effects of the substituents, the extent of solvation of the anion, steric effects and additional effects (like intramolecular hydrogen bonding, etc.)

If the NH center of acidity is replaced by NOH center of acidity, then the following changes take place. Nitrogen is replaced by the more electronegative oxygen as the first atom, this change enhances the acidity of the NOH acid relative to the NH acid. If the nitrogen in the NH acid is attached to –R substituents, which efficiently delocalize the charge from the N^- center in the anion, then this delocalization will be lost in the corresponding anion of the NOH acid. The more the charge in the anion is localized on the center of acidity, the better is the anion solvated. There is a destabilization by repulsion of the lone pairs of electrons in the anion of the NOH acid. The relative acidity of NOH and NH acids is determined by the interplay of these factors.

For several of the NOH acids studied in this work, the pK_a values of the respective NH acids have also been determined experimentally. The data are presented in Table 2. It can be seen, that in water the electronegativity of oxygen together with the solvation effects clearly outweigh the resonance effects. DMSO is a solvent with weak ability to solvate anions. Nevertheless, in DMSO the NOH acid is still more acidic in all cases. NHS and NHP are only by about 0.5 pK_a units more acidic than the corresponding NH acids. This effect

can probably be attributed to intramolecular hydrogen bonding of the OH fragment with the carbonyl oxygen.

Table 2. Comparison of acidities of some NOH acids with those of the respective NH acids.

	Water			DMSO		
	pK_a	pK_a of the NH analogue	ΔpK_a	pK_a	pK_a of the NH analogue	ΔpK_a
HOBt	4.6	8.4	3.8	9.3	11.9	2.6
NHS	6.1	9.6	3.5	14.0	14.6	0.6
NHP	6.3	8.3	2.0	12.9	13.4	0.5

Correlation of acidities of the NOH acids in water and in DMSO is as follows:

$$pK_a(\text{DMSO}) = (2.2 \pm 0.7) + (1.58 \pm 0.17)\, pK_a(H_2O) \qquad (11)$$

$$N=17 \quad r^2=0.85 \quad s=0.56$$

This relationship is a part of a more general correlation, that includes also alcohols and phenols:

$$pK_a(\text{DMSO}) = (1.5 \pm 0.2) + (1.77 \pm 0.03)\, pK_a(H_2O) \qquad (12)$$

$$N=33 \quad r^2=0.994 \quad s=0.8$$

2.3. N-substituted Aromatic Sulfonamides

Aromatic sulfonic acids have for long been used in the derivatization of amines to protect the amino group.[30] Simple sulfonamides like tosylamides are among the most stable derivatives of amines and thus require rather harsh conditions for removing the protection, which restricts their use to very stable compounds. The scope of application of these protecting groups widened considerably with the advent of efficient electrochemical cleavage methods.[31] Electrochemical cleavage methods often permit selective deprotection because many other protecting groups are available, that are stable under the conditions of arenesulfonyl cleavage. One family of candidates for such selective deprotection reactions are the N-substituted tosylcarbamates. Preliminary works[32] suggested, that it might be worthwhile to investigate the acidity of N-alkylated benzenesulfonamides, as it is highly relevant to the cleavage reaction.

The results of the pK_a determinations along with some values from the literature are presented in Table 5, ref. IV. For the majority of the compounds pK_a data are also available in DMSO.

It is interesting to compare the pK_a values of N-benzyl sulfonamides to N-methylsulfonamides and sulfonamides without substitution on nitrogen. In water benzenesulfonamide has pK_a=10.10[33] and the pK_a of N-methylbenzenesulfonamide is 11.43. pK_a of benzenesulfonamide in DMSO is 16.1,[34] no data could be found on N-methylbenzenesulfonamide. In water any alkyl substitution at the amide nitrogen will hinder the solvation of the anion and hence decrease the acidity. The ability of DMSO to solvate anions is weak and the N-benzyl benzenesulfonamide is stronger than the unsubstituted benzenesulfonamide by 0.4 pK_a units.

The correlations of the pK_a in water and DMSO with Hammett's σ constants are as follows (see IV for details):

$$H_2O \quad pK_a = (11.2 \pm 0.1) - (1.48 \pm 0.12)\,\sigma_{m,p} \qquad (13)$$

$$N=10 \quad s=0.12 \quad r^2=0.947$$

$$DMSO \quad pK_a = (15.8 \pm 0.1) - (2.1 \pm 0.1)\,\sigma_p \qquad (14)$$

$$N=7 \quad s=0.12 \quad r^2=0.990$$

The sensitivity towards substituent effects is *ca.* 1.5 times higher in DMSO than in water.

There is strong correlation between the electronic properties of the substituents and the pK_a-s on one hand and the yields of the cleavage reaction on the other hand (see IV for detailed discussion).

2.4. 3-Aminopropionamidines

Aminopropionamidines are important intermediates in the synthesis of Distamycin A (DA, see V for structure of DA) and its analogues. DA is a basic polyamide with a wide variety of antibiotic properties.[35, 36] The chemistry of these compounds has received considerable interest and several synthetic strategies to DA and its analogues have been developed (see V and references therein). Crucial step in the synthesis of DA is a coupling reaction between the 3-amino group of the unprotected amidine moiety and the preformed trimeric pyrrolecarboxylic acid precursor.[35] The amidine has three basicity centers, however, and in principle any of them can react with the acid derivative, thus yielding unwanted side-products. As all the basicity centers have different basicity, the reaction can be directed towards the wanted product by controlling the pH of the solution. To be able to do this, the pK_a values of the basicity centers must be known.

The results of the pK_a measurements are presented in Table 1, ref. V. It can be seen, that for diprotonated amidines 1–4 (numeration from ref. V) the pK_a1

corresponds to deprotonation of the 3-ammonium group and pK_a2 to deprotonation of the amidinium moiety (see V for detailed discussion on assignment of the pK_a values to the different centers). The differences between the pK_a values of these groups are around 4 pK_a units both in water and in DMSO. These differences are sufficiently large to permit deprotonation of the amino-group, while the amidine-fragment remains protonated, and hence protected. This procedure requires careful monitoring of the pH of the solution. The present experimental results provide firm experimental basis for the application of the direct attachment of the unprotected aliphatic side-chain to the trimeric pyrrole-carboxylic acid.

2.5. Pros and Cons for Water as a Medium for Acid-Base Studies

Although water has many advantages as a solvent for acid-base studies (well established and reliable pH scale, simplicity of the acid-base equilibria, no need to work under dry atmosphere, relevance to biochemical processes), there are still several important disadvantages:

1. The range of acidities and basicities that can be studied in water is determined by its relatively large autoprotolysis constant and is limited to approximately 14 pK_a units. Strong acids and strong bases cannot, therefore, be studied in aqueous solutions.
2. It must be stressed that only the gas-phase acidities and basicities are intrinsic properties of molecules. In the solution the solvation often changes the acid-base properties of a molecule considerably and the pK_a-s determined in condensed phase are properties of the solution as a whole. Due to the very high solvating power of water, the pK_a-s determined in aqueous solution only very vaguely reflect the intrinsic properties of molecules.
3. Water is not a good solvent for nonpolar molecules. Many important and interesting compounds cannot therefore be studied in water because of the solubility problems.

These shortcomings are absent from many nonaqueous solvents.

3. SPECTROPHOTOMETRIC ACIDITY SCALE OF STRONG NEUTRAL BRØNSTED ACIDS IN ACETONITRILE

Strong acids and their derivatives are receiving increasing attention from both practical (reagents in organic synthesis,[3, 37] catalysts in industry[2]) and theoretical[10, 11] points of view. Therefore substantial theoretical and experimental effort has been devoted to development of strongly acidic media and molecules with high intrinsic acidity.[37] Several families of interesting acids have been created: cyanocarbon acids,[38, 39] Kuhn's acidic hydrocarbons,[40] acids with Yagupolskii's substituents,[41] superacidic metal hydrides,[42] etc.

3.1. The Problem

Quantitative measurements of acidity are a vital part of studies involving superacids. Contrary to the success in creating superacids, significant experimental difficulties have been met here and up to date little consistent acidity data is available for strong acids. In some cases the situation is almost ridiculous. For the pK_a of perchloric acid in aqueous solution, for example, the values found in the literature range from –1.6 to –14.[10] The uncertainty exceeds 12 orders of magnitude!

Significant effort has been devoted to acidity studies in aqueous solutions of strong acids (sulfuric acid, perchloric acid, etc.).[43, 44] Aqueous media have the advantage of allowing to use the acidity scale extended from water. The measurements are complicated,[25, 45] however. The reasons are the leveling of acidities and the fact that with increasing acidity of the medium, the medium itself changes and pK_a values of acids with different acidities are therefore not strictly comparable to each other.

In the gas phase no leveling occurs and acids of very high and very low acidity can in principle be studied. With very strong acids the gas phase measurements have often failed, however, because the latter are usually not volatile enough and tend to undergo fragmentation in the course of the experiments.[10]

The amount of acidity measurements of strong neutral Brønsted acids performed in nonaqueous solvents is smaller than in aqueous medium.[8, 38, 46–49] This is true even for DMSO, where due to efforts of Bordwell and others more than 2000 pK_a values for different classes of Brønsted acids have been determined.[8, 9, 49] DMSO is a rather basic leveling solvent and thus not very suitable for studies of strong acids (however, see ref. 48). Several acidity orders of

strong acids have also been reported[10, 50] but quantitative acidity data for strong acids continues to be scarce. The main problems arising in most nonaqueous solvents are the various association processes between charged (and also neutral) species in these solvents (see below) and difficulties in reliable and reproducible determination of medium acidity in these media. Hence the pK_a–s determined in different laboratories often differ more than the experimental errors stated.

In the view of this situation a pressing need exists for a self-consistent scale of acidity of strong acids in solution.

3.2. The Method

As the solvent for setting up the acidity scale, AN was chosen. AN has many properties that make it suitable for this work. It has low basicity and very low ability to solvate anions.[15] The low basicity gives AN an advantage over the other very popular solvent for acid-base studies — DMSO — which is considerably more basic (stronger acceptor of hydrogen bond). AN has high dielectric constant (D=36.0[15]) and hence favors the dissociation of ion pairs into free ions. The autoprotolysis constant of AN is very low: pK_{auto}=33[51] and recently even a value pK_{auto}=44[52] has been suggested (but not proved). All these properties put together make it a good differentiating solvent for strong acids. Additional advantages of AN are its transparency down to 190 nm and relative ease of purification.

Starting from the classical works of groups of Kolthoff and Coetzee, considerable amount of acidity data for various compounds in acetonitrile have been accumulated. Analysis of literature shows that a rather continuous and self-consistent acidity scale in the pK_a range of 14–27 exists in acetonitrile.[9, 15, 53–55] Measurements in the lower pK_a range have been made too,[38, 46, 47] but here the things are far from satisfactory both in terms of the amount of data available and its self-consistency. The present work was undertaken to improve the situation by building a unified self-consistent scale of acidity in AN in the range of 4–16 pK_a units which would be a logical extension of the pK_a scale for the relatively weak acids into the domain of strong and very strong neutral Brønsted acids.

Because of the problems with measuring the acidity of the medium — $a(H^+)$ — in nonaqueous solutions, a method that eliminates the need for its determination was used. This method of acidity measurements gives relative acidities of the acids HA_1 and HA_2 according to the following equilibrium:

$$HA_2 + A_1^- \rightleftarrows A_2^- + HA_1 \qquad (15)$$

The pK of this equilibrium is the relative acidity (ΔpK_a) of the acids HA_1 and HA_2:

$$\Delta pK_a = pK_a(HA_2) - pK_a(HA_1) = \log \frac{a(A_1^-) \cdot a(HA_2)}{a(A_2^-) \cdot a(HA_1)} \quad (16)$$

The method consists in UV-VIS spectrophotometric titration of a solution, where both of the acids are present, with a transparent acid or base (see VI and VII for detailed descriptions of the method).

3.3. Results

The results of the measurements are presented in Table 3. Each arrow represents the ΔpK_a from one titration experiment. To make the results more reliable and to be able to estimate the consistency of the results, multiple overlapping measurements were carried out. The entire acidity range covered involves at least two independent pathways of measurements and the relative acidity of any two acids can be obtained by combining at least two independent sets of measurements.

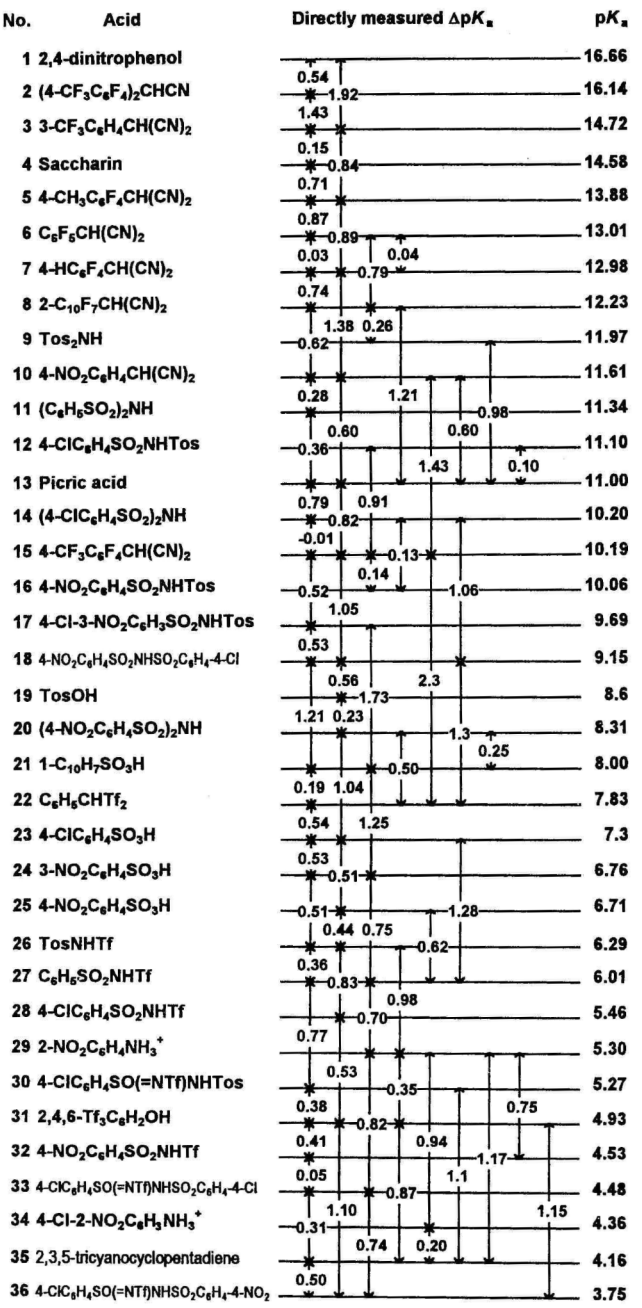
In order to assign absolute pK_a values to the acids of Table 3, the scale was anchored to picric acid — a reference compound with pK_a reliably established.[56] Picric acid (pK_a=11.0 in AN) is a "well-behaved" compound, it does not undergo homo- or heteroconjugation reactions to a marked extent and has favorable UV-VIS spectral characteristics (see VI for detailed justification of picric acid as the reference).

The pK_a values for individual acids were found minimizing the sum of squares of differences between directly measured ΔpK_a values and the assigned pK_a values using a least squares procedure (see VI for details). For these results s is equal to 0.04 pK_a units. This is a low enough value for the scale to be considered self-consistent.

The spectra of all the compounds (with the exception of the sulfonic acids **19** and **23**, see VI for detailed discussion on this subject) in solutions of different acidity did not show any irregular behavior. The spectra of partially ionized acids could always be expressed as linear combinations of the spectra of the neutral and the anion. With most of the compounds the spectra contained isosbestic points and these were always sharp. These observations rule out the possibility that conjugation reactions take place to an appreciable extent under the experimental conditions used as the homo- and heteroconjugation reactions are known to cause distortions in spectra.[57]

The pK_a values determined in this work together with those from other authors[9, 15, 53–55] set up a continuous acidity scale in AN ranging from pK_a 4 to 27.

Table 3. Results of the acidity measurements in AN together with the absolute pK_a values of the acids.



3.4. Discussion

The Method. The presence of the acids in the same solution eliminates many possible sources of error or reduces their influence: (1) The disturbing effects (traces of water in the medium, concentration errors) affect both acids with the same magnitude and are expected to partially cancel out. Thus one can expect that the effect of traces of water on the measurements will be less pronounced than in such measurements where pK_a of a single acid is measured at a time. (2) The solutions can be very dilute and consequently very weakly buffered with this method. If a minor acidity change of the solution occurs, it will affect both of the acids and its effect will cancel out. (3) An important point is that the method eliminates the need for quantitative measurement of acidity of the medium.

A disadvantage of the method is that acidity of only such acids can be measured that absorb in the UV-VIS spectral region and for which the spectra of the acid and the anion are different. Also the pK_a–s of the acids must not be very different from each other (preferably not more than 1.5–2 pK_a units).

Sulfonimides and sulfonic acids. pK_a values for aromatic sulfonimides are almost lacking from the literature. One reason is that sulfonimides are strong acids and their acidity cannot be measured in nondifferentiating solvents. On the other hand, aromatic sulfonimides totally lack volatility and therefore no gas-phase data are available. To the best of our knowledge there has been only one work[33] where pK_a data of some aromatic sulfonimides in water have been reported.

Applying the Hammett equation to the aromatic sulfonimides **9**, **11**, **12**, **14**, **16**, **18** and **20**, the following relationship was found:

$$pK_a = (11.25 \pm 0.05) - (1.97 \pm 0.07)(\sigma_1 + \sigma_2) \qquad (17)$$

r^2=0.993, s=0.11, where σ_1 and σ_2 are the Hammett constants of the corresponding substituents (taken from ref. 58).

The aromatic sulfonic acids **19**, **23**, **24** and **25** show a similar sensitivity towards substitution

$$pK_a = (8.0 \pm 0.2) - (1.9 \pm 0.4)\,\sigma \qquad (18)$$

r^2=0.92, s=0.3, although the correlation is poorer. It is of interest to compare these data to those for substituted benzoic acids. Applying the Hammett equation to a set of substituted benzoic acids (4–H, 4–Br, 4–NO_2, 4–COOH, pK_a values from ref. 9) gives:

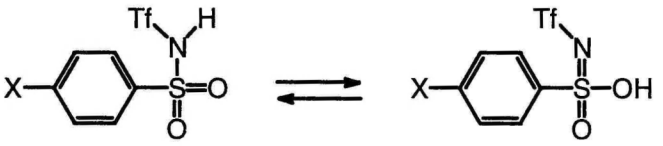
$$pK_a = (20.8 \pm 0.1) - (2.6 \pm 0.2)\,\sigma \qquad (19)$$

r^2=0.987, s=0.12. It can be seen that the acidity of benzoic acids is about 1.3 times more sensitive towards substitution in the aromatic ring than the acids with acidity center SO_2XH. The probable cause is that –SO_2- fragment in the

anion is bigger, more polarizable and more electronegative than the corresponding –CO- fragment in carboxylates, and can therefore "hold" more charge and has lesser tendency to delocalize it into the aromatic ring.

Yagupolskii's substituents. Compounds **30**, **33** and **36** can be considered as derivatives of **12**, **14** and **18** respectively where an =O fragment of a sulfonyl group adjacent to the NH acidity center is replaced by =N–Tf. The acidifying effects of the substitution are 5.8, 5.7, 5.4 pK_a units for **12**, **14** and **18** respectively. The following values of pK_a have been found for $C_6H_5SO_2NH_2$, $CH_3C_6H_4SO(=N–Tf)NH_2$ and $CH_3C_6H_4S(=N–Tf)_2NH_2$ in DMSO: 16.0,[22] 8.0,[59] 3.4.[59] It can be seen that the acidity increase is not additive: the first substitution increases the acidity by 8 pK_a units while the second substitution by 4.6 pK_a units (the small effect of the 4-methyl group can be neglected here). It has not yet been possible to measure the acidities of these compounds or the sulfonimides in the gas phase[10] but there is a value of gas phase acidity available for a "superacidic" aniline 4–($CF_3SO(=N–Tf)$)–$C_6H_4NH_2$ ΔG_{acid} = 313.4 kcal/mol.[10] This compound is 13 orders of magnitude (!) more acidic in the gas phase than the corresponding unmodified aniline 4–Tf–$C_6H_4NH_2$ (ΔG_{acid} = 331.3 kcal/mol[7]).

The sulfonimides **26**, **28** and **32** can be considered as derivatives of sulfonic acids in which an = O fragment of the sulfonyl group is replaced with = N–Tf. These compounds can exist in two tautomeric forms:



a b (20)

Evidence (NMR) has been presented, that **a** is the dominating form in acetone and chloroform.[41] The differences in acidities between **26**, **28**, **32** and the corresponding sulfonic acids **19**, **23** and **25** are 2.3, 1.8 and 2.2 pK_a units respectively. These results can be regarded as evidence in favor of the structure **a** in AN, as otherwise the differences should be similar to the ones obtained for sulfonimides.

Phenols. pK_a value –1.0 for **31** has been reported in aqueous H_2SO_4.[60] This is about 1.3 pK_a units lower than the pK_a of picric acid.[60] In AN, according to Table 3, **31** is about 6 pK_a units more acidic than picric acid. This qualitatively higher difference leads to a conclusion that some solvent effect is in operation here. 2-nitrophenols are known to give intramolecular hydrogen bonding[61] in AN. In water, on the other hand, this hydrogen bonding is absent due to the competition from water.[61] This intramolecular hydrogen bond causes considerable extra-stabilization of the neutral in AN compared to water. There are no

data in the literature on hydrogen bond acceptor properties of trifluoromethanesulfonyl group but it is likely that these are weak in comparison with nitro group because the hydrogen bond basicity of sulfones is generally very low. Another factor might be that the picrate anion, due to its nitro groups, is likely to be more solvated in water than the deprotonated **31**.

Phenylmalononitriles. An interesting result with this class of compounds is that the pK_a-s of **6** and **7** in AN are practically equal or that of **7** is even slightly lower. The same behavior of these two compounds has been observed by one of us also in dimethoxyethane.[62] This is not completely unexpected: a similar effect is seen when comparing phenol to 4-fluorophenol: the latter is by only 0.2 pK_a units more acidic in water than the former.[8] The reason for this might be that although fluorine is an electronegative substituent, it is also a weak resonance donor.[58] The F is in the 4 position to the acidity center, which means that the inductive/field effect (but not the resonance effect) is weakened by the distance. The final factor is the strong electron-deficiency of the ring that still weakens the inductive/field effect by saturation. These arguments have to be treated with caution however because the same is not observed in the gas phase where **6** is more acidic by about 2 kcal/mol.

The correlation between the pK_a-s in AN and the gas phase acidities[10] is poor:

$$pK_a=(-108 \pm 36) + (0.40 \pm 0.12)\ \Delta G_{acid} \qquad (21)$$

r^2=0.69, s=0.91. This is surprising, because of all the compounds' classes in this scale the phenylmalononitriles should be relatively weakly influenced by solvation and they are very suitable for measurements both in AN and in the gas phase.

4. ACIDITY SCALE IN HEPTANE

4.1. The Problem

The common solvents for acid-base measurements are the polar ones (high dielectric constant, strong solvating power) in which the interactions between the solvent and the solute are strong and the acidities are heavily influenced by the medium.[63] On the other hand, considerable amount of data has been accumulated on the acidities in the gas phase (D=1) where the medium influence is absent. There is a large gap between these two extremes — the solvents with low dielectric constant and weak solvating power, in which a very limited number of acid-base investigations has been carried out (see VII).

This is not surprising. The equilibria that establish in nonpolar solvents are extremely complex (see 1. THE MAIN CONCEPTS). The concentration of free ions is generally next to nonexistent. The ions are associated not only in ion pairs but also in tetramers, hexamers, etc. Neutral molecules also undergo association with each other and with associates of ions.

Acidity data in solvents of low polarity are very valuable for several reasons: systems of extremely high acidity can be studied in nonpolar solvents, acidities of very weak acids can be measured in nonpolar solvents, many processes in organic synthesis and in chemical industry involving acids and bases are carried out in nonpolar media and acidity data in nonpolar media are needed to be able to understand and to quantitatively describe these processes.

The first ion-pair acidity scales in low-polarity media were set up by Conant *et al.*[64] in diethyl ether (dielectric constant D=4.20) and McEwen[65] in benzene (D=2.27). Since then several others have been created: in cyclohexylamine[18] (D=4.73), in 1,2-dimethoxyethane[66] (D=7.20) and in tetrahydrofuran[67] (D=7.58). All these scales were built using metalation with alkali metals for deprotonation of the acids under study. This approach has been criticized by Konovalov *et al.*[68], who state that because the ions in nonpolar media exist as ion-pairs (or larger associates), the alkali metal cations in nonpolar solvents will have strong specific interaction with the anions of the acids studied. The extent of the interaction is dependent on the anion as well as the cation and therefore these scales cannot be used for carrying out accurate analysis of substituent effects. These authors propose to use [2.1.1]cryptate of lithium cation as the counterion. The interactions between this ion and the anions are limited to electrostatic and van der Waals forces. The specific interactions are eliminated because the metal cation is coordinatively saturated and the cryptate ion is large (radius 5 Å)[68]. Using this technique the Russian authors have built acidity scales in tetrahydrofuran[69] (D=7.58), N-methylmorpholine[70] (D=4.3) and benzene[71] (D=2.27).

The least polar solvent in which a scale of acidity has been set up is benzene[71]. It would be of considerable interest to perform acidity measurements also in media with $D<2$. This is because $D=2$ is a kind of half-way between polar solvents and the gas phase. The goal of this investigation was to set up an acidity scale in heptane ($D=1.92$).

4.2. The Method

When measuring acidities in polar solvents, equilibrium 2 is studied usually. In nonpolar solvents equilibria 8 and 9 are often studied. In alkanes it is, however, almost impossible to study any of them directly because they are very strongly shifted to the left. Equilibrium 15 is studied instead. The experimental method is essentially the same as used with strong acids in AN (see VI and VII).

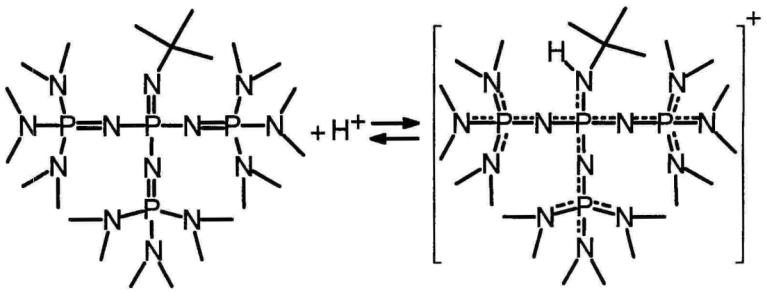
Analyzing alkane solutions of ionic compounds according to equilibrium 15 is certainly a simplification. In reality various association processes between ions (ion pairing), between ions and neutrals and between neutrals can occur as well (see section 1). It is however possible to choose the experimental conditions in such a way, as to minimize the association processes.

Alkanes are solvents with very weak solvating power towards polar and especially ionic species. To prevent extensive aggregation and eventually precipitation of ionic compounds in such solvents the ions should have the following properties:

(1) The charge of the ion should be as delocalized as possible (the ion should have no well defined ionic centers, such as $-O^-$ or $-NH_3^+$).
(2) The ion should be as large as possible.

The neutral acids themselves should also be as nonpolar as possible and should not have polar centers, such as –OH. This restricts both the number of acids that can be studied in heptane and the choice of the method of deprotonation of the acids and the counterion. To the best of our knowledge no systematic acidity measurements have been performed in alkanes to date.

An ideal deprotonating agent would be a very strong base, which is soluble in heptane, and able to deprotonate acids in nonpolar medium and the protonated form of this base would meet all the criteria set up for ions above. There are bases — phosphazenes[12, 13] — which meet all these requirements. Phosphazene *t*-Bu-P_4 was used for the work. It is a very strong base [pK_a(DMSO)=30.2[13]] which upon protonation gives a bulky cation (its radius has been estimated to about 7 Å[VII]) with strongly delocalized charge:



(22)

t-Bu-P_4

It is also important to note that the protonated basicity center of this phosphazenium ion is sterically strongly hindered and has, therefore, a low ability to specifically interact (e.g., hydrogen bonding) with the anions of the acids, especially, if those are bulky too and devoid of well-defined charged centers. An additional advantage of *t*-Bu-P_4 is that its cation is transparent practically across the entire UV spectral range.

4.3. Results and Discussion

As a result of the measurements, a scale of acidity in heptane has been created. It is presented on Figure 1. The acids as well as their salts with *t*-Bu-P_4 are sufficiently soluble in heptane.

Each arrow on figure 1 represents one measurement of relative acidity. To make the results more reliable and to be able to estimate the consistency of the results, multiple overlapping measurements were carried out. The entire range from **1** to **6** involves two independent pathways of measurements and the relative acidity of any two acids can be obtained by combining at least two independent sets of measurements. The uncertainties of the results are best estimated from Figure 1 by observing how good the agreement between different pathways of measurements is. The most uncertain measurements are those of the pairs **1–4**, **2–4** and **4–6**. These pairs of acids have large ΔpK_a-s and this is the reason for the low precision of these results. We estimate the uncertainties of these three measurements as large as 0.2 pK_a units and the uncertainties of the rest of the measurements 0.05 to 0.1 pK_a units. Taking into account that the large ΔpK_a values cannot be measured with high precision, the agreement between different pathways is good and the scale can be considered self-consistent.

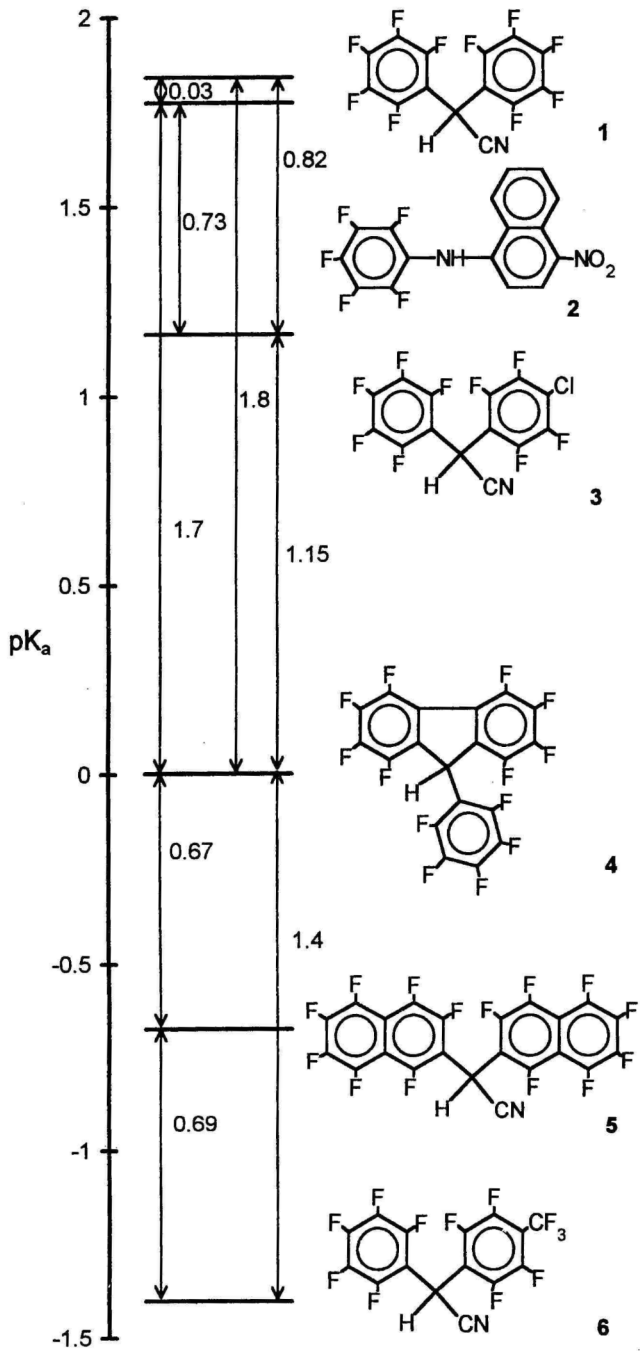


Figure 1. Interlocking ladder of relative acidities in heptane.

The method used lets us obtain only relative acidities. Compound **4** has been taken as an arbitrary reference compound and the acidities of all others are expressed relative to **4**. We assign the following ΔpK_a values (all relative to **4**) to the acids investigated: **1** 1.8; **2** 1.8; **3** 1.1_5; **4** 0; **5** -0.6_7; **6** –1.4. No attempt is made in this work to convert the relative acidities to absolute numbers.

The actual state of the ions in solution is an important issue. It is well known that ions in nonpolar media exist as ion pairs or higher aggregates. Depending on the ions involved and the solvating properties of the medium, two types of ion pairs can be distinguished: contact ion pairs and solvent-separated ion pairs[14]. It has been shown that as the ions get larger, the spectral properties of contact ion pairs approach those of solvent-separated ion pairs and that the spectral properties of solvent-separated ion pairs and free ions generally do not differ[14]. Konovalov *et al.*[68] have carried out detailed spectrophotometric and conductometric investigations of the state of lithium [2.1.1]cryptate ion in solvents of low polarity. These investigations are particularly relevant to our case because the phosphazenium ion present in our solutions is similar in size to the cryptate ion used by Konovalov *et al.* These investigators varied the solvent polarity (ranging from DMSO to hexane) as well as the degree of charge delocalization of the anions. It was found that the cryptate ion and the anion exist as ion pairs in all the solvents studied (except DMSO in which the ion pairs dissociate) and that in all the media the spectral characteristics of the ion pair are indistinguishable from those of solvent separated ion pairs. The authors proposed a term "cryptate-separated ion pair" for this type of ion pairs. The results of conductometric investigations showed, that if the concentration of the cryptate ion in solution is less than $1 \cdot 10^{-4}$ mol/L then the ion pairs in a solvent with $D<15$ do not associate significantly into larger aggregates[68].

Taking into account the structural properties of the compounds involved in the equilibria, the results of Konovalov *et al.* and the very low concentrations of the acids used in this work, we predict that the ions exist as "loosely bound" ion-pairs, analogous to the cryptate-separated ion pairs described by Konovalov *et al.* This means that although neither of the two ions in the ion pair are solvated in heptane to an appreciable extent, there are no specific interactions between the ions because they are bulky and have delocalized charge.

Some support for this prediction can also be drawn from the fact that Beer's law holds for the salts and that isosbestic points are observed. This means that under the experimental conditions used, the state of the ion pair in terms of specificity of interactions between the ions does not change with increasing concentration of the salt relative to the neutral acid. On the other hand, as the spectral properties of the distant ion pairs and free ions do not differ, these results do not say anything about the extent to which the ion pairs dissociate into free ions as well as about possible aggregation of the loosely bound ion pairs.

It is not possible to thoroughly discuss substituent effects or correlations of the results with measurements in other media because at present the scale contains too few compounds and these are not very common. However, acidities of compounds **1**, **3**, **4**, and **6** have been measured in the gas phase (ΔG_{acid}=312.4[10], 311.8[59] 301.8[10] and 307.5[10] kcal/mol respectively) and in DME solution[72] (pK_a=6.4, 5.4, 5.3 and 3.9 respectively).

The correlation of pK_a(heptane) vs. pK_a(DME) is not very good: r^2=0.91, slope 0.70 (pK_a in heptane is on abscissa) and standard error s=0.38. No obvious outlier was detected. It must be noted, that these pK_a values in DME have been obtained using Li^+ as the counterion and the anions exist in DME solution as contact ion pairs with Li^+.[72] Specific interactions between ions cannot be neglected here but there are too few data to draw far-reaching conclusions.

The correlation between the acidities in heptane and in the gas phase is good: r^2=0.993 and slope 0.92 (ΔG_{acid} values are transformed to pK_a scale prior to the correlation analysis) if the compound **4** is excluded from the correlation analysis. This compound severely deviates from the correlation line. If we take that one of the measurements (that is pK_a in heptane or ΔG_{acid} in the gas phase) is correct, then the other one must be in error by approximately 5 orders of magnitude (!) in order to fit into the correlation. Compound **4** is of different family from compounds **1**, **3**, and **6** and this can be partially the reason for the enormous deviation. It can be expected that charge in the deprotonated **4** is more delocalized than in **1**, **3**, and **6**, which have CN group attached directly to the acidic center. This CN group will carry significant negative charge in these anions and they are more strongly solvated in liquid phase than the deprotonated **4**. The three anions are also expected to interact more strongly with traces of water and with counterions than the deprotonated **4**. Thus one can expect that going from the gas phase to the liquid phase the increase in acidity of **1**, **3**, and **6** is larger than that of **4**. This is really the case: the pK_a of **4** in heptane (and in DME too) relative to the other three compounds is about 5 units higher than predicted from the gas phase measurements. Nevertheless, neither heptane nor DME has strong ability to solvate anionic centers and this difference in solvation is probably not the only reason for this phenomenon. Further experiments are necessary.

Work is in progress in our laboratory to further extend the acidity scale. Also the actual state of the ions in solution needs to be further studied by other methods.

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BRØNSTEDI HAPETE HAPPE-ALUSE TASAKAALUDE UURIMINE VEES JA MITTEVESIKESKKONDADES

Kokkuvõte

Väitekirja esimeses osas (tööd I–V) uuriti mitmesuguste orgaanilise sünteesi seisukohalt tähtsate NH- ja NOH-hapete (mitmesugused imiidid, hüdroksübensotriasoolid, asendatud benseensulfoonamiidid, protoneeritud amidiinid) happelisust. Paljudel juhtudel on nende ainete happelisusel oluline seos reaktsioonivõimega sünteesireaktsioonides. Toodi välja mitmeid seaduspärasusi molekulide ehituse, happelis-aluseliste omaduste ja reaktsioonivõime vahel.

Väitekirja teise osa (töö VI) teemaks on tugevate hapete happelisuse mõõtmine — keemia seisukohast väga oluline, kuid seni suhteliselt tagasihoidliku eduga uuritud valdkond.

Käesolevas töös on koostatud tugevate neutraalsete Brønstedi hapete spektrofotomeetriline happelisuse skaala dipolaarses aprotoonses lahustis atsetonitriilis. Skaala koostamiseks uuriti 36 erinevasse aineklassi (fenoolid, sulfoonhapped, disulfoonimiidid, Yagupolskij meetodil modifitseeritud sulfoonimiidid ning mitmesugused CH-happed) kuuluvat hapet. Mõõtmiste tulemusena koostati happelisuse skaala ulatusega umbes 13 pK_a ühikut atsetonitriilis. Kõige happelisematel skaalasse kuuluvatel ühenditel on pK_a väärtus umbes 4 atsetonitriilis.

Skaala koostamiseks kasutati mõõtmismetoodikat, mis välistab keskkonna happelisuse mõõtmise — ühe suurema veaallika sedasorti mõõtmiste juures. Kasutatud meetod võimaldab määrata vaid happepaaride ΔpK_a väärtusi. Leidmaks uuritavate ainete pK_a väärtusi, ankurdati skaala usaldusväärselt määratud pK_a väärtusega aine — pikriinhappe — külge.

Kui koostatud skaala siduda varasemate uurimustega, on sisuliselt loodud ühtne happelisuse skaala atsetonitriilis, mis katab pK_a vahemiku 4 kuni 27. Töö tulemused demonstreerivad ilmekalt, et tugevate hapete happelisuse usaldusväärne mõõtmine on täiesti teostatav, ja valmistavad ette pinna veelgi happelisemate hapete uurimiseks ning samalaadseteks eksperimentideks teistes keskkondades.

Väitekirja kolmandas osas (töö VII) on analoogset mõõtmismeetodit kasutades püstitatud happelisuse skaala apolaarses lahustis heptaanis. See on esimene süstemaatiline happe-aluse tasakaalu uurimine alkaani keskkonnas. Alkaanides on väga raske ioonseid tasakaalusid uurida, sest ioonsed ühendid lahustuvad seal väga halvasti ning happe-aluse reaktsioonid suurema osa hapete ja aluste vahel ei lähe kaugemale vesiniksideme tekkest. Määrava tähtsusega uuenduseks selle töö juures on alkaanides lahustuva superaluselise fosfaseeni

t-Bu-P_4 kasutamine happeid deprotoneeriva alusena. See aine on väga tugev alus ja protoneerumisel annab suurte mõõtmete ja delokaliseeritud laenguga katiooni, mille interaktsioon lahuses leiduvate anioonidega on nõrk.

Saadud tulemused näitavad, et happe-aluse tasakaalude uurimine alkaanides on eksperimentaalselt teostatav, ning avavad uue lehekülje apolaarsete keskkondade kasutamisel happe-aluse tasakaalude uurimiseks.

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PUBLICATIONS

I

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Acidity of Benzoylcarbamates in Dimethyl Sulfoxide. Confirmation of Mixed *N*/*O* Alkylation in the Mitsunobu Reaction

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Seventeen benzoyl-, 4-methoxybenzoyl- and 4-nitrobenzoyl-carbamates have been synthesized *via* their corresponding isocyanates and their acidities determined in dimethyl sulfoxide solution. Their pK_a values span an interval of nearly 5 pK units (10.4–15.2). Selected derivatives have been investigated as amine synthons in the Mitsunobu reaction. In all cases mixtures of *N*- and *O*-alkylated products are obtained.

Phthalimide and its potassium salt are generally applied to *N*-alkylation with alcohols under Mitsunobu conditions and with halides under Gabriel conditions.[1] Recently, several other reagents have also been explored in this context,[2] particularly various diacylimides, acylcarbamates and imidodicarbonates. Wada and Mitsunobu[3] studied the reaction between simple alcohols, benzyl benzoylcarbamate, triphenylphosphine (TPP) and diethyl azodicarboxylate (DEAD) and obtained *N*-alkylated products in 66–68% yields. However, in another trial with a protected uridine derivative,[4] a competing *O*-alkylation took place. Alkylation of the sodium salt of benzyl benzoylcarbamate with the corresponding bromide gave predominantly *N*-alkylation.[4]

In connection with a recent study dealing with ^{15}N-labelled chiral Boc-amino acids using a series of imidodicarbonates under Mitsunobu conditions,[5a] we noticed that the yields correlated remarkably well with the pK_a of the imidodicarbonate measured in dimethyl sulfoxide (DMSO).[5b] In the case of ethyl lactate, we concluded that a pK_a in DMSO of around 13.5 or lower was required in order to achieve a satisfactory reaction under the usual experimental conditions.

This paper describes the synthesis of a set of benzoylcarbamates in which the carbamate part is directly related to *N*-protecting groups used in the synthesis of peptides and similar compounds. When attached to an amino acid, selective removal of the benzoyl group would consequently lead to the corresponding urethane-protected derivative.[6] With respect to the benzoyl part of the molecules, both unsubstituted and 4-NO_2- and 4-MeO-substituted derivatives have been made and their pK_a values were measured in DMSO. To the best of our knowledge, no such measurements with this type of compounds have been carried out before. Finally, the behaviour of a few benzoylcarbamates in the Mitsunobu reaction was reinvestigated.

Results and Discussion

The benzoylcarbamates studied in this paper were all made according to Scheme 1.

$$R^1C_6H_4\text{–}CO\text{–}NH_2 \longrightarrow R^1C_6H_4\text{–}CO\text{–}N{=}C{=}O \longrightarrow R^1C_6H_4\text{–}CO\text{–}NH\text{–}CO\text{–}OR^2$$

Scheme 1 R^1 = H, 4-MeO or 4-NO_2; R^2 = Me, Bu^t, CH_2CCl_3, Bzl, $CH_2C_6H_4$-4-NO_2, 4-$CH_2C_5H_4N$ or 9-fluorenylmethyl

A solution of the isocyanate in dichloromethane was allowed to react with a small excess of the appropriate alcohol under anhydrous conditions and the resulting acylcarbamates were worked up as described in the Experimental section. The unsubstituted benzoylisocyanate was distilled, whereas the substituted ones were used without distillation or other purification. All compounds made are listed in Table 1. To the best of our knowledge, nine of the 17 substituted benzoylcarbamates synthesized in the present work have not been described before in the literature. Of the remaining eight compounds, four showed significantly higher melting points than those reported earlier.

Most of the benzoylcarbamates studied are practically insoluble (less than 10^{-3} mol dm^{-3}) in water. Therefore, and for comparison with the acidity of the earlier measured series of imidodicarbonates and tosylcarbamates,[5b] the acidity of the compounds studied in the present work was predominantly determined in DMSO solution (Table 1). Only the pK_as for two benzoylcarbamates, $BzNHCO_2Me$ and BzNHPoc, could also be measured in aqueous solution using direct potentiometric titration of the neutral acid with the alkali.

The acidity of the benzoylcarbamates measured in this work in DMSO solution is closely comparable with the acidity of the other wide family of Gabriel reagents,[2] most of which were imidodicarbonates.[5b] However, the following differences between the behaviours of these two classes should be mentioned.

1. The acidifying effect of replacement in the imidodicarbonates Z_2NH (Z = CO_2CH_2Ph) and Boc_2NH (Boc = CO_2Bu^t) of one Z- or Boc group with the benzoyl group ranges from 0.5 ± 0.1 pK_a units (*e.g.* for the transfers between Z_2NH and $BzNHCO_2CH_2Ph$, $ZNHCOOCH_2CCl_3$ and $BzNHCOOCH_2CCl_3$) to 1.9 pK_a units (transfer from Boc_2NH to BzNHBoc).

2. For the same group, R^1, in the series of the benzoyl carbamates the introduction of the (+R) electron-donating MeO substituent into the benzene ring *para* to the carbonyl group, decreases the acidity of these NH acids only slightly (0.1–0.5 pK_a units). However, introduction of the strong electron acceptor NO_2 group into the same position in the benzoyl group increases the acidity by 1.4–1.9 pK_a units.

3. For a fixed R^1, however, changes in R^2 can cause even more significant changes in the acidity of the NH acids studied in this work. Thus, for R^1 = Mbz or Bz the replacement of R^2 = Bu^t with CH_2CCl_3 group increases the acidity of the corresponding benzoyl carbamates by 2.6–2.7 pK_a units, whereas for R^1 = Nbz the analogous substituent effect is even larger (3.1 pK_a units). However, for the same R^1, the acidity of the members of the present series of NH acids is only moderately sensitive to substitutions in the phenyl ring of the CH_2Ph group (R^2 =

Table 1 Data on synthetic acylcarbamates

Compound	Yield (%)	M.p./ °C	Lit. m.p./ °C	pK_a in DMSO
Mbz[a]–NH–CO–OMe	69	114.5		14.3
Mbz–NH–CO–OBu^t	65	125.5	119–120[7]	15.2
Mbz–NH–CO–OCH_2CCl_3[b]	62	172–173		12.6
Mbz–NH–CO–OCH_2Ph	72	118	103–105[8]	13.9
Mbz–NH–CO–$OCH_2C_6H_4$–4-NO_2[c]	62	172.5		13.6
Bz–NH–CO–OMe	56	118	117–118[9]	14.0[d]
Bz–NH–CO–OBu^t	86	152–155 (decomp.)	136–137[7] 146–147[10]	15.0
Bz–NH–CO–OCH_2CCl_3	99	126.5–127.5[11]		12.3
Bz–NH–CO–OCH_2Ph	91	117–117.5[12]	96–97[8]	13.7
Bz–NH–CO–$OCH_2C_6H_4$–4-NO_2	93	155–155.5[11]		13.1
Bz–NH–Poc[a]	93	140–141		12.8[e]
Bz–NH–Fmoc[a]	92	161–162		14.5
Nbz[a]–NH–CO–OMe	41	197		12.5
Nbz–NH–CO–OBu^t	41	155.5–156	142–143.5[7]	13.5
Nbz–NH–CO–OCH_2CCl_3	48	171		10.4
Nbz–NH–CO–OCH_2Ph	51	151.5		12.2
Nbz–NH–CO–OCH_2–C_6H_4–4-NO_2	46	164		11.7

[a] The following abbreviations have been used: Mbz is 4-methoxybenzoyl-; Nbz is 4-nitrobenzoyl-; Poc is 4-pyridylmethyloxycarbonyl-; Fmoc is 9-fluorenemethyloxycarbonyl-. [b] Carbon analysis 0.56% too low. [c] Carbon analysis 0.48% too low. [d] pK_a = 10.30 in aqueous solution, see the text. [e] pK_a = 10.30 in aqueous solution, see the text.

substituted benzyl group): the largest increase in the acidity (R^1 = Ph; R^2 changes from CH_2Ph into $CH_2C_6H_4$–4-NO_2) is only 0.6 pK_a units (compare also ref. 5*b*).

In water, the only measured compounds, $BzNHCO_2Me$ and BzNHPoc, have the same acidity, being 0.3 pK_a units weaker than phenol [$pK_a(H_2O)$ = 10.00].[13] In DMSO solution, BzNHPoc exceeds $BzNHCO_2Me$ by 1.2 pK_a units, whereas both are much stronger acids than phenol [pK_a(DMSO) = 18.0].[14] Evidently, determination of the pK_as of this series of Gabriel reagents could be performed by titration of solutions of their water-soluble alkali metal salts with a strong acid.

An investigation of the Mitsunobu alkylation of some selected acylcarbamates using benzyl alcohol as the model alkylating agent (Scheme 2) has revealed that significant

$$R^1C_6H_4\text{–CO–NH–CO–}OR^2 + \text{Bzl–OH} \xrightarrow{\text{i}} R^1C_6H_4\text{–CO–N(Bzl)–CO–}OR^2 + R^1C_6H_4\text{–C(OBzl)=N–CO–}OR^2$$

Scheme 2 *Reagents:* i, TPP and DEAD in THF. R^1 = H or 4-NO_2; R_2 = Bu^t, CH_2CCl_3, Bzl and $CH_2C_6H_4$–4-NO_2.

amounts of *O*-benzyl isomer, in addition to the *N*-benzyl derivative, are formed under our usual reaction conditions. Since these isomers are not readily removed from the crude mixtures by silica chromatography, these substrates appear less suitable than imidodicarbonates as amine synthons in this conversion. Typically the amount of *O*-benzyl derivatives present in the crude product mixture after chromatographic removal of the Mitsunobu side products is in the range of 20–25%. Particularly with the Nbz derivatives, the *O*-alkyl isomers sometimes seem to be sensitive to the chromatographic separation procedure and therefore the *O*-alkyl/*N*-alkyl ratios are significantly lowered in some cases. In a model experiment using ethyl (*S*)-lactate, thus mimicking our earlier alanine syntheses,[5*a*] more than half of the product formed (58%) was the *O*-alkyl isomer. The *N*- and *O*-alkyl isomers generally exhibited very similar chromatographic behaviour, thus making their separation rather impractical. In an attempt partly to circumvent this problem, the 42:58 mixture just mentioned was treated with 3 equiv. of Bu^{t}NH$_2$ in EtOH. After 24 h at room temperature, chromatographic work-up afforded Troc-(*R*)-alanine ethyl ester (Troc is trichloroethyloxycarbonyl) in 82% yield, as calculated from the content of *N*-alkyl isomer. The *O*-alkyl isomer appeared to be decomposed to products which were readily separated from the desired product in this case. Also, according to the same approach, the Nbz–N(Bzl)–CO–OBu^t isomer (77:23 *N*/*O*-Bzl) mixture underwent nucleophilic cleavage in the presence of a small excess of 2-diethylaminoethylamine (DEAEA) in MeCN after a convenient extractive work-up.[6] Some (nonoptimized) results of Mitsunobu alkylations of selected substrates are compiled in Table 2.

To summarize, the acidity within the series of benzoylcarbamates prepared is slightly higher than for imidodicarbonates[5*b*] and it has been confirmed that acylcarbamates undergo Mitsunobu reactions,[3,4] but these are not as clean as with imidodicarbonates,[5*a*] and mixed *N*/*O*-alkylation does indeed take place as reported.[3,4] Nevertheless, selective monodeacylation of the crude mixture before work-up as reported in this paper might occasionally be synthetically useful.

Experimental

General Procedures.—M.p.s were recorded on a Gallenkamp apparatus and are uncorrected. All solvents used as reaction media were of the best commercial grade and were dried over molecular sieves (4A). All reagents used in the Mitsunobu reaction were purified as described earlier[5*a*] and were dried thoroughly before use. TLC analyses were performed on 0.25 mm thick precoated silica plates (Merck DC-Fertigplatten Kieselgel 60 F_{254}) with MePh–MeCN (2:1) or light petroleum–Et_2O mixtures as developer. Spots were visualized by inspection under UV light at 254 nm or preferentially, after brief heating, by exposure to Cl_2 followed by dicarboxidine spray. ^{1}H NMR spectra were routinely recorded on a JEOL JNM-EX 270 at 270 MHz in $CDCl_3$. In all cases the NMR data were in full agreement with the proposed structures. Elemental analyses were carried out on all solid, novel compounds by Mikro Kemi AB, Uppsala, Sweden and gave satisfactory results for CHN (±0.3%, unless otherwise indicated). Yields, m.p.s and other information about the compounds are compiled in Tables 1 and 2.

Preparation of Alkyl N-*Benzoylcarbamates.—General procedure.* Freshly distilled benzoyl isocyanate[15] (7.35 g, 50 mmol) in dry CH_2Cl_2 (50 cm^3) was added dropwise with stirring under

Table 2 Mitsunobu alkylation of selected acylcarbamates

Substrate	Alkylating agent	Total yield[a] (%)	*O*-Alkylation[b] (%)
Bz–NH–CO–OCH_2Ph [11]	BzlOH	98	25
Bz–NH–CO–OCH_2CCl_3 [11]	BzlOH	94	19
Bz–NH–CO–$OCH_2C_6H_4$-4-NO_2 [11]	BzlOH	71	20
Nbz–NH–CO–OCH_2CCl_3	BzlOH	82	9[c]
	Et (*S*)-lactate	69	58
Nbz–NH–CO–OBu^t	BzlOH	65	23[d]

[a] After flash chromatography of the crude product on silica. [b] Relative to the total yield, determined by ^{1}H NMR spectroscopy, of the product mixture after flash chromatography. The isomers were not separated. [c] *N*-Alkyl/*O*-alkyl ratio *ca.* 3.35 (corresponding to *ca.* 23% *O*-alkyl derivative) before chromatography. $\delta_H(CDCl_3)$ *N*-Bzl isomer: 8.26 and 7.67 (ABq, 4 H, Nbz), 5.14 (s, 2 H, Bzl), 4.67 (s, 2 H, Troc); *O*-Bzl isomer: 8.26 and 7.86 (ABq, 4 H, Nbz), 5.40 (s, 2 H, Bzl), 4.77 (s, 2 H, Troc). [d] *N*-Alkyl/*O*-alkyl ratio *ca.* 3.0 (corresponding to *ca.* 25% of *O*-alkyl isomer) before chromatography. $\delta_H(CDCl_3)$ *N*-Bzl isomer: 8.26 and 7.64 (ABq, 4 H, Nbz), 5.01 (s, 2 H, Bzl), 1.18 (s, 9 H, Bu^t); *O*-Bzl isomer: 8.26 and 7.85 (ABq, 4 H, Nbz), 5.32 (s, 2 H, Bzl), 1.44 (s, 9 H, Bu^t).

argon to an ice-cold solution of the alcohol (5% excess except for 4-pyridylmethanol and 4-nitrobenzyl alcohol when equivalent amounts were used), also in CH_2Cl_2 (25–100 cm^3), over 1–2 h. After standing overnight at room temp., the solvent was removed, leaving a solid residue which was thoroughly rinsed with ether (light petroleum for the 9-fluorenemethyl derivative) and dried *in vacuo*. The yield of crude, essentially pure product was nearly quantitative. In the reactions with the two alcohols mentioned, the products precipitated from the reaction mixtures and were collected. They were further purified by recrystallization and in one case (BzNHCO$_2$Bu^t) by column chromatography on silica (CH_2Cl_2–acetone, 4:1) followed by recrystallization. For additional details, see Table 1.

Preparation of 4-methoxybenzoyl- and 4-nitrobenzoyl-carbamates. For the synthesis of the 4-methoxybenzoyl- and 4-nitrobenzoyl-carbamates, the crude isocyanates were used.[16] The isocyanate (≤ 10 mmol), dissolved in dry CH_2Cl_2 (10 cm^3), was added dropwise with stirring under argon to an ice-cold solution of the alcohol (1.0 equiv., 1.1 equiv. for Bu^{t}OH) in CH_2Cl_2 (5–15 cm^3) over 20 min. After another 30 min at 0 °C and 2 h at room temp., the solvent was evaporated (Nbz–NH–CO–OMe and Nbz–NH–CO–OCH_2Ph crystallized directly from the reaction mixture) giving solids or oils which were triturated with diethyl ether or chromatographed (Nbz–NH–CO–OBu^t and Nbz–NH–CO–OCH_2CCl_3 in CH_2Cl_2–acetone, 9:1) on silica and then purified by recrystallization. For additional details, see Table 1.

Mitsunobu Alkylation of Acylcarbamates. Typical Procedure: Benzylation of NbzNHCO$_2$Bu^t.—A solution of NbzNHCO$_2$Bu^t (393 mg, 1.48 mmol) and benzyl alcohol (177 mg, 1.63 mmol) in dry THF (3.0 cm^3) was chilled in ice under dry argon and treated with triphenylphosphine (467 mg, 1.78 mmol) in small portions with rapid stirring. Neat diethyl azodicarboxylate (336 mg, 1.93 mmol) was introduced dropwise with vigorous agitation over a period of 20 min and stirring in ice for 1 h and at ambient temperature for 5 h. The solvent was stripped off at reduced pressure and the remaining sticky mass was dissolved in Et_2O and chromatographed on silica using light petroleum–Et_2O (3:1) as eluent. A central fraction weighing 342 mg was collected and ^{1}H NMR spectroscopy indicated that it consisted of a mixture of *N*-Bzl and *O*-Bzl derivative (ratio 77:23; the crude product before chromatography showed the ratio 75:25). The combined yield of *N*- and *O*-Bzl derivatives was 65%. For ^{1}H NMR data, see Table 2.

Nucleophilic Cleavage of N-*Alkyl*/O-*Alkyl Isomer Mixture. Model Experiment:* N^2-*Diethylaminoethylamine-mediated Cleavage of* N-/O-*Bzl Mixture Derived from 4-Nitrobenzoyl tert-Butyl Carbamate.*—The above product mixture (308 mg, 0.86 mmol) was suspended in dry MeCN (1.9 cm^3) and treated with DEAEA (184 mm^3, 1.5 equiv.) in small portions with rapid stirring. The resulting brick-red slurry was stirred overnight at room temperature, whereafter most of the solvent was stripped off at reduced pressure. The oily residue was partitioned between Et_2O (40 cm^3) and 1 mol dm^{-3} $KHSO_4$ (20 cm^3), and the extract was washed and dried as usual to give crude BzlNHBoc (*ca.* 120 mg, *ca.* 90% pure, *ca.* 80% yield as calculated from this component in the crude mixture).

pK_a Determination in DMSO Solutions.—The pK_a determinations were performed at 25 °C using potentiometric titration of the NH acids with a solution of Bu_4NOH in a mixture of benzene and Pr^{i}OH (4:1). The detailed description of the technique used was given previously.[5b]

pK_a Determinations in Water.—A standard potentiometric technique was used for measuring the acidity of a few title compounds.[13] The measured pK_as for DMSO as well as for aqueous solution are listed in Table 1.

Acknowledgements

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II

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The Acidity of Substituted 1-Hydroxybenzotriazoles in Water and
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The Acidity of Substituted 1-Hydroxybenzotriazoles in Water and Dimethyl Sulfoxide

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J. Chem. Research (M), 1993, 3008–3028

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Several *N*-hydroxy compounds such as 1-hydroxysuccinimide and 1-hydroxybenzotriazole have found wide application in peptide synthesis for the preparation of active esters, as racemization-suppressing additives in peptide-fragment coupling reactions and, more recently, as components of peptide coupling reagents.[7] For this reason we decided to study the acidity of a number of substituted 1-hydroxybenzotriazoles (**2**–**13**),[5] 1-hydroxy-4- (**17**) and -7-azabenzotriazoles (**18**),[8] 3-hydroxy-4-oxo-3,4-dihydro-1,2,3-benzotriazine (**14**),[6] 1-hydroxysuccinimide (**15**)[1,3] and 1-hydroxyphthalimide (**16**)[13b] by determination of their pK_a values in aqueous solution and in dimethyl sulfoxide (DMSO).

Unsubstituted 1-hydroxybenzotriazole has pK_a values of 4.60 and 9.3 in water and in DMSO, respectively, whereas those for the substituted derivatives fall within the ranges 3.10–5.07 and 7.0–9.5. The corresponding values for **17**, **18** and **14** in order of descending acidity are also within these ranges, whereas **15** and **16** are less acidic, especially in DMSO. Table 1 lists the detailed results obtained for the aforementioned 18 *N*-hydroxy compounds. The pK_a in DMSO for the acidic dissociation of protonated pyridine oxide is also included. Samples **2**–**13** were obtained from Dr. W. König of Hoechst AG, Frankfurt, Germany, and **17** and **18** from Professor L. A. Carpino, University of Massachusetts, Amherst, USA. All pK_a determinations in water (at 25 °C) were performed by a standard potentiometric technique.[21] The corresponding determinations in DMSO solution were also performed at 25 °C using potentiometric titration with a solution of Bu_4NOH in a mixture of benzene and Pr^iOH. A detailed description of the technique used has been given earlier.[15]

Table 1 pK_a values for substituted 1-hydroxybenzotriazoles and a few other OH and related NH acids in water and DMSO

Entry	pK_a H_2O[a]	pK_a DMSO[b]	$-\Delta pK_a$ [$=pK_a(H_2O) - pK_a(DMSO)$]
Substituted 1-hydroxybenzotriazoles			
Unsubstituted (**1**)	4.60	9.3	4.7
4-Cl (**2**)	3.90	8.4	4.5
5-Cl (**3**)	4.18	8.5	4.3
6-Cl (**4**)	4.15	8.6	4.4
6-Br (**5**)	3.97	8.4	4.4
6-CF_3 (**6**)	3.80	7.4	3.6
5-MeO (**7**)	5.07	9.5	4.4
4-Me, 5-Cl (**8**)	4.09	8.9	4.8
5-Me, 6-Cl (**9**)	4.57	8.9	4.3
4-Me, 6-NO_2 (**10**)	3.43	7.0	3.6
4-Cl, 6-NO_2, 7-Me (**11**)	3.17	7.1	3.9
5-Cl, 6-Me, 7-NO_2 (**12**)	3.21	7.0	3.8
4-Me, 5-Cl, 6-NO_2 (**13**)	3.10	7.0	3.9
Other compounds			
3-Hydroxy-4-oxo-3,4-dihydro-1,2,3-benzotriazine (**14**)	3.97	8.9	4.9
1-Hydroxysuccinimide (**15**)	6.09	14.0	7.9
1-Hydroxyphthalimide (**16**)	6.32	12.9	6.6
1-Hydroxy-4-azabenzotriazole (**17**)	3.14[c]	8.1	5.0
1-Hydroxy-7-azabenzotriazole (**18**)	3.47[c]	8.7	5.2
$C_5H_5NOH^+$ (**28**)	0.8[d]	2.4	1.6

[a] ±0.03 pK_a units. [b] ±0.1 pK_a units. [c] See also ref. 13*a*. [d] Ref. 12.

In addition, an attempt was made to correlate the pK_a values in DMSO with those in water. Fig. 1 shows a plot for the 19 *N*-hydroxy compounds investigated in this work plus 14 other OH acids from the literature[12,14] (alcohols, carboxylic and mineral acids and protonated forms of amine oxides; these compounds are listed in Table 1 in the full-text version). The resulting set of compounds covers a wide pK_a range (from −0.6 to 16 in H_2O and from 1.6 to 33 in DMSO).

This fit is characterized (for 33 points) by the equation

$$pK_a(DMSO) = (1.5 \pm 0.2) + (1.77 \pm 0.03)pK_a(H_2O) \quad (1)$$
$$r = 0.997;\ s = 0.8$$

(r and s are the correlation coefficient and standard deviation, respectively).

As can be seen from Fig. 1, of the *N*-hydroxy compounds **1**–**18** now under study, only 1-hydroxysuccinimide (**15**) deviates significantly from the others in its behaviour. The remaining 17 *N*-hydroxy compounds fit the relation

$$pK_a(DMSO) = (2.2 \pm 0.7) + (1.58 \pm 0.17)pK_a(H_2O) \quad (2)$$
$$n = 17;\ r = 0.923;\ s = 0.56$$

The further inclusion, besides the 33 OH acids described by eqn. (1), of an additional 46 points[12] for aliphatic carboxylic acids and substituted benzoic acids leads to the more general linear plot

$$pK_a(DMSO) = (3.2 \pm 0.2) + (1.66 \pm 0.03)pK_a(H_2O) \quad (3)$$
$$n = 79;\ r = 0.987;\ s = 1.1$$

the slope of which is rather close to those related to eqns. (1) and (2) and the intercept of which is somewhat shifted upwards along the ordinate axis.

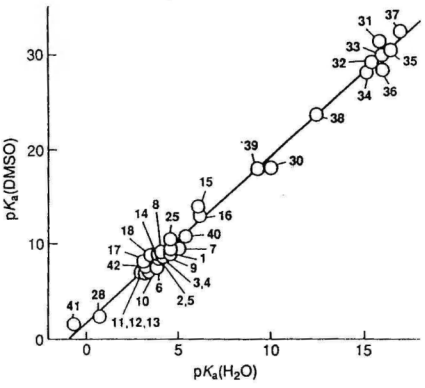

Fig. 1 Plot of pK_a(DMSO) *vs.* $pK_a(H_2O)$ for the set of NOH and OH acids listed in Table 1

*To receive any correspondence.

In conclusion we should like to point out that the data of König and Geiger[6,23] on the relative efficiencies of **15**, **1** and **14** with respect to suppression of racemization can be rationalized on the basis of the pK_a values of these compounds. The same applies to the data of Carpino[8] on **1** and **18**, whereas, as briefly mentioned, **17** is less efficient than **18**,[8] indicating that factors other than acidity may also be important in this context.

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Technique used: Potentiometric titration

References: 24

Table 1: pK_a values for substituted 1-hydroxybenzotriazoles and a few other OH and related NH acids in water and DMSO (the table in the full-text version contains additional literature data[12] on compounds **25** and **30–42** included in Fig. 1)

Fig. 2: Plot of pK_a(DMSO) *vs.* $pK_a(H_2O)$ for the subset of NOH acids comprising entries 1–18 listed in Table 1

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III

The Acidity of Some Neutral NH-Acids in Water and Dimethyl Sulfoxide

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Recently we reported the pK_a values for a wide range of imidodicarbonates and related compounds in dimethyl sulfoxide (DMSO).[1,2] Some of these derivatives were employed as efficient Gabriel[3] reagents for the synthesis of protected ^{15}N-labelled α-amino acids from the corresponding α-hydroxy acids using the Mitsunobu reaction.[4] These investigations indicated a strong correlation between the acidity of the NH function of these derivatives and the yield in the latter reaction.

Several of these NH-acids are poorly soluble in water. Therefore, only pK_as for a limited number of the above-mentioned compounds could be determined by direct potentiometric titration of the neutral acids with aqueous KOH. In the present study we have instead measured these pK_as in aqueous solution at 25 °C by titration of the corresponding, more soluble potassium salts of some of them (*i.e.* imidodicarbonates, tosyl- and benzoyl-carbamates) with HCl. In addition, the pK_as of imides of triflic and trifluoroacetic acids, saccharin and some other alicyclic sulfonamides were measured by direct titration of neutral NH-acids with alkali. The pK_as of a few NH-acids were also determined in DMSO solution at 25 °C.

The results of the present measurements of pK_a values for several NH-acids containing protecting groups used in peptide synthesis[7] are listed in Table 1. For comparison, literature data on the acidities of some other groups of neutral NH-acids (anilines, NH_3, cyclic NH-acids, amides, imides) in aqueous solution and DMSO are also listed in Table 1 of the full-text version.

In order to evaluate the effect of structure and solvent on the acidity of neutral NH-acids upon changing from water to DMSO, we performed a statistical analysis of the data in terms of eqn. (1), where m and n are constants.

$$pK_a(\text{DMSO}) = m + n pK_a(H_2O) \quad (1)$$

The results of this analysis are given in Table 2. Roughly linear family relationships were established between the acidities of imides, amides, heterocyclic NH-acids and substituted anilines in aqueous solution and in DMSO.

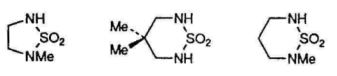
Similar to the general behaviour[11,12] of any other class of neutral Brönsted acids, the transfer from aqueous solution to a non-hydrogen bonding dipolar aprotic solvent (DMSO, MeCN, *etc.*) or gas phase (mostly due to the destabilization of the anionic form relative to the neutral acid) is accompanied by a decrease in acidity of the acid. The solvent-induced change in acidity (ΔpK_a) for the compounds measured in the present work ranges from 5.9–6.5 (*e.g.*, **1**, **19–21**) to 1.1 [$(CF_3CO)_2NH$] pK_a units and the weaker acids [NH_3, $MeCONH_2$, $CO(NH_2)_2$ *etc.*] seem to have the largest acidity drops due to poor charge delocalization in their corresponding anions, A^-.

Extremely strong solvent effects were found to be characteristic for carbamide ($\Delta pK_a = 13.6$), various amides (for $MeCONH_2$ $\Delta pK_a = 10.4$, for $PhCONH_2$ $\Delta pK_a = 8.9$) and sulfonamides (6.0–6.7 pK_a units).

Table 1 Acidities of some neutral NH-acids in aqueous solution and in DMSO at 25 °C

Compound	Acid[a]	pK_a		
		H_2O	DMSO	ΔpK_a [$= pK_a$ (DMSO) $- pK_a$ (H_2O)]
1	Boc_2NH	11.0	16.9[1]	5.9
2	BocNHBz	10.3	15.0[2]	4.7
3	MeOCONHBz	10.3[2]	14.0[2]	3.7
4	PocNHBz	9.8 (see[2])	12.8[2]	3.0
5	Succinimide	9.6[8]	14.6[5]	5.0
6	Phthalimide	8.3[8]	13.4[5]	5.1
7	ZNHBz	9.4	13.7[2]	4.3
8	Z_2NH	10.3	14.2[1]	3.9
9	TrocNHZ	9.8	12.7[1]	2.9
10	$(EtO)_2P(O)NHBoc$	9.3	14.5	5.2
11	TrocNHBz	9.1	12.3[2]	3.2
12	TosNHBoc	5.05	8.5[1]	3.4
13	TosNHZ	4.21	7.5[1]	3.3
14	TosNH-4-NO_2-Z	3.8	7.0[1]	3.2
15	4-$MeSO_2C_6H_4SO_2NHBoc$	3.76	7.2	3.4
16	Saccharin	1.6 (see[6])	3.8 (see[5])	2.2
17	$(CF_3SO_2)_2NH$	1.21 (see[9])	2.4	1.2
18	$(CF_3CO)_2NH$	1.2	2.3[1]	1.1
19	[b]	10.39	16.8	6.4
20	[b]	10.78	17.3	6.5
21	[b]	11.2	17.7	6.5

[a]The following abbreviations have been used: Boc = C(O)OBu^t, Z = $C(O)OCH_2Ph$, Troc = $C(O)OCH_2CCl_3$ and Bz = C(O)Ph. A fuller version of this table is given in the full text. [b]See structures below.



19 **20** **21**

*To receive any correspondence.

Table 2 Statistical analysis of data from Table 1 in terms of eqn. (1)[a]

	Compounds	*m*	*n*	*s*	*r*	*N*
1	Imides and amides[b]	1.16 (0.45)	1.43 (0.05)	0.96	0.986	26
2	Amides[c]	0.27 (0.52)	1.64 (0.04)	0.32	0.999	6
3	Imides[d]	1.52 (0.46)	1.36 (0.05)	0.92	0.984	11
4	Heterocyclic NH acids and NH_3[e]	3.29 (0.35)	1.14 (0.02)	0.55	0.998	10
5	Anilines, $PhNH_3^+$ and PyH^+[f]	−1.81 (0.21)	1.19 (0.01)	0.21	0.999	12

[a] *m* and *n* are regression coefficients, *s* is the standard deviation, *r* is the correlation coefficient and *N* the number of points used. The reliability intervals of regression coefficients are indicated in parentheses. The numbering of points corresponds to Table 1 of the full-text version. [b] 1–3, 5–8, 10–21, 35–38 and 40. [c] 34–38 and 41. [d] 1–3, 5–8, 10–21 and 40. [e] 22–32. [f] 42–54.

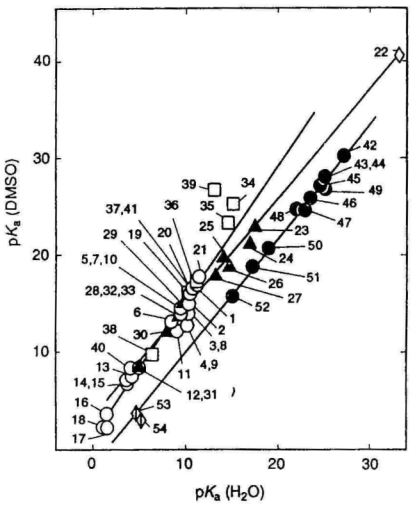


Fig. 1 Plot of pK_a(DMSO) *vs.* pK_a(H_2O) for the substances listed in Table 1: ◇ = ammonia, Φ = anilinium and pyridinium ions, ● = anilines, ▲ = heterocyclic NH-acids, □ = amides and ○ = imides

As evident from Table 2 and Fig. 1, the group of compounds consisting of imides and amides displays 1.43 times higher sensitivity towards substituent effects in DMSO as compared with aqueous solution. This correlation (see series 1 inTable 2) spans over 22 pK_a units on the DMSO scale and can in statistical terms be considered significant. The values for PocNHBz, TrocNHBz, CH_3CONH_2 and, especially, carbamide deviate from this relationship. In terms of slope and intercept the NH acid family comprising amides and imides resembles those characterizing the acidic dissociation of OH acids.[13]

The separate statistical treatment of the series of amides (Table 2, series 2) and imides (Table 2, series 3) leads to values for the regression coefficients of eqn. (1) which in statistical terms deviate slightly. The acidic dissociation of amides seems to be more sensitive to solvent effects than is the same process for imides.

The acidities of heterocyclic NH-acids (Table 2, series 4) and substituted anilines (Table 2, series 5) have significantly lower, and almost equal sensitivities ($1.14 \leqslant n \leqslant 1.19$) for substituent effects towards the medium effects. While the straight lines for these two series in Fig. 1 (see also Table 2, series 4 and 5) run almost parallel, their intercepts differ by more than 5 powers of ten. Also, as one can see from Table 1 in the full-text version, of all families of neutral NH-acids, anilines display the lowest average solvent effect (ΔpK_a) on their pK_a values. The points for the cationic acids $C_6H_5NH_3^+$ and $C_5H_5NH^+$ fit the straight line for the acidic dissociation of the anilines as neutral Brönsted acids, whereas the ΔpK_a values for these two cationic acids are negative.[14]

Technique used: potentiometric titration

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IV

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Synthesis and Cathodic Cleavage of a Set of Substituted
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Sulfonylcarbamates: pK_a of Sulfonamides, pages 2025–2031,

Synthesis and cathodic cleavage of a set of substituted benzenesulfonamides including the corresponding *tert*-butyl sulfonylcarbamates: pK_a of sulfonamides

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From a series of substituted benzenesulfonic acids, most of which have previously been employed for the protection of amino functions and including a few such known to facilitate cleavage by acid, benzylamides **1a–k** have been derived and studied. Initially their electrochemical cleavage potentials were determined by cyclic voltammetry in order to further explore selective deprotection within this substance group. In parallel, the corresponding *tert*-butyl sulfonylcarbamates **2a–k** have also been prepared and studied. Among the sulfonamides investigated S–N bond cleavage was found to take place over a wide range of potentials from −1.67 to −2.64 V (excluding the nitro derivative), the most acid-labile groups requiring more negative potentials, whereas this cleavage was facilitated by 0.19–0.30 V for the sulfonylcarbamates. Small scale electrolyses of **2** at controlled potential with determination of the cleavage products formed were subsequently performed. For the *N*-benzylbenzenesulfonamides **1**, the pK_as in DMSO and in some cases also in water have been determined and found to be in the range 14.0–16.4 and 10.07–11.53, respectively.

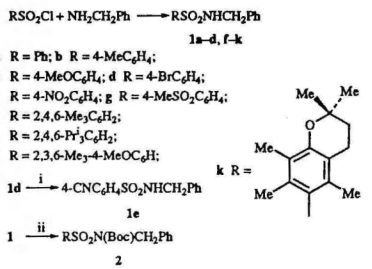
For a long time aromatic sulfonic acids have been used in the derivatization of amines and the protection of amino functions. Simple sulfonamides are among the most stable derivatives available for such compounds,[1a] thus requiring rather drastic conditions for subsequent regeneration of the amines. Hence, for cleavage of the prototype *N*-tosyl group, reagents like sodium in liquid ammonia,[2] refluxing concentrated strong acid such as HBr in the presence of phenol[3] and sodium naphthalenide[4] have been applied. The need for such harsh conditions restricted the use of tosyl and other related protecting groups to only very stable molecules and excluded the simultaneous application of many other labile protecting groups currently used. However, the scope for this application widened with the advent of efficient electrochemical methods for tosyl cleavage.[5] In parallel, efforts have been made to modify the tosyl group to make it more labile to acid. As a result of these efforts, a new generation of arenesulfonyl protecting groups have emerged primarily for the purpose of semi-permanent protection of the guanidine function in arginine.[6] Among these are the 4-methoxybenzenesulfonyl (Mbs),[7] the 4-methoxy-2,3,6-trimethylbenzenesulfonyl (Mtr)[8] and, more recently, the 2,2,5,7,8-pentamethylchromane-6-sulfonyl (Pmc) residues.[9]

Nowadays a very large number of useful and convenient protecting groups for various functional groups, including those present in peptides, are available,[1b] many of which are stable when subjected to the conditions under which sulfonamides undergo electrochemical cleavage. Therefore, in recent years we have investigated different aspects of cathodic S–N bond cleavage with particular reference to selective deprotection. Thus, these experiments have shown that selective detosylation of a primary sulfonamide can be accomplished on a preparative scale in the presence of a secondary one.[10] Further cleavage experiments on imidodicarbonates and acylcarbamates, including tosylcarbamates,[11] indicated that it might be worthwhile to investigate a series of substituted benzenesulfonylcarbamates in order to find out whether selective cleavage could be accomplished by substitution within the benzene ring. Such selectivity was previously achieved by the introduction of a second acyl group on the nitrogen atom as first reported by Singer and Sharpless.[12]

Results

Synthesis of the compounds studied

The *N*-benzylbenzenesulfonamides **1a–1d** and **1f–1k** were conveniently prepared from the appropriate arenesulfonyl chloride and benzylamine according to Scheme 1, as described



Scheme 1 *Reagents:* i, CuCN; ii, Boc_2O, DMAP

in detail in the Experimental section. We found that this procedure, using triethylamine as base and dichloromethane as solvent, gave a more facile work-up in comparison with performing the reaction in pyridine.[10] Compound **1e** was obtained by refluxing **1d** with an excess of CuCN in dry DMF.[13] This route to **1e** was chosen because of the high yield in this exchange reaction and also because the otherwise required 4-cyanobenzenesulfonyl chloride[14] was not readily available, thus requiring additional synthetic efforts.

The sulfonamides **1a–k** were smoothly converted into the corresponding *tert*-butyl sulfonylcarbamates $RSO_2N(Boc)$-

Table 1 Chemical properties of RSO_2NHBzl (compounds **1a**, **1c**–**k**)

Compound (formula)	R	Yield (%) (crude)	Mp (°C) (recr. solv.)	δ_H(270 MHz; rel. TMS)	Elemental analyses found (calc.)
1a ($C_{13}H_{13}NO_2S$)	Ph	100	86.5–87[a] (Et_2O–LP)	4.13 (2 H, d, NCH_2), 4.91 (1 H, t, NH), 7.16–7.30 (5 H, complex signal, Bzl aryl-H), 7.47–7.62 and 7.85–7.89 (together 5 H, complex signal, SO_2Ph-H)	– –
1c ($C_{14}H_{15}NO_3S$)	4-$MeOC_6H_4$	95	107.5–108 (CH_2Cl_2–Et_2O)	3.87 (3 H, s, MeO), 4.10 (2 H, d, NCH_2), 4.86 (1 H, t, NH), 6.96 and 7.80 (4 H, ABq, SO_2 aryl-H), 7.17–7.31 (5 H, complex signal, Bzl aryl-H)	C, 60.7; H, 5.6; N, 5.1 (C, 60.6; H, 5.5; N, 5.1)
1d ($C_{13}H_{12}BrNO_2S$)	4-BrC_6H_4	99	121–122[b] (EtOAc–heptane)	4.13 (2 H, d, NCH_2), 5.00 (1 H, t, NH), 7.14–7.30 (5 H, complex signal, Bzl aryl-H), 7.61 and 7.69 (4 H, ABq, SO_2 aryl-H)	– –
1e ($C_{14}H_{12}N_2O_2S$)	4-CNC_6H_4	99	141–142 (EtOAc–heptane)	4.19 (2 H, d, NCH_2), 5.19 (1 H, t, NH), 7.13–7.28 (5 H, complex signal, Bzl aryl-H), 7.74 and 7.90 (4 H, ABq, SO_2 aryl-H)	C, 61.7; H, 4.6; N, 10.2 (C, 61.7; H, 4.4; N, 10.3)
1f ($C_{13}H_{12}N_2O_4S$)	4-$NO_2C_6H_4$	100	126.5–127[c] (EtOAc–heptane)	4.22 (2 H, d, NCH_2), 5.18 (1 H, t, NH), 7.14–7.26 (5 H, complex signal, Bzl aryl-H), 7.97 and 8.29 (4 H, ABq, SO_2 aryl-H)	– –
1g ($C_{14}H_{15}NO_4S_2$)	4-$MeSO_2C_6H_4$	81	171–172 (EtOAc)	3.10 (3 H, s, $MeSO_2$), 4.21 (2 H, d, NCH_2), 4.91 (1 H, t, NH), 7.16–7.29 (5 H, complex signal, Bzl aryl-H), 8.02 and 8.05 (4 H, ABq, SO_2 aryl-H)	C, 51.6; H, 4.7; N, 4.3 (C, 51.7; H, 4.6; N, 4.3)
1h ($C_{16}H_{19}NO_2S$)	2,4,6-$Me_3C_6H_2$	96	100–101 (Et_2O)	2.31 (3 H, s, 4-Me), 2.63 (6 H, s, 2,6-Me_2), 4.06 (2 H, d, NCH_2), 4.74 (1 H, t, NH), 6.96 (2 H, s, SO_2 aryl-H), 7.15–7.30 (5 H, complex signal, Bzl aryl-H)	C, 66.7; H, 6.3; N, 4.7 (C, 66.4; H, 6.6; N, 4.8)
1i ($C_{22}H_{31}NO_2S$)	2,4,6-$Pr^i_3C_6H_2$	98	94–94.5 (Et_2O–heptane)	1.25 [12 H, d, 2,6-($CHMe_2$)$_2$], 1.27 (6 H, d, 4-$CHMe_2$), 2.92 (1 H, m, 4-$CHMe_2$), 4.15 (2 H, d, NCH_2), 4.17 [2 H, m, 2,6-($CHMe_2$)$_2$], 4.57 (1 H, t, NH), 7.18 (2 H, s, SO_2 aryl-H), 7.17–7.32 (5 H, complex signal, Bzl aryl-H)	C, 71.0; H, 8.2; N, 3.6 (C, 70.7; H, 8.4; N, 3.7)
1j ($C_{17}H_{21}NO_3S$)	2,3,6-Me_3-4-$MeOC_6H$	98	128–129 (CH_2Cl_2–Et_2O)	2.13, 2.55 and 2.69 (3 × 3 H, 3 s, aryl-Me_3), 3.86 (3 H, s, MeO), 4.06 (2 H, d, NCH_2), 4.68 (1 H, t, NH), 6.59 (1 H, s, SO_2 aryl-H), 7.13–7.30 (5 H, complex signal, Bzl aryl-H)	C, 63.7; H, 6.7; N, 4.2 (C, 63.9; H, 6.6; N, 4.4)
1k ($C_{21}H_{27}NO_3S$)	2,2,5,7,8-Me_5-chroman-6-yl	96	132–132.5 (CH_2Cl_2–Et_2O)	1.33 (6 H, s, aliph. Me_2), 1.84 (2 H, t, CCH_2), 2.12, 2.53 and 2.55 (3 × 3 H, 3 s, aryl-Me_3), 2.64 (2 H, t, aryl-CH_2), 4.08 (2 H, d, NCH_2), 4.64 (1 H, t, NH), 7.14–7.28 (5 H, complex signal, Bzl aryl-H)	C, 67.6; H, 7.1; N, 3.8 (C, 67.5; H, 7.3; N, 3.7)

[a] Lit.,[16] mp 88 °C; LP = light petroleum (bp 40–65 °C). [b] Lit.,[17] mp 117 °C. [c] Lit.,[18] mp 126.0–128.8 °C (*sic*).

CH_2Ph **2a–k** by exhaustive *tert*-butoxycarbonylation using a slight excess of Boc_2O in dry acetonitrile, in the presence of a catalytic amount of 4-dimethylaminopyridine (DMAP).[15] After conventional work-up the desired products were all obtained as solids. The relevant data for compounds **1** and **2** are collected in Tables 1 and 2.

Cyclic voltammetry experiments

The sulfonamides **1a–k** as well as their corresponding *tert*-butyl sulfonylcarbamates **2a–k** were investigated by cyclic voltammetry. The experiments were performed at a vitreous carbon electrode at a substrate concentration of approximately 0.005 mol dm^{-3} in DMF, using Bu_4NBF_4 (0.1 mol dm^{-3}) as supporting electrolyte in the absence of a proton donor. A few typical cyclic voltammograms are shown in Fig. 1. Since the Boc group is not electroactive, the peaks observed in the voltammograms of **2** were obviously related to the substituted benzenesulfonyl group. The assignment of the first reduction peak to the cleavage of the substituted sulfonyl protecting group was achieved by electrolysing the *tert*-butyl sulfonylcarbamate at a potential slightly more negative than that corresponding to this peak followed by HPLC analysis of the products. Table 3 presents the potential, E_p, corresponding to the first cathodic peak for each of the substituted benzylamides **1a–k**, the potential, E'_p, for the corresponding *tert*-butyl sulfonylcarbamates **2a–k** and the shifts, ΔE and $\Delta E'$, caused by the substituent in both types of compounds, together with that, ΔE°, caused by the Boc group.

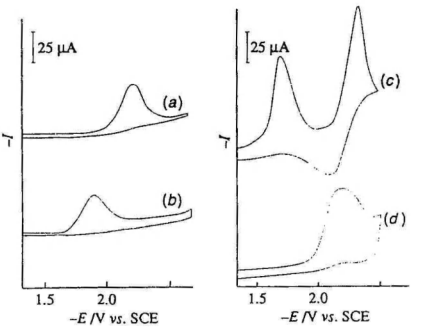


Fig. 1 Cyclic voltammograms at a vitreous carbon electrode of 0.005 mol dm^{-3} solutions of (*a*) **1a** (*b*) **2a** (*c*) **1e** (*d*) **1d** in DMF with 0.1 mol dm^{-3} Bu_4NBF_4 as supporting electrolyte at a sweep rate of 100 mV s^{-1} (SCE = saturated calomel electrode)

Electrolyses

As mentioned above, to confirm the previous assignment of the first voltammetry peak to cleavage of the substituted benzenesulfonyl group, small-scale electrolyses at controlled potential were carried out. In addition, the yields of deprotected product were determined to assess the feasibility of preparative

Table 2 Chemical properties of $RSO_2N(Boc)Bzl$ (compounds **2a**, **2c–k**)

Compound (formula)	R	Yield (%) (crude)	Mp (°C)[a] (recr. solv.)	δ_H(270 MHz; rel. TMS)	Elemental analyses found (calc.)
2a ($C_{18}H_{21}NO_4S$)	Ph	96	94.5–95.5 (Et_2O–LP)	1.30 (9 H, s, Boc-Me_3), 5.05 (2 H, s, NCH_2), 7.27–7.46 (5 H, complex signal, Bzl aryl-H), 7.53–7.59 and 7.66–7.71 (together 5 H, complex signal, SO_2Ph-H)	C, 62.2; H, 6.2; N, 3.9 (C, 62.2; H, 6.1; N, 4.0)
2c ($C_{19}H_{23}NO_5S$)	4-$MeOC_6H_4$	93[a]	100–101 (Et_2O–heptane)	1.34 (9 H, s, Boc-Me_3), 3.85 (3 H, s, MeO), 5.03 (2 H, s, NCH_2), 6.87 and 7.61 (4 H, ABq, SO_2 aryl-H), 7.29–7.41 (5 H, complex signal, Bzl aryl-H)	C, 60.5; H, 6.4; N, 3.6 (C, 60.5; H, 6.1; N, 3.7)
2d ($C_{18}H_{20}BrNO_4S$)	4-BrC_6H_4	91	121.5–122 (Et_2O–LP)	1.35 (9 H, s, Boc-Me_3), 5.03 (2 H, s, NCH_2), 7.30–7.39 (5 H, complex signal, Bzl aryl-H), 7.49 and 7.54 (4 H, ABq, SO_2 aryl-H)	C, 50.3; H, 4.7; N, 3.0 (C, 50.7; H, 4.7; N, 3.3)
2e ($C_{19}H_{20}N_2O_4S$)	4-CNC_6H_4	97	107–107.5 (Et_2O–LP)	1.35 (9 H, s, Boc-Me_3), 5.05 (2 H, s, NCH_2), 7.33–7.38 (5 H, complex signal, Bzl aryl-H), 7.69 and 7.71 (4 H, ABq, SO_2 aryl-H)	C, 61.0; H, 5.5; N, 7.4 (C, 61.3; H, 5.4; N, 7.5)
2f ($C_{18}H_{20}N_2O_6S$)	4-$NO_2C_6H_4$	96	131–132 (CH_2Cl_2–Et_2O)	1.36 (9 H, s, Boc-Me_3), 5.07 (2 H, s, NCH_2), 7.37 (5 H, perturbed signal, Bzl aryl-H), 7.78 and 8.23 (4 H, ABq, SO_2 aryl-H)	C, 55.1; H, 5.2; N, 7.1 (C, 55.1; H, 5.1; N, 7.1)
2g ($C_{19}H_{23}NO_6S_2$)	4-$MeSO_2C_6H_4$	94	116–116.5 (Et_2O)	1.35 (9 H, s, Boc-Me_3), 3.06 (3 H, s, $MeSO_2$), 5.06 (2 H, s, NCH_2), 7.34–7.40 (5 H, complex signal, Bzl aryl-H), 7.79 and 7.97 (4 H, ABq, SO_2 aryl-H)	C, 53.3; H, 5.3; N, 3.1 (C, 53.6; H, 5.4; N, 3.3)
2h ($C_{21}H_{27}NO_4S$)	2,4,6-$(Me_3)C_6H_2$	89[a]	115–115.5 (Et_2O–heptane)	1.26 (9 H, s, Boc-Me_3), 2.32 (3 H, s, 4-Me), 2.61 (6 H, s, 2,6-Me_2), 5.02 (2 H, s, NCH_2), 6.97 (2 H, s, SO_2 aryl-H), 7.26–7.38 and 7.47–7.50 (5 H, complex signal, Bzl aryl-H)	C, 65.0; H, 6.8; N, 3.4 (C, 64.8; H, 7.0; N, 3.6)
2i ($C_{27}H_{39}NO_4S$)	2,4,6-$(Pr^i_3)C_6H_2$	100	106–106.5 (crude)	1.13 (9 H, s, Boc-Me_3), 1.25 [18 H, d ($CHMe_2)_2$], 2.92 (1 H, m, 4-C*H*Me_2), 3.97 [2 H, m, 2,6-($CHMe_2)_2$], 5.00 (2 H, s, NCH_2), 7.16 (2 H, s, SO_2 aryl-H), 7.24–7.38 and 7.49–7.53 (5 H, complex signal, Bzl aryl-H)	C, 68.7; H, 8.2; N, 3.0 (C, 68.5; H, 8.3; N, 3.0)
2j ($C_{22}H_{29}NO_5S$)	2,3,6-(Me_3)-4-$MeOC_6H$	92[a]	137–138 (CH_2Cl_2–hexane)	1.14 (9 H, s, Boc-Me_3), 2.16, 2.48 and 2.69 (3 × 3 H, 3 s, aryl-Me_3), 3.87 (3 H, s, CH_3O), 5.03 (2 H, s, NCH_2), 6.61 (1 H, s, SO_2 aryl-H), 7.26–7.37 and 7.47–7.50 (together 5 H, complex signal, Bzl aryl-H)	C, 62.8; H, 6.6; N, 3.3 (C, 63.0; H, 7.0; N, 3.3)
2k ($C_{26}H_{35}NO_5S$)	2,2,5,7,8-(Me_5)-chroman-6-yl	63[a,b]	148.5–149 (CH_2Cl_2–hexane)	1.10 (9 H, s, Boc-Me_3), 1.33 (6 H, s, 2,2-Me_2), 1.84 (2 H, t, CCH_2), 2.13 and 2.49 (3 H + 6 H, 2 s, 5,7,8-Me_3), 2.66 (2 H, t, aryl-CH_2), 5.03 (2 H, s, NCH_2), 7.23–7.37 and 7.48–7.51 (together 5 H, complex signal, Bzl aryl-H)	C, 66.2; H, 7.4; N, 3.0 (C, 65.9; H, 7.4; N, 3.0)

[a] Recrystallized; LP = light petroleum (bp 40–65 °C). [b] Sluggish reaction requiring 2 equiv. of Boc_2O and prolonged reaction time for completion.

Table 3 Peak potentials and peak potential shifts obtained by cyclic voltammetry of compounds RSO_2NHBzl and $RSO_2N(Boc)Bzl$[a]

		RSO_2NHBzl **1**		$RSO_2N(Boc)Bzl$ **2**		
Compound	R	$-E_p$/V (*vs.* SCE)	ΔE^b/V	$-E'_p$/V (*vs.* SCE)	$\Delta E'^b$/V	$\Delta E''^c$/V
a	Ph	2.30	—	2.05	—	0.25
b	4-MeC_6H_4	2.41	−0.11	2.14	−0.09	0.27
c	4-$MeOC_6H_4$	2.50	−0.20	2.28	−0.23	0.22
d	4-BrC_6H_4	~2.2	~0.1	~1.95	~0.1	~0.25
e	4-CNC_6H_4	1.67	0.63	1.44	0.61	0.23
f	4-$NO_2C_6H_4$	(0.75)		(0.70)[d]		
g	4-$MeSO_2C_6H_4$	1.81	0.49	1.51	0.54	0.30
h	2,4,6-$Me_3C_6H_2$	2.40	−0.10	2.19	−0.14	0.21
i	2,4,6-$Pr^i_3C_6H_2$	2.47	−0.17	2.26	−0.21	0.21
j	2,3,6-Me_3-4-$MeOC_6H$	2.59	−0.29	2.40	−0.35	0.19
k	2,2,5,7,8-Me_5-chroman-6-yl	2.64	−0.34	2.43	−0.38	0.21

[a] Cathode: vitreous carbon. Solvent: DMF. Supporting electrolyte: Bu_4NBF_4 0.1 mol dm^{-3}. [b] $\Delta E = E_p - E_H$, $\Delta E' = E'_p - E'_H$ where E_H and E'_H are the peak potentials of the unsubstituted compounds **1a** and **2a**, respectively, and E_p and E'_p are those of the substituted derivatives **b–k**. [c] $\Delta E'' = E'_p - E_p$. [d] No cleavage.

cathodic cleavage under the experimental conditions previously developed.[10,11,19] All the *tert*-butyl sulfonylcarbamates were electrolysed in acetonitrile (~0.005 mol dm^{-3} of substrate) containing Et_4NCl (0.1 mol dm^{-3}) as supporting electrolyte and Et_3NHCl (0.015 mol dm^{-3}) as proton donor. The reactions were carried out at a potential 50 mV more negative than that related to the first reduction peak of the corresponding voltammogram, as obtained from Table 3. All reactions were monitored by HPLC and interrupted when essentially all the starting material had been consumed. The yields of Boc-NHBzl as measured by

Table 4 Yields of Boc-NHBzl from small scale electrolyses at controlled potential of compounds $RSO_2N(Boc)Bzl$ **2**[a]

Compound 2	R	Yield by HPLC (%)
a	Ph	95
b	4-MeC_6H_4	96
c	4-$MeOC_6H_4$	92
d	4-BrC_6H_4	79
e	4-CNC_6H_4	40
f	4-$NO_2C_6H_4$	0
g	4-$MeSO_2C_6H_4$	67
h	2,4,6-$Me_3C_6H_2$	79
i	2,4,6-$Pr^i_3C_6H_2$	86
j	2,3,6-Me_3-4-$MeOC_6H$	81
k	2,2,5,7,8-Me_5-chroman-6-yl	67

[a] Cathode: vitreous carbon. Solvent. acetonitrile. Supporting electrolyte: Et_4NCl 0.1 mol dm^{-3}. Substrate concentration: 0.005 mol dm^{-3}. Proton donor: Et_3NHCl 0.015 mol dm^{-3}.

Table 5 Acidities of some NH-acids RSO_2NHCH_2Ph in dimethyl sulfoxide and aqueous solution at 25 °C

Compound	R	pK_a DMSO	pK_a H_2O[a]
1a	Ph	15.7	11.25[16]
1b	4-MeC_6H_4	16.1	11.55[16]
1c	4-$MeOC_6H_4$	16.4	11.53
—	4-FC_6H_4	—	11.05[16]
—	4-ClC_6H_4	—	10.75[16]
1d	4-BrC_6H_4	15.3	10.71
1e	4-CNC_6H_4	14.3	10.35
—	3-$NO_2C_6H_4$	—	9.84[16]
1f	4-$NO_2C_6H_4$	14.0	10.07
1g	4-$MeSO_2C_6H_4$	14.4	10.25
1h	2,4,6-$Me_3C_6H_2$	16.4	
1i	2,4,6-$Pr^i_3C_6H_2$	15.9	
1j	2,3,6-Me_3-4-$MeOC_6H$	16.2	
1k	2,2,5,7,8-Me_5-chroman-6-yl	16.4	

[a] The pK_a values in ref. 16 were determined at 20 °C.

HPLC analysis of the electrolyses products are presented in Table 4. In none of these electrolyses was concomitant base-induced cleavage of the Boc-group observed.

Determination of pK_a values for compounds 1

For a large number of arenesulfonamides, including **1a** and **1b**, pK_a values in water have previously been determined and correlated with respect to substituents present in the benzenesulfonyl moiety.[16] We have now extended this work to include additional compounds in an aqueous medium and furthermore determined the pK_a values of compounds **1a–k** in DMSO. Such determinations were recently performed for a series of compounds consisting of imidodicarbonates and a few sulfonylcarbamates and for which the pK_a data turned out to be most illuminating.[20] The results of these measurements, together with some relevant literature data,[16] are compiled in Table 5.

Discussion

Cyclic voltammetry data

The voltammograms of compounds **2a–c** and **h–k** showed only one irreversible cathodic peak. The 4-bromo derivative (compound **2d**) presented two such peaks, which overlapped to form a broad wave with a current maximum at approximately −2.2 V *versus* SCE. As previously reported by other authors,[21] for the 4-cyano derivatives (compound **2e**) two cathodic waves were also noticed, *i.e.* (i) an irreversible peak at −1.67 V *versus* SCE and (ii) a peak at a more negative potential with a corresponding anodic peak in the reverse sweep. The 4-nitro derivative **2f** displayed three cathodic peaks and none could be detected in the reverse sweep. Finally, the 4-methylsulfonyl derivative **2g** presented two cathodic peaks and no anodic signals in the reverse sweep.

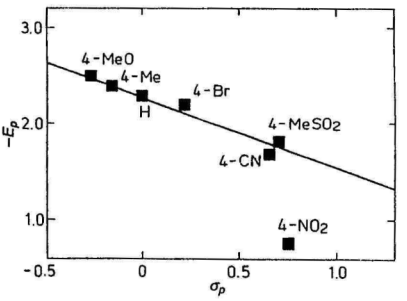


Fig. 2 Plot of peak potentials E_p *vs.* σ_p for *para*-substituted *N*-benzylbenzenesulfonamides **1**

A preliminary assignment of the first cathodic peak to cleavage of the protecting group allows the following conclusions to be drawn from the results in Table 3 with regard to the effect of the substituents on the peak potentials. Benzenesulfonyl has a cleavage potential slightly less negative than the corresponding 4-methyl substituted group (tosyl). This is in agreement with the mild electron-donating properties of alkyl groups. However, the effect of further substitution with alkyl groups is negligible. Substitution with a methoxy group shifts the reduction potential to more negative values due to its electron-releasing resonance effect; the effect of simultaneous alkyl and methoxy substitution is roughly additive in compounds **2j** and **k**. In agreement with previous observations, the methylsulfonyl[22] and the cyano[21,22] groups shift the reduction potential towards values less negative than those associated with reduction of the unsubstituted benzenesulfonyl group, whereas bromine substitution causes a small shift to less negative values of the reduction potential. Finally, the 4-nitrobenzenesulfonyl derivative **2f** displayed cathodic peaks at significantly less negative potentials, in agreement with those found previously for other nitro substituted protecting groups.[19,23,24] For this compound, however, at this potential no cleavage was observed.[25]

The electrochemical cleavage of the substituted benzenesulfonyl groups in compounds **1** could be rationalized by setting up a simple Hammett-type equation [eqn. (1)] in coordinates

$$-E_p = (2.30 \pm 0.08) - (0.78 \pm 0.08)\sigma_p \qquad (1)$$
$$n = 5 \quad s = 0.08 \quad r = 0.977$$

E_p *vs.* σ_p[26] (Fig. 2). *ortho*-Substituted derivatives were excluded from this correlation.

Compound **1f** deviates remarkably from this relationship (*ca.* 1 V) and this deviation cannot be eliminated by using π-electron acceptor (−R) substituent constants σ_p^- instead of σ_p.[26]

Electrolysis

Cathodic reduction of compounds **2a–c** gave high yields of Boc-NHBzl, whereas lower yields were obtained with the polysubstituted benzenesulfonyl derivatives. This might be due to steric hindrance to coplanarity as referred to by Zuman,[27] since in compounds **2h–k** an alkyl group is *ortho* to the sulfonyl function. In fact, this author postulated that such an electron

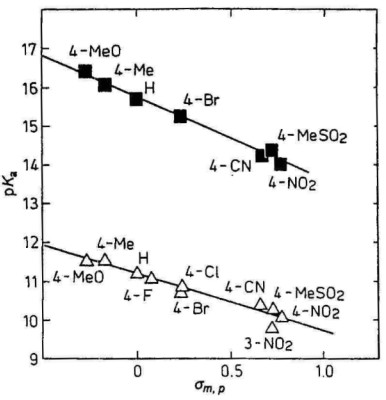


Fig. 3 Plot of pK_as *vs.* $\sigma_{m,p}$ for *para*-substituted *N*-benzylbenzenesulfonamides **1**; ■: in DMSO; △: in H_2O

interaction leading to conjugation effects is only fully possible when the interacting bonds are coplanar. Bulky substituents in the vicinity of these bonds may prevent them from achieving coplanarity and so limit their interaction. The author found that such an effect resulted in a more negative half-wave potential for *ortho* substituted derivatives as compared with the *meta* and *para* analogues.

During electrolysis of the bromo derivative, formation of the unsubstituted *tert*-butyl sulfonylcarbamate could be detected by HPLC analysis. The amount of this compound increased at the beginning of the electrolysis but then decreased steadily to almost zero. As the unsubstituted compound thus formed has a reduction potential similar to that of the bromo derivative, it underwent further electrolysis to Boc-NHBzl. This behaviour further suggests that the two overlapping peaks detected in the cyclic voltammograms of *N*-benzyl-4-bromobenzenesulfonamide and the respective *tert*-butyl sulfonylcarbamate corresponded to cleavage both of the protecting group and to that of the C–Br bond.

For the cyano derivative **2e** the yield of Boc-NHBzl was fairly low. At the end of the electrolysis the catholyte gave several HPLC peaks in addition to that corresponding to Boc-NHBzl. This might be due to electrolytic cleavage of the C–CN bond, which was noticed in certain aromatic nitriles with electron-deficient rings.[28–30] Other side reactions of cyano substituted groups such as the reduction of the cyano function[28] or formation of the dianion derived from 4-cyanobenzenesulfinic acid, which could react with the starting material,[21] have also been proposed to occur.

When electrolysis was carried out with the nitro derivative under comparable experimental conditions, no Boc-NHBzl could be detected. The same was the case in experiments using DMF instead of acetonitrile and when MeOH was substituted for Et_3NHCl as proton donor or when no proton donor was used and this is in agreement with previous work.[23,31]

The yield obtained in the electrolysis of the methylsulfonyl derivative was only moderate. However, since an HPLC peak corresponding to **2a** was not observed, this could not be related to cleavage of the methylsulfonyl group, which is known to occur in aqueous solution.[22]

pK_a Data for compounds 1

Compounds **1a–k** are moderately weak acids in both DMSO and aqueous media.[16] A closer comparison of their pK_a values with those of other compounds[20,32,33] recently investigated shows that the weaker ones approach Boc_2NH [pK_a (DMSO) = 16.9,[20] pK_a (H_2O) = 11.0[33]] in acidity, whereas at the other end of the scale the slightly more acidic ones are in the region between Z_2NH [pK_a (DMSO) = 14.2,[20] pK_a (H_2O) = 10.3[33]] and ZNHCOPh [pK_a (DMSO) = 13.7,[32] pK_a (H_2O) = 9.4[33]]. The literature data[16] further indicates that for fixed benzenesulfonyl groups in aqueous solution the *N*-benzyl compounds are slightly more acidic (by *ca.* 0.2–0.3 pK_a units) than the corresponding *N*-methyl derivatives.

The maximum variation in acidity in DMSO within the series of compounds studied is 2.4 pK_a units whereas in aqueous solution the range is even lower. As a rule, for these compounds, going from water to DMSO decreases the acidity by 4–5 pK_a units which is characteristic of NH-acids of similar structure.[33]

Inspection of Tables 3 and 5 shows that a rough qualitative correlation exists between the electrochemical cleavage potentials E_p and the pK_a values within this series of compounds. As a rule acid-labile compounds like **1c**, **1j** and **1k** are the least acidic and require the most negative potential for electrochemical cleavage. Therefore, the acidic deprotection and electrochemical cleavage might turn out to be complementary methods for this type of derivative.

As reflected by the Hammett plot, for the *para* and *meta* substituted derivatives, the acidity of compounds **1a–g** (or **j**) increases with increasing σ-constants of the substituent attached to the aromatic ring:

$$\text{DMSO} \quad pK_a = (15.8 \pm 0.1) - (2.1 \pm 0.1)\sigma_p \qquad n = 7 \quad s = 0.12 \quad r = 0.995$$

$$H_2O \quad pK_a = (11.2 \pm 0.1) - (1.48 \pm 0.12)\sigma_{m,p} \qquad n = 10 \quad s = 0.12 \quad r = 0.973$$

As shown by the corresponding *p*-values, the sensitivity towards substituent effects is *ca.* 1.5 times higher in DMSO than in water. Like E_p, pK_a also exhibits a low sensitivity to change on successive introduction of several alkyl groups into the benzenesulfonyl moiety.

In contrast to the cleavage potentials, the Hammett plots for the pK_a-values do not reveal any exceptional substituent effect of the 4-NO_2-group in **1f** (Fig. 3). The anomalous cathodic behaviour of **2f** is presumably due to reduction of the nitro function.

Conclusions

In benzylamides, the unsubstituted benzenesulfonyl group has a cleavage potential 0.1 V less negative than that exhibited by tosyl and the yields obtained in the cathodic cleavage of both are comparable. Hence, the former should be used instead of the latter in combination with other groups when a shift of this size may improve selective cleavage of the S–N bond. The 4-methoxybenzenesulfonyl group has a cleavage potential 0.1 V more negative than tosyl and good yields are also obtained in its reductive cleavage. It could offer a similar advantage over tosyl if it is to remain intact in an electrochemical experiment.

On the other hand, protecting groups of this type containing substituents with strong electron-withdrawing effects, which significantly shift the cathodic cleavage to less negative potentials, seem to be subject to side reactions that lower the yield of deprotected product. These difficulties could not be overcome by changes in experimental conditions. No cleavage could be achieved for compound **2f**.

Experimental

General procedures

All solvents used in the synthetic procedures were dried over molecular sieves (4 Å). Analytical grade Et_4NCl was used

without further purification. Et_3NHCl and Bu_4NBF_4 were prepared by procedures described elsewhere.[11] Acetonitrile was purified by distillation from CaH_2 under nitrogen. DMF was stored over $MgSO_4$ and then distilled from CaH_2 at reduced pressure. All HPLC experiments were run on a Shimadzu instrument, type 6A, connected to a Merck prepacked column, LiChrospher 100 RP-18, 5 μm, 250 × 4 mm with a mixture of acetonitrile and water as eluent. The peaks were measured with a Shimadzu integrator, type C-R6A Chromatopack.

Preparation of *N*-benzyl-4-bromobenzenesulfonamide 1d. Typical procedure

Freshly distilled benzylamine (4.33 g, 40.4 mmol) in dichloromethane (DCM, 100 cm^3) was chilled in ice with the exclusion of moisture and then triethylamine (4.40 g, 44 mmol) was added to it. The resulting solution was treated dropwise under stirring with 4-bromobenzenesulfonyl chloride (10.24 g, 40.0 mmol) also dissolved in DCM (40 cm^3) over 1 h at 0 °C and then left overnight at ambient temperature. After concentration to *ca.* 100 cm^3 the solution was partitioned between EtOAc (600 cm^3) and 1 mol dm^{-3} $KHSO_4$ (300 cm^3) and the organic extract was washed successively with 1 mol dm^{-3} $KHSO_4$, 1 mol dm^{-3} $NaHCO_3$ and sat. NaCl (3 × 150 cm^3 each). The extract was dried (Na_2SO_4) and then evaporated to give the title compound **1d** as a white solid (12.93 g, 99%), TLC gave one spot (toluene–MeCN, 2:1; Cl_2–dicarboxidine[34]); the product was recrystallized from EtOAc–heptane (1:4) (25 cm^3 g^{-1}; carbon) to give white fluffy crystals, mp 121–122 °C (lit.,[17] 117 °C). For additional data, see Table 1.

Preparation of *N*-benzyl-4-cyanobenzenesulfonamide 1e

Recrystallized **1d** (4.89 g, 15.0 mmol) was dissolved in *N*,*N*-dimethylformamide (DMF) (23 cm^3) and finely ground, carefully dried CuCN (2.00 g, 22.5 mmol) was added to it. The slurry was stirred at 150 °C under nitrogen for 18 h, giving a clear, yellowish solution which was treated with $FeCl_3$ (8 g, 49 mmol) in 2 mol dm^{-3} HCl (15 cm^3) at 70 °C giving a dark sludge. After being stirred at this temperature for 30 min, the resulting mixture was partitioned between EtOAc (600 cm^3) and 1 mol dm^{-3} HCl (300 cm^3). The green, aq. phase was discarded and the pale yellow organic extract was washed in turn with 1 mol dm^{-3} HCl and sat. NaCl (3 × 150 cm^3 each) and dried (Na_2SO_4). Evaporation provided a dirty yellow solid residue which was taken up in DCM (75 cm^3). The turbid solution was treated with carbon, filtered and taken to dryness to give the title compound **1e** (4.03 g, 99%), TLC as above gave one spot; an analytical specimen was obtained by recrystallisation from EtOAc–heptane (1:3) (40 cm^3 g^{-1}) as white, shiny flakes, mp 141–142 °C (see also Table 1).

4-Dimethylaminopyridine (DMAP) catalysed *tert*-butoxycarbonylation of sulfonamides. Preparation of *N*-benzyl-*N*-*tert*-butoxycarbonyl-4-cyanobenzenesulfonamide 2e. Typical procedure

A solution of **1e** (1.36 g, 5.00 mmol) and Boc_2O (1.20 g, 5.50 mmol) in MeCN (15 cm^3) was treated with DMAP (61 mg, 0.50 mmol) and left overnight under nitrogen. Most of the solvent was evaporated off and the oily residue was partitioned between diethyl ether (100 cm^3) and 0.2 mol dm^{-3} citric acid (50 cm^3). The pale yellow ethereal extract was washed successively with 0.2 mol dm^{-3} citric acid, 1 mol dm^{-3} $NaHCO_3$ and sat. aq. NaCl (3 × 25 cm^3) and dried ($MgSO_4$). After carbon treatment evaporation gave a colourless solid (1.80 g, 97%), TLC as above gave one spot; white, fluffy needles were obtained after recrystallization from diethyl ether–light petroleum (1:3) (45 cm^3 g^{-1}), mp 107–107.5 °C (see also Table 1).

Electrochemical apparatus and experimental procedures

The electrochemical apparatus and experimental procedures used for cyclic voltammetry were identical with those described elsewhere.[11] In all cases solutions of the substrate (approximately 0.005 mol dm^{-3}) in DMF containing Bu_4NBF_4 (0.1 mol dm^{-3}) as the supporting electrolyte were used. The sweep rate was 100 mV s^{-1}.

The electrochemical apparatus and experimental procedures used for small-scale controlled-potential electrolysis were also identical with those described elsewhere.[11] In all cases acetonitrile was used as solvent with Et_4NCl (0.1 mol dm^{-3}) as supporting electrolyte and Et_3NHCl (0.015 mol dm^{-3}) as a proton donor. The substrate concentration used was approximately 0.005 mol dm^{-3}.

Determination of pK_a values

The pK_a measurements of NH acids in dimethyl sulfoxide (DMSO) were performed as described earlier.[20,32,33] The experimental uncertainties range within ± 0.2–0.3 pK_a units. The pK_a measurements for compounds **1c–g** in aqueous solution were performed using a spectrophotometric technique.[35] The experimental uncertainty of these pK_a values is ± 0.02–0.05 pK_a units.

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BASICITY OF 3- AMINOPROPIONAMIDINE DERIVATIVES IN WATER AND DIMETHYL SULPHOXIDE. IMPLICATION FOR A PIVOTAL STEP IN THE SYNTHESIS OF DISTAMYCIN A ANALOGUES

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The acid–base properties of eight 3-aminopropionamidine derivatives $R_1R_2N(CH_2)_2C(=NH)NR_3R_4$ (1, $R_1 = R_2 = R_3 = R_4 = H$; 2, $R_1 = R_3 = R_4 = H$, $R_2 = Me$; 3, $R_1 = R_2 = R_4 = H$, $R_3 = Me$; 4, $R_1 = R_2 = H$, $R_3 = R_4 = Me$; 5, $R_1 = Tos$, $R_2 = R_3 = R_4 = H$; 6, $R_1 = Tos$, $R_2 = Me$ $R_3 = R_4 = H$; 7, $R_1 = Tos$, $R_2 = R_4 = H$, $R_3 = Me$; 8, $R_1 = Tos$, $R_2 = H$, $R_3 = R_4 = Me$; Tos = 4-toluenesulphonyl) related to the antiviral natural product distamycin A were investigated in water and dimethyl sulphoxide (DMSO). The measured pK_a values for the ammonium function in 1–4 in water ranged between 7·48 and 7·73, whereas the corresponding values in DMSO were 9·4 ± 0·3. The amidinium moiety of these compounds displayed pK_a values in the range 11·4–12·0 and 13·4–13·6 in water and DMSO, respectively. The tosylamide group in compounds 5–8 was deprotonated in the expected pH region and exhibited pK_a values between 9·49 and 10·02 in water, but was considerably less acidic in DMSO ($14·5 \leq pK_a \leq 15·7$). The behaviour of the amidinium cation of 5–8 in water and DMSO resembled that of 1–4. The measured pK_a values are discussed and the solvent-induced pK_a shifts are explained in terms of solvent and substituent effects. The observed pK_a differences between the ammonium and the amidinium functions in 1–4 render these compounds suitable intermediates in an alternative synthesis of distamycin A.

INTRODUCTION

Distamycin A (DA) (Figure 1) is a basic polyamide with a wide range of antibiotic properties.[1] The chemistry of this naturally occurring compound has received considerable interest since its discovery three decades ago. As a consequence, several synthetic routes to the parent compound and to a huge number of analogues have been devised. Some years ago, an alternative synthetic strategy to DA in which the preformed unprotected aliphatic amidine side-chain was attached to a trimeric pyrrolecarboxylic acid precursor as the final step was designed.[2] The yield in this coupling ranged between 40 and 80%, but was later increased to 80–90% by careful monitoring of the reaction.[3,4] In practice, this coupling was achieved by treatment of the corresponding succinimidyl ester with a considerable excess of 3-aminopropionamidine dihydrobromide in aqueous dioxane under essentially neutral conditions (pH ≈ 6–7).

In order to simplify the procedure and to optimize the reaction conditions further, we explored miscellaneous alternative condensation agents, such as dicyclohexylcarbodiimide (DCC) and carbonyldiimidazole in this respect. Although various reaction conditions were tried, the crude reaction product always contained side products and only a modest quantity of DA could be isolated after a laborious workup. We have recently found that the yield of the desired product improved significantly when 2-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU) was used as a dehydrating agent in an aprotic polar solvent under anhydrous conditions.[5] This direct approach also exploits the fact that the amidine function generally is significantly more basic than the amino group, thus allowing selective acylation of the amine in the presence of an unprotected amidine moiety. However, it is well known that acylation of the amidine nitrogens, and also hydrolysis of the amidine function, might occur under the influence of strong alkali.[6,7] With the aim of

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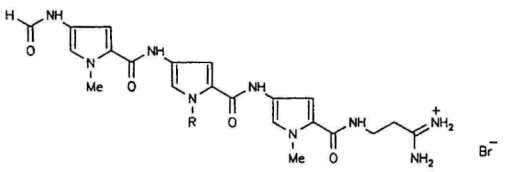

Figure 1. Distamycin A (hydrobromide), R = Me; compound **9** (hydrobromide), R = H (see Table 1)

elucidating this crucial step in the synthesis of DA and to gain further insight into the properties of these versatile precursors, we have now determined the pK_a values in water and DMSO of a small series of relevant 3-aminopropionamidine derivatives.

DA exerts its principal action by binding preferentially to AT-rich regions of the minor groove in helical DNA.[8,9] It is reasonable to assume that several properties of DA, such as its acid–base behaviour and its ability to interact via hydrogen bonds, contribute to its binding efficiency to DNA. The protolysis of DA is primarily governed by its amidine functions. Therefore, the goal of this study was to measure the acid–base properties (pK_a) of DA and the related 3-aminopropionamidine derivatives in order to gain further insight into the mechanism of action of DA.

RESULTS AND DISCUSSION

The pK_a values of a wide range of substituted amidine analogues have been amply reviewed recently.[10] Continued interest in this class of substances is further reflected in miscellaneous contemporary reports dealing with related aspects of their acid–base chemistry.[11,12]

The results of our pK_a measurements (in aqueous solution and in DMSO) of selected salts of 3-aminopropionamidine derivatives $R_1R_2N(CH_2)_2C(=NH)NR_3R_4$ related to DA are compiled in Table 1. All of the compounds **1–8** have three non-equivalent nitrogen atoms which may serve as sites for protonation or deprotonation. The R_1R_2N group behaves as a normal amine function and is attached to a $(CH_2)_2C$ fragment. Depending on the pH, it can act either as a basicity centre (for protonation on N) or as an acidity centre (for deprotonation of the R_1R_2N moiety of R_1 and/or $R_2 = H$). The imino (=NH) group and the remaining NR_3R_4 function can also display this dualistic behaviour, depending on the nature of the substituents and the pH of the surrounding medium. For the uncharged amidine molecule, the strong basicity is primarily governed by protonation of the =NH site to yield the very stable amidinium cation.[10] With few exceptions, the acidity of the =NH group is low (the pK_a in DMSO is usually in the range 16–31 pK_a units[13–15]).

The NR_3R_4 group behaves as an amine function, the basicity of which is generally lower than that of the =NH group.[10,15] Unless R_1–R_4 are not strongly electronegative substituents (e.g. CF_3SO_2, NO_2, CN and

Table 1. Acidity of $R_1R_2N(CH_2)_2C(=NH)NR_3R_4 \cdot a$HX in water and DMSO

No.	R_1	R_2	R_3	R_4	*a*HX	$R_1R_2N^c$	$C(=NH)NR_3R_4^c$	$R_1R_2N^c$	$C(=NH)NR_3R_4^c$
1	H	H	H	H	2HBr	7·50	11·6	9·7	13·6
2	H	ME	H	H	2HBr	7·73	11·4	9·2	13·6
3	H	H	Me	H	2HBr	7·53	11·9	9·4	13·4
4	H	H	Me	Me	2HBr	7·48	12·0	9·7	13·4
5	Tos[d]	H	H	H	HCl	9·49[e]	10·8	15·7[e]	13·3
6	Tos	Me	H	H	HCl	—	11·5	—	13·3
7	Tos	H	Me	H	HCl	10·02[e]	11·9	14·5[e]	13·3
8	Tos	H	Me	Me	HCl	9·84[e]	11·4	14·7[e]	13·0
9	—[g]	H	H	H	HBr	—[f]	11·2	—[f]	12·8

[a] ±0·03 pK_a units for pK_{a_1}, ±0·2 pK_a units for pK_{a_2}.
[b] ±0·2 pK_a units.
[c] Protonation or deprotonation centre.
[d] 4-Toluenesulphonyl.
[e] Refers to neutral tosylamide.
[f] Not determined.
[g] Tripyrrolecarboxamide residue lacking a methyl substituent on the second pyrrole fragment (see Figure 1).

$PhSO_2$), the NH acidity of the R_1R_2N and NR_3R_4 groups is extremely low.[13–17] This is evidently not the case for **5–8**, which contain the TosNH fragment. By analogy with $PhSO_2NH_2$[$pK_a(H_2O) = 10{\cdot}3$,[15] pK_a (DMSO) = 16·0[13,16]] or $PhSO_2NHMe$ [pK_a (H_2O) = 11·6[15]], one might expect the acidity of **5–8** to be at least comparable to, or even higher than, those of these two sulphonamides.

In most of the potentiometric titration experiments with the salts given in Table 1, in DMSO two definite equivalence points were monitored corresponding to consecutive deprotonations of those compounds. In water, **1–4** gave one well defined equivalence point. For **5**, **7** and **8** the equivalence point was very weak, almost non-existent. Compound **6** did not give an equivalence point at all. The reason for the absence of the second (or even the first) equivalence point on the titration curves is definitely the high values of the corresponding pK_a.

The DA analogue **9** (see Figure 1) has four carboxamide moieties, one pyrrole NH fragment and one protonated amidine group. The potentiometric titration curve for this compound also shows only one stoichiometric point in DMSO (none in water), which, by analogy with **6**, refers to protonation of the amidine function.

Assignment of the protonation centres for **1–4** seems to be straightforward. In these compounds, the $R_1R_2N(CH_2)_2$ fragment can be considered to be an amine function attached to the electron-withdrawing $C(=NH_2^+)NR_3R_4$ group. The pK_a (H_2O) for $EtNH_3^+$ is 10·7,[15] whereas in DMSO the corresponding value is in the range 10·6 – 10·9.[13,18] The replacement of an H in the methyl group of $EtNH_3^+$ by the positively charged $C(=NH_2^+)NR_3R_4$ group should theoretically reduce the basicity of the R_1R_2N fragment, as, is borne out in practice [$7{\cdot}5 \leq pK_a(H_2O) \leq 7{\cdot}8$; $9{\cdot}2 \leq pK_a$ (DMSO) $\leq 9{\cdot}7$] (see Table 1).

The second pK_a value for **1–4** evidently corresponds to the deprotonation of the amidinium fragment, thus closely resembling the pK_a pattern for simple amidines [pK_a (H_2O) is usually in the range 11–12[15] whereas pK_a (DMSO) is normally around 13–15[13,18–21]].

Compound **6**, owing to the absence of an NH bond in the R_1R_2N fragment, cannot be deprotonated at that site. In agreement with the literature[10,15,18] and the above discussion, the measured pK_a value corresponds to the deprotonation of the amidinium fragment.

The behaviour of the three remaining Tos-substituted 3-aminopropionamidines, **5**, **7** and **8**, is more complicated. These compounds could be considered as analogues of simple sulphonamides [pK_a (H_2O) for 4-$MePhSO_2NHMe$ is 11·7;[15] for further examples, see Refs 10–15] which carry the neutral or charged amidine function $C(=NH)NR_3R_4$. The latter should make these compounds (i.e. **5**, **7** and **8**) more acidic than the above-mentioned reference compound. Table 1 shows that this is indeed the case in aqueous solution, although this effect never exceeds 1 pK_a unit (see **7**). At the same time, the TosNH and TosNMe fragments decrease moderately the basicity of the amidine function in **5–8**.

However, the behaviour of compounds **5**, **7** and **8** in DMSO seems to be different from that in aqueous solution. The lower pK_a values (13·0–13·3) for these compounds seem to be associated with deprotonation of the amidine function (cf. also **6**), which is slightly affected by the remote neutral TosNH (or TosNMe) group. Consequently, the higher pK_a values for compounds **5**, **7** and **8** seem to reflect the deprotonation of the NH fragment of the sulphonamide function. Obviously, the acidifying effect [compared with the reference compound $PhSO_2NH_2$ (pK_a in DMSO = 16·0)[13,16]] of the deprotonated neutral amidine function [$C(\geq NH)NR_3R_4$] is not very significant. The solvent-induced reversal of the order of deprotonation of the TosNH group and the amidine function in **5**, **7** and **8** is evidently due to solvent effects of different intensity in this process when water is replaced by DMSO. As judged from Table 1, the solvent effects upon going from H_2O to DMSO on the R_1R_2N function in **1–4** or on the amidine function of all compounds studied amounts to as much as 2 pK_a units. At the same time, the solvent effects for **5**, **7** and **8**, associated with the acidic dissociation of the TosNH function, range from 4·9 (**8**) to 6·2 (**5**) pK_a units. These findings are further supported by literature data,[18] which show that the transfer of cationic acids from water to DMSO is relatively insensitive to solvent effects, whereas the acidity of neutral NH acids is much more solvent dependent.[17,22,23]

The acidifying effect of an adjacent CO group in **9** is, as expected, considerably less pronounced than that of the Tos function.[13–16] Under aqueous conditions, acidic dissociation of the neutral carboxamide moiety (CONH) does not occur, and the measured pK_a value in Table 1 in both solvents refers to deprotonation of the amidinium function, which, in turn, should exercise a moderate acidifying effect on the remote aliphatic 2-pyrrolecarboxamide fragment. Therefore, one can conclude that the 3-aminopropionamidine derivatives and **9** behave similarly.

CONCLUSION

The observed differences between the pK_a values of the amidinium and ammonium groups in **1–4** are sufficiently large to permit selective deprotonation of the latter, which, in turn, facilitates its acylation by a suitable DA carboxylic acid precursor. Such coupling reactions require meticulous monitoring of the pH in order to avoid excess base. In an aqueous environment it is important to suppress undesired hydrolysis of the amidine group, which often occurs under alkaline conditions. Our recent experience prompted us to focus on the use of anhydrous conditions to achieve this

crucial step and, owing mainly to its favorable solubility properties, DMF is the preferred solvent in this context. We measured the pK_a values in DMSO to facilitate meaningful comparison with data available previously.

The present results therefore provide a firm experimental basis for application of the 3-aminopropionamidine derivatives **1–4** for the final direct attachment of the unprotected aliphatic side-chain to the trimeric pyrrole-carboxylic acid. By choosing a suitable pH in aqueous solutions or by employing otherwise carefully controlled reaction conditions in anhydrous media in this crucial last step in our synthetic scheme, it is possible to acylate selectively the amino group in the presence of the unblocked protonated amidinium function in satisfactory yield with a minimum of side products.

EXPERIMENTAL

Compounds **1–8** were prepared by standard methods as described previously.[3] The DA analogue **9** originated from the same work.[3]

DMSO was purified as described earlier.[16–18]

The procedures for the determination of the pK_a values in water and DMSO were similar to those described earlier.[16–19,24] Potentiometric titration at 298 K with a glass electrode was used in both solvents; 0·1 M KOH was used as a titrant in water and a 0·01 M molar solution of Bu_4NOH in propan-2-ol–benzene (1:4, v/v) in DMSO. In water the glass electrode was calibrated using standard buffers, in DMSO benzoic acid served as reference compound.

The calculation method used was different from that used previously. Most of the acids studied in this work are diprotic and the two pK_a values are close to each other. Hence, the titration of the second acidic group begins before that of the first group has finished. This means that three different forms of the compound are present in the solution simultaneously: AH_2^{2+}, AH^+ and A in the case of **1–4** and AH_2^+, AH and A^- in the case of **5**, **7** and **8**. Therefore, a more complex data treatment was necessary. The calculation method used takes into account the presence of all three forms of a compound in solution and is described in Ref. 25.

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VI

SPECTROPHOTOMETRIC ACIDITY SCALE OF STRONG NEUTRAL BRØNSTED ACIDS IN ACETONITRILE

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Abstract

A continuous self-consistent quantitative UV-vis spectrophotometric pK_a scale of strong acids in acetonitrile has been created. The 36 compounds studied include phenols, phenylmalononitriles, sulfonimides, sulfonic acids and sulfonimides modified with Yagupolskii's superacceptor substituents. The scale spans for about 13 pK_a units and consists of 74 independent equilibrium constant measurements, each describing relative acidity of two acids. The method of measurements eliminates the need for the direct determination of the acidity of the medium. The most acidic compounds studied have pK_a values around 4 in acetonitrile and can be regarded as true superacids. The scale is anchored to the pK_a value 11.0 of picric acid. The status of 2,4,6–$(SO_2CF_3)_3C_6H_2OH$ as the most acidic phenol presently known (pK_a=4.9) is confirmed. It is shown that the replacement of an =O fragment with =N–SO_2CF_3 in a –SO_2- group in aromatic sulfonimides results in the acidity increase of more than 10^5 times. The most acidic compound in the scale is 4–$ClC_6H_4SO(=NSO_2CF_3)NHSO_2C_6H_4$–4–$NO_2$ (pK_a=3.75). The present results together with those from the other authors furnish a unified scale of acidity in acetonitrile ranging from pK_a=4 to 27 and set solid ground for pK_a measurements of strong acids in acetonitrile.

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Introduction

Strong acids and their derivatives are receiving increasing attention from both practical (reagents in organic synthesis,[1, 2] catalysts in industry[3]) and theoretical[4, 5] points of view. Therefore substantial theoretical and experimental effort has been devoted to development of strongly acidic media and molecules with high intrinsic acidity.[1] Several families of interesting acids have been created: cyanocarbon acids,[6, 7] Kuhn's acidic hydrocarbons,[8] acids with Yagupolskii's substituents,[9] superacidic metal hydrides,[10] etc.

Quantitative measurements of acidity are a vital part of studies involving superacids. On the contrary to the success in creating superacids, significant experimental difficulties have been met here and up to date little consistent acidity data is available for strong acids. In some cases the situation is almost ridiculous. For the pK_a of perchloric acid in aqueous solution, for example, the values found in the literature range from –1.6 to –14.[4] The uncertainty exceeds 12 orders of magnitude!

The acidity of an acid can be measured in different ways. Gas-phase measurements yield intrinsic acidities, free of any medium effects. A truly absolute scale of acidity in the gas phase has been established, ranging for almost 90 orders of magnitude.[4, 11] With very strong acids the gas phase measurements have often failed however, because the latter are usually not volatile enough and tend to undergo fragmentation in the course of the experiments.[4]

Significant effort has been devoted to acidity studies in aqueous solutions of strong acids (sulfuric acid, perchloric acid, etc.). These measurements are complicated,[12] however, because of the leveling of acidities

The amount of acidity measurements of strong neutral Brønsted acids performed in nonaqueous solvents is smaller than in aqueous medium.[6, 13–17] This is true even for dimethyl sulfoxide (DMSO) solution, where due to efforts of Bordwell and others more than 2000 pK_a values for different classes of Brønsted acids have been determined.[16, 17, 18] DMSO is a rather basic leveling solvent and thus not very suitable for studies of strong acids (however, see ref 15). Several acidity orders of strong acids have also been reported[4, 19] but quantitative acidity data for strong acids continues to be scarce. The main problems arising in most nonaqueous solvents are the various association processes between charged (and also neutral) species in these solvents (see below) and difficulties in reliable and reproducible determination of medium acidity in these media. Hence the pK_a-s determined in different laboratories often differ more than the experimental errors stated.

In the view of this situation a pressing need exists for a self-consistent scale of acidity of strong acids in solution. We report here a spectrophotometric pK_a scale of strong acids in acetonitrile (AN).

AN has many properties that make it suitable for our work. It has low basicity and very low ability to solvate anions.[20] The low basicity gives AN an

advantage over the other very popular solvent for acid-base studies — DMSO — which is considerably more basic (stronger acceptor of hydrogen bond). AN has high dielectric constant (D=36.0[20]) and hence favors the dissociation of ion pairs into free ions. The autoprotolysis constant of AN is very low: pK_{auto}=33.[21, 22] All these properties put together make it a good differentiating solvent for strong acids. Additional advantages of AN are its transparency down to 190 nm and relative ease of purification.

Starting from the classical works of groups of Kolthoff and Coetzee, considerable amount of acidity data for various compounds in acetonitrile have been accumulated. Analysis of literature shows that a rather continuous and self-consistent acidity scale in the pK_a range of 14–27 exists in acetonitrile.[18, 20, 23–25] Measurements in the lower pK_a range have been made too,[6, 13, 14] but here the things are far from satisfactory both in terms of the amount of data available and its self-consistency. The present work was undertaken to improve the situation by building a unified self-consistent scale of acidity in AN in the range of 4–16 pK_a units which would be a logical extension of the pK_a scale for the relatively weak acids into the domain of strong and very strong neutral Brønsted acids.

Acidity of an acid HA in solvent S refers to the equilibrium:

$$HA + S \rightleftarrows A^- + SH^+ \qquad (1)$$

and is expressed as the equilibrium constant K_a or its negative logarithm pK_a:

$$K_a = \frac{a(SH^+) \cdot a(A^-)}{a(HA)} \qquad (2)$$

where a are the activities of the corresponding species. The acid-base equilibria in weakly solvating solvents like acetonitrile are more complex than in water. In addition to the equilibrium 1 there are other equilibria present in the system.[20] In AN the poorly solvated anions eagerly form hydrogen-bonded complexes with hydrogen-bond donors present in the solution. When the donor is the conjugate acid of the anion, the homoconjugation process takes place:

$$A^- + HA \overset{K_{AHA}}{\rightleftarrows} A^- \cdots HA \qquad (3)$$

K_{AHA} (the homoconjugation constant) is the constant of formation of the homoconjugate complex $A^- \cdots HA$:

$$K_{AHA} = \frac{a(A^- \cdots HA)}{a(A^-) \cdot a(HA)} \qquad (4)$$

If the donor is some other acid HX then the heteroconjugation process is present:

$$A^- + HX \overset{K_{AHX}}{\rightleftarrows} A^- \cdots HX \qquad (5)$$

These side-reactions have to be suppressed or taken into account if the accurate acidity data are to be obtained.

Because of the problems with measuring the acidity of the medium — $a(H^+)$ — in nonaqueous solutions, we use a method that eliminates the need for its determination. Our method of acidity measurement gives relative acidities of the acids HA_1 and HA_2 according to the following equilibrium:

$$HA_2 + A_1^- \rightleftarrows A_2^- + HA_1 \tag{6}$$

The pK of this equilibrium is the relative acidity (ΔpK_a) of the acids HA_1 and HA_2:

$$\Delta pK_a = pK_a(HA_2) - pK_a(HA_1) = \log \frac{a(A_1^-) \cdot a(HA_2)}{a(A_2^-) \cdot a(HA_1)} \tag{7}$$

The method consists in UV-vis spectrophotometric titration of a solution, where both of the acids are present, with a transparent acid or base.

Experimental Section

Method of pK_a determination. Relative acidities were measured using a UV-vis spectrophotometric titration technique that was similar to one applied previously to acidity measurements in heptane.[26] An acetonitrile solution containing two acids, HA_1 and HA_2 (or the salts of the acids in some cases, see below), was prepared. The acidity of the solution was varied adding small amounts of acidic or basic titrant. A spectrum was recorded after each addition of titrant. This way 10 to 30 spectra with different acidity of the solution were obtained including those where both acids were in fully anionic or neutral form. Both of the acids were also titrated separately to obtain the spectra of the neutral and the ionized form of both acids. To test the reversibility of the protonation/deprotonation process, after finishing of addition of one titrant, several portions of the other one were added. From each titration experiment the ΔpK_a was determined as the mean of 5 to 20 values.

The calculation methods for ΔpK_a were essentially the same as described previously.[26] Two additional features were included, however.

1. With some acids it was necessary to take the homoconjugation process into account. Two cases have to be treated separately:

a. One of the acids (HA) forms the homoconjugation complex and the other does not. In this case the analytical concentration C of the acid HA can be expressed as follows:

$$C = [A^-] + [HA] + 2[A^- \cdots HA] \tag{8}$$

We assume that the molar absorption coefficient ε of the homoconjugation complex HA···A$^-$ between acid HA and its anion A$^-$ can be expressed as a sum:

$$\varepsilon(A^-\cdots HA)=\varepsilon(HA)+\varepsilon(A^-) \qquad (9)$$

From the equations 8 and 9 it follows that for the homoconjugating acid the indicator ratio I (see ref. 26) as it is found from the spectrum of the mixture is not equal to the conventional [A$^-$]/[HA] but:

$$I = ([A^-] + [A^-\cdots HA]) / ([HA] + [A^-\cdots HA]) \qquad (10)$$

Using equations 4, 8 and 10, and assuming that the activities in eq 4 can be replaced with concentrations, the relative concentration of the complex A$^-$···HA can be found:

$$\frac{[A^-\cdots HA]}{C} = \frac{1+\frac{1}{C\cdot K_{AHA}}}{2} - \sqrt{\left(\frac{1+\frac{1}{C\cdot K_{AHA}}}{2}\right)^2 - \alpha\cdot(1-\alpha)} \qquad (11)$$

where α=1/(1+1/I). Now [A$^-$]/[HA] can be calculated:

$$\frac{[A^-]}{[HA]} = \frac{\alpha - \frac{[A^-\cdots HA]}{C}}{1-\alpha-\frac{[A^-\cdots HA]}{C}} \qquad (12)$$

With known [A$^-$]/[HA] the calculation of ΔpK_a is straightforward (see ref 26).

b. Both of the acids form homoconjugation complexes. In this case we assume that they also form heteroconjugation complexes. In this work we take homoconjugation into account only when dealing with sulfonic acids (see results section). We assume that for all the sulfonic acids the homoconjugation constants are equal and that all the heteroconjugation constants are equal to the homoconjugation constants. In this case it can be shown that the four species HA_1, HA_2, A_1^- and A_2^- are consumed proportionally to their concentrations for the formation of the homo- and heteroconjugation complexes and the relative decrease of their concentrations will cancel out, so that the formation of the complexes can be ignored when calculating ΔpK_a.

2. Two acids in the present work are cationic acids. When calculating the relative acidity of a neutral and a cationic acid according to the eq 13

$$HA + B \rightleftarrows A^- + BH^+ \qquad (13)$$

then the assumption that the ratios of the activity coefficients are equal (see ref 26) is not valid any more and the ΔpK_a value is:

$$\Delta pK_a = \log\frac{[B]\cdot[HA]}{[A^-]\cdot[BH^+]} - 2\cdot\log f \qquad (14)$$

where the activity coefficients $f = f(A^-) = f(BH^+)$ and $f(B) = f(HA) = 1$ (these approximations are valid since very dilute solutions are used). The value of log$f$ was calculated using the Debye-Hückel equation[20]:

$$\log f = -\frac{1.64Z^2\sqrt{J}}{1+0.48a\sqrt{J}} \tag{15}$$

where J is the ionic strength of the solution, Z is the charge of the ion, a is the size parameter of the ion that was taken 6 Å. The log$f$ is not very sensitive to this parameter.

Chemicals. The following compounds were synthesized according to a procedure from the literature[27]: **9** (mp 173–174; ^{13}C NMR: 145.73, 138.71, 130.50, 128.42, 21.53), **11** (mp 158–159; ^{13}C NMR: 142.02, 134.30, 129.97, 128.27), **12** (mp 162.5–163.3; calcd for $C_{13}H_{12}ClNO_4S_2$ C 45.15, H 3.50, N 4.05; found C 45.41, H 3.53, N 4.43; ^{13}C NMR: 145.79, 140.55, 140.44, 138.64, 130.52, 130.14, 130.02, 128.40, 21.53), **14** (mp 208.8–210.4; ^{13}C NMR: 141.48, 140.17, 130.03, 129.95), **16** (mp 202.4–203.8; calcd for $C_{13}H_{12}N_2O_6S_2$ C 43.81, H 3.39, N 7.86; found C 43.58, H 3.47, N 8.01; ^{13}C NMR: 151.33, 148.33, 142.31, 140.61, 128.43, 127.72, 126.22, 123.28, 20.71), **17** (mp 151.3–151.8; calcd for $C_{13}H_{11}ClN_2O_6S_2$ C 39.95, H 2.84, N 7.17; found C 40.01, H 2.77, N 7.47; ^{13}C NMR: 148.65, 145.16, 143.20, 139.41, 133.65, 132.60, 131.39, 130.33, 128.24, 125.32, 21.49) **18**[28] (mp 222.7–223.4; ^{13}C NMR: 151.09, 149.73, 142.59, 139.54, 129.81, 129.53, 124.77), **20**[29] (mp 239–242 dec.; ^{13}C NMR: 150.96, 150.68, 129.41, 124.70). The starting materials were sulfonyl chlorides from Aldrich. The compounds were purified by recrystallization from mixtures of ethyl alcohol and concentrated hydrochloric acid.

The sulfonic acids **19**, **23**, **24** and **25** were synthesized[30] from the corresponding sulfonyl chlorides (from Aldrich). The sulfonic acid **21** was obtained from REAKHIM. Sulfonic acids are inconvenient to handle and were used as salts. The acid **19** was converted to tetramethylammonium salt according to ref 31: **19a** (mp 255.0–255.9 dec; calcd for $C_{11}H_{19}NO_3S$ C 53.85, H 7.81, N 5.71; found C 54.18, H 7.64, N 5.57; ^{13}C NMR: 144.03, 141.63, 129.85, 126.93, 56.20, 21.30). The salt was purified by recrystallization from aqueous acetone. The acids **21**, **23**, **24** and **25** were converted into the corresponding triethylammonium salts according to ref 31: **21a** (mp 149.6–150.3; calcd for $C_{16}H_{23}NO_3S$ C 62.11, H 7.49, N 4.53; found C 62.08, H 7.72, N 4.41; ^{13}C NMR: 142.27, 135.52, 132.27, 130.30, 129.27, 127.74, 127.53, 127.11, 126.52, 125.32, 47.96, 9.12), **23a** (mp 93.0–95.3; calcd for $C_{12}H_{20}ClNO_3S$ C 49.06, H 6.86, N 4.77; found C 49.46, H 6.93, N 4.71; ^{13}C NMR: 145.45, 137.07, 129.41, 128.65, 48.2 (obscured by solvent), 9.25), **24a** (mp 78.2–78.9; calcd for $C_{12}H_{20}N_2O_5S$ C 47.36, H 6.62, N 9.20; found C 47.61, H 6.89, N 9.03; ^{13}C NMR: 149.37, 148.70, 132.99, 131.01, 125.66, 121.89, 48.2 (obscured by solvent), 9.32) and **25a** (mp 120.9–122.5; calcd for $C_{12}H_{20}N_2O_5S$ C 47.36, H 6.62, N 9.20; found C

47.10, H 6.90, N 9.46; ^{13}C NMR: 152.65, 150.07, 128.33, 124.59, 48.2 (obscured by solvent), 9.30). The salts were purified by recrystallization from acetone.

The following compounds were of commercial origin, some of them were purified prior to use: **1** (REAKHIM, sublimed *in vacuo*, mp 113.2–113.7), **4** (Aldrich, 99+%), **13** (REAKHIM, recrystallized from EtOH, mp 121.2–122.7), TfOH (Aldrich, 99+%), tetramethylammonium hydroxide (Aldrich, 25% solution in MeOH), Et_3N (REAKHIM, distilled under atmospheric pressure, stored under argon in refrigerator, small amounts for measurements distilled second time as needed), $HClO_4$ (REAKHIM, "special purity"), acetic acid (REAKHIM, "chemically pure").

The synthesis and purification of the following compounds has been described previously: **2**,[32] **3**,[33] **5**,[34] **6**,[35] **7**,[36] **8**,[36] **10**,[33] **15**,[35] **22**,[37] **26**,[9] **27**,[9] **28**,[9] **29**,[39] **30**,[9] **31**,[38] **32**,[9] **33**,[9] **34**,[39] **36**.[9] A sample of **35**[6] was donated by the late Prof. R. W. Taft.

^{13}C NMR. The spectra were run on a Bruker AC-200 instrument. The solvent was CD_3OD, except for **16**. DMSO-d_6 was used with this compound. Tetramethylsilane was used as the internal standard.

Solvent. Acetonitrile suitable for our work must be dry and must not contain impurities that absorb UV radiation. Impurities with UV spectrum that changes with changing acidity of the medium are especially dangerous. Merck "Lichrosolv" AN was used. It was distilled from P_2O_5 through a 1.2m 2cm id column packed with PTFE chips prior to use to reduce its water content and to further purify it. Alternatively REAKHIM "pure" AN was distilled through the same column from $KMnO_4$ and then from P_2O_5. Preference was given to the acetonitrile from Merck. The solvent was stored in dark bottles in a desiccator over P_2O_5.

Experimental Setup. The setup was very similar to that described previously.[26] Only significant differences are given here.

Solution of TfOH in AN was used as the acidic titrant in most cases. In a few experiments solution of $HClO_4$ was used. This solution was prepared from a 25% solution of $HClO_4$ in acetic acid. Solution of triethylamine in acetonitrile was used as the basic titrant. The standard syringe techniques could not be used due to the strongly acidic media involved. Instead the vials, solvent bottle and the spectrophotometer cell (all capped with rubber septa) were interconnected with thin PTFE tubing, through which the solutions were siphoned by means of aspiration with a syringe.

The concentrations of the acids were in the following ranges: **2**, **3**, **5**, **6**, **7**, **8**, **15**, **16**, **18**, **20**, **24**, **25**, **29**, **31**, **32**, **34**, **35**, **36**: 1 .. $7 \cdot 10^{-5}$ M; **1**, **10**, **13**: 1 .. $3 \cdot 10^{-5}$ M; **4**, **9**, **11**, **12**, **14**, **17**, **22**, **26**, **27**, **28**, **30**, **33**: $8 \cdot 10^{-5}$ .. $5 \cdot 10^{-4}$ M; **19**, **23**: 1 .. $1.5 \cdot 10^{-3}$ M. The concentrations of the titrants were chosen for each titration

experiment according to the concentrations of the acids and ranged from $5 \cdot 10^{-3}$ to $5 \cdot 10^{-2}$ M. All solutions were made fresh daily.

The water content of the solution in the cell was determined after the measurement using Karl Fisher titration. This approach ensures that the amount of water in the solution during titration is less or equal to that determined. The water content of the solution was mostly between 1mM and 2mM and never higher than 3.5mM.

Spectrophotometry. Perkin-Elmer Lambda 2S UV-vis spectrophotometer equipped with cell holders thermostated to 25°C was used for all measurements. The spectrophotometer was controlled from a PC and the spectra were stored in digital form. Fused silica cells with optical pathlength 1 cm were used. The reference cell contained pure AN.

Results

The results of the measurements are presented in Table 1. Each arrow represents the ΔpK_a from one titration experiment. To make the results more reliable and to be able to estimate the consistency of the results, we carried out multiple overlapping measurements. The entire acidity range covered involves at least two independent pathways of measurements and the relative acidity of any two acids can be obtained by combining at least two independent sets of measurements.

In order to assign absolute pK_a values to the acids of Table 1 the scale has to be anchored to a reference compound with pK_a reliably established. This compound should be a "well-behaved" compound, that is it should not undergo homo- or heteroconjugation reactions to a marked extent and it should have favorable UV-vis spectral characteristics. For several of the acids belonging to the scale, pK_a value in AN has been reported in the literature. These acids are presented in Table 2. Analysis of the data in Table 2 shows that picric acid is the compound of choice as it is a well-behaved compound and its pK_a in acetonitrile has been determined with great care by Kolthoff *et al*[42] using three different experimental methods and has been found to be 11.0 ± 0.1. Using **13** as the anchoring point has the only disadvantage that it stands far away from the stronger members of the scale. A reliable absolute pK_a value for a "well-behaved" strong acid would be very desirable. The other acids from Table 2 are not as suitable as references. **29** and **34** are cationic acids (see below), **19** is not a "well-behaved" compound, **1** and **35** stand in far ends of the scale and the quality of their pK_a values is not as high as that of **13** (see refs 40 and 6). The agreement between the values from this work and those from the literature can be considered satisfactory. The most deviating result is that of **35**. As the

experimental part of the original reference[6] does not describe the pK_a measurements, it is not possible to discuss this deviation thoroughly. Partially it can be due to the "distance" between **35** and **13**.

The pK_a values for individual acids were found minimizing the sum of squares of differences between directly measured ΔpK_a values and the assigned pK_a values:

$$u = \sum_{i=1}^{n_m} (\Delta pK_a^i - (pK_a(HA_2) - pK_a(HA_1)))^2 \qquad (16)$$

The sum is taken over all the measurements whereby ΔpK_a^i is the result of a relative acidity measurement of acids HA_1 and HA_2 (HA_2 is the acid whose pK_a is higher). pK_a(HA_1) and pK_a(HA_2) are the absolute pK_a values for the two acids as found by the least squares procedure. The precision and the consistency of the results can be assessed using a standard deviation as defined by eq 17:

$$s = \sqrt{\frac{u}{n_m - n_c}} \qquad (17)$$

where n_m=74 is the number of measurements, n_c=36–1=35 is the number of pK_a-s determined. For our results s=0.04 pK_a units. This is a low enough value for the scale to be considered self-consistent. This value was also taken as the basis for giving the absolute pK_a values with 2 decimal digits in Table 1. This approach to estimate the precision of the results has a drawback however: the precision of the measurements is different for different classes of compounds, being dependent on the spectral properties of the compounds, namely the difference between the spectrum of the anion and the neutral and the wavelength(s) at which the measurements were carried out. The precision is highest for the phenylmalononitriles and phenols and lowest for acids **19** and **23**. The pK_a values for the latter two acids are given with lower precision in Table 1.

It is important to note that this estimate of precision must be interpreted as the precision of single measurements and not the precision of the absolute pK_a values. The reference compound **13** has acidity that is about 7 pK_a units away from the strongest acids of the scale and for obtaining their acidity a large number (about 10) of ΔpK_a values has to be added, that significantly decreases the precision of the pK_a values for the compounds that stand far away from the reference compound. Still another point is the accuracy of the pK_a values which is also significantly lower.

The spectra of the compounds (with the exception of the sulfonic acids **19** and **23**) in solutions of different acidity did not show any irregular behavior. The spectra of partially ionized acids could always be expressed as linear combinations of the spectra of the neutral and the anion. With most of the compounds the spectra contained isosbestic points and these were always sharp. These observations rule out the possibility that conjugation reactions take place to an appreciable extent under our experimental conditions as the homo- and

heteroconjugation reactions are known to cause distortions in spectra.[44] The protonation-deprotonation process was reversible with all acids.

The spectra of **19** and **23** were slightly distorted and the spectra of partially ionized acids could not be expressed as linear combinations of spectra of anion and neutral. The concentrations of **19** and **23** were sufficiently high to permit the homoconjugation reaction to occur. The homoconjugation constant K_{AHA} for **19** is 800 L/mol.[18] The same value was used for **23** as the values of K_{AHA} do not differ very much within classes of acids as long as the acidities are not too different and steric factors are not involved. The resulting corrections to the ΔpK_a values were in the range of 0.05 .. 0.2 pK_a units. The assumption in eq 9 is reasonable with **19** and **23** because the acidity center OH is not directly conjugated with the aromatic ring and no significant intramolecular charge transfer is involved in the anions on excitation. However, this assumption would probably not be valid for compounds with the acidity center conjugated directly to the aromatic ring (phenols, anilines) because the wavelengths and intensities of the spectral bands with intramolecular charge-transfer character of the deprotonated species are very sensitive to hydrogen bonding.[44, 45]

Some of the measurements were made using $HClO_4$ instead of TfOH. because of the procedure of preparing of solutions of $HClO_4$, substantial amounts of acetic acid (AcOH) — a potential hydrogen bond donor — were introduced with this titrant. Two of the measurements were performed with both titrants and the agreement is good (see Table 1). The rest of the measurements agree well with the overlapping measurements made with TfOH. Thus we have reason to believe that AcOH does not interfere seriously. This is not unexpected because AcOH (pK_a in AN 22.3[18]) is a very weak acid compared to those studied in this work and the hydrogen bond donating ability of an acid in the conjugation reactions is directly related to its acidity.[46] Also, the basicity of AcOH (pK_a in AN 1.1[18]) as well as its concentration is too low to enable significant stabilization of the neutral acids by hydrogen bond.

We have included two cationic acids (**29** and **34**) into the scale. The log*f* values were in the range of 0.02 .. 0.05. However, as there is no general procedure for calculating activity coefficients for ions in nonaqueous media, these cationic acids cannot be rigorously regarded as belonging in the scale.

The pK_a values determined in this work together with those from other authors[18, 20, 23–25] set up a continuous acidity scale in AN ranging from pK_a 4 to 27.

Discussion

The Method. The presence of the acids in the same solution eliminates many possible sources of error or reduces their influence: (1) The disturbing effects (traces of water in the medium, concentration errors) affect both acids with the same magnitude and are expected to partially cancel out. Thus we expect that the effect of traces of water on the measurements will be less pronounced than in such measurements where pK_a of a single acid is measured at a time. (2) The solutions can be very dilute and consequently very weakly buffered with this method. If a minor acidity change of the solution occurs, it will affect both of the acids and its effect will cancel out. (3) An important point is that the method eliminates the need for quantitative measurement of acidity of the medium.

A disadvantage of the method is that acidity of only such acids can be measured that absorb in the UV-VIS spectral region and for which the spectra of the acid and the anion are different. Also the pK_a-s of the acids must not be very different from each other (preferably not more than 1.5–2 pK_a units).

Sulfonimides and sulfonic acids. pK_a values for aromatic sulfonimides are almost lacking from the literature. One reason is that sulfonimides are strong acids and their acidity cannot be measured in non-differentiating solvents. On the other hand, aromatic sulfonimides totally lack volatility and therefore no gas-phase data are available. To the best of our knowledge there has been only one work[47] where pK_a data of some aromatic sulfonimides in water have been reported.

Applying the Hammett equation to the aromatic sulfonimides **9**, **11**, **12**, **14**, **16**, **18** and **20**, the following relationship was found:

$$pK_a = (11.25 \pm 0.05) - (1.97 \pm 0.07)(\sigma_1 + \sigma_2) \qquad (18)$$

r^2=0.993, s=0.11, where σ_1 and σ_2 are the Hammett constants of the corresponding substituents (taken from ref 48).

The aromatic sulfonic acids **19**, **23**, **24** and **25** show a similar sensitivity towards substitution

$$pK_a = (8.0 \pm 0.2) - (1.9 \pm 0.4)\,\sigma \qquad (19)$$

r^2=0.92, s=0.3, although the correlation is poorer. It is of interest to compare these data with those obtained for substituted benzoic acids. Applying the Hammett equation to a set of substituted benzoic acids (4–H, 4–Br, 4–NO_2, 4–COOH, pK_a values from ref 18) gives:

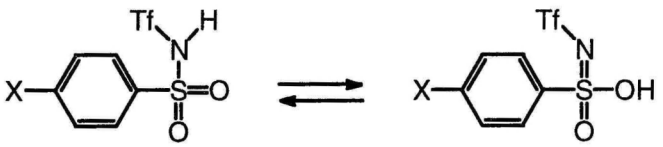
$$pK_a = (20.8 \pm 0.1) - (2.6 \pm 0.2)\,\sigma \qquad (20)$$

r^2=0.987, s=0.12. It can be seen that the acidity of benzoic acids is about 1.3 times more sensitive towards substitution in the aromatic ring than the acids with acidity center SO_2XH. The probable cause is that $-SO_2-$ fragment in the anion is bigger, more polarizable and more electronegative than the correspond-

ing –CO- fragment in carboxylates, and can therefore "hold" more charge and has lesser tendency to delocalize it into the aromatic ring.

Yagupolskii's substituents. Compounds **30**, **33** and **36** can be considered as derivatives of **12**, **14** and **18** respectively where an =O fragment of a sulfonyl group adjacent to the NH acidity center is replaced by =N–Tf. The acidifying effects of the substitution are 5.8, 5.7, 5.4 pK_a units for **12**, **14** and **18** respectively. The following values of pK_a have been found for $C_6H_5SO_2NH_2$, $CH_3C_6H_4SO(=N–Tf)NH_2$ and $CH_3C_6H_4S(=N–Tf)_2NH_2$ in DMSO: 16.0,[49] 8.0,[50] 3.4.[50] It can be seen that the acidity increase is not additive: the first substitution increases the acidity by 8 pK_a units while the second substitution by 4.6 pK_a units (the small effect of the 4-methyl group can be neglected here). It has not yet been possible to measure the acidities of these compounds or the sulfonimides in the gas phase[4] but there is a value of gas phase acidity available for a "superacidic" aniline 4–($CF_3SO(=N–Tf)$)–$C_6H_4NH_2$ ΔG_{acid}= 313.4 kcal/mol.[4] This compound is 13 orders of magnitude (!) more acidic in the gas phase than the corresponding unmodified aniline 4–Tf–$C_6H_4NH_2$ (ΔG_{acid} = 331.3 kcal/mol[11]).

The sulfonimides **26**, **28** and **32** can be considered as derivatives of sulfonic acids in which an =O fragment of the sulfonyl group is replaced with =N–Tf. These compounds can exist in two tautomeric forms:



a b (21)

Evidence (NMR) has been presented by one of us that **a** is the dominating form[9] in acetone and chloroform. The differences in acidities between **26**, **28**, **32** and the corresponding sulfonic acids **19**, **23** and **25** are 2.3, 1.8 and 2.2 pK_a units respectively. These results can be regarded as evidence in favor of the structure **a** in AN, as otherwise the differences should be similar to the ones obtained for sulfonimides.

Phenols. pK_a value –1.0 for **31** has been reported in aqueous H_2SO_4.[51] This is about 1.3 pK_a units lower than the pK_a of picric acid.[51] In AN, according to Table 1, **31** is about 6 pK_a units more acidic than picric acid. This qualitatively higher difference leads to a conclusion that some solvent effect is in operation here. 2-nitrophenols are known to give intramolecular hydrogen bonding[40] in AN. In water, on the other hand, this hydrogen bonding is absent due to the competition from water.[40] This intramolecular hydrogen bond causes considerable extra-stabilization of the neutral in AN compared to water. There are no data in the literature on hydrogen bond acceptor properties of trifluoromethane-

sulfonyl group but it is likely that these are weak in comparison with nitro group because the hydrogen bond basicity of sulfones is generally very low. Another factor might be that the picrate anion, due to its nitro groups, is likely to be more solvated in water than the deprotonated **31**.

Phenylmalononitriles. An interesting result with this class of compounds is that the pK_a-s of **6** and **7** in AN are practically equal or that of **7** is even slightly lower. The same behavior of these two compounds has been observed by one of us also in dimethoxyethane.[35] This is not completely unexpected: a similar effect is seen when comparing phenol to 4-fluorophenol: the latter is by only 0.2 pK_a units more acidic in water than the former.[17] The reason for this might be that although fluorine is an electronegative substituent, it is also a weak resonance donor.[48] The F is in the 4 position to the acidity center, which means that the inductive/field effect (but not the resonance effect) is weakened by the distance. The final factor is the strong electron-deficiency of the ring that still weakens the inductive/field effect by saturation. These arguments have to be treated with caution however because the same is not observed in the gas phase where **6** is more acidic by about 2 kcal/mol.

The correlation between the pK_a-s in AN and the gas phase acidities[4] is poor:

$$pK_a=(-108 \pm 36) + (0.40 \pm 0.12)\ \Delta G_{acid} \qquad (22)$$

r^2=0.69, s=0.91. This is surprising, because of all the compounds' classes in this scale the phenylmalononitriles should be relatively weakly influenced by solvation and they are very suitable for measurements both in AN and in the gas phase.

Conclusion

The present results together with those from the other authors furnish a unified acidity scale in AN ranging from pK_a 4 to 27 and help to establish a solid basis for the reliable pKa determinations of strong acids in AN. We have demonstrated that the acidities of strong acids are readily measurable and that AN is a suitable medium for this work.

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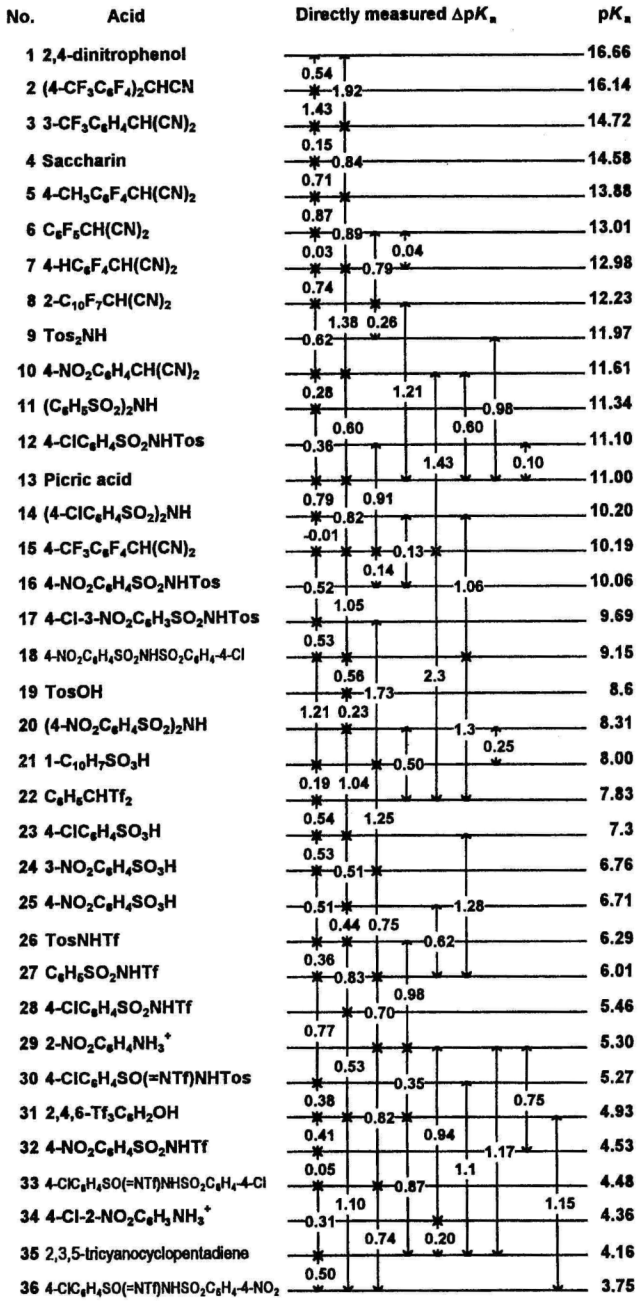
Table 1. pK_a values of the acids derived from the results of the ΔpK_a measurements.



[a] perchloric acid was used as the acidic titrant. Tos denotes 4–CH_3–C_6H_4–SO_2-; Tf denotes CF_3SO_2-.

Table 2. Comparison of the pK_a values determined in this work with those reported in the literature (values of obviously low quality have been omitted).

Acid	pK_a in AN		Difference
	This work	Lit.	
2,4-dinitrophenol	16.66	16.0[a]	+0.7
		18.4[b]	–1.7
picric acid		11.0[c]	
TosOH	8.6	8.01[d]	+0.6
		8.73[b]	–0.1
2–$NO_2C_6H_4NH_3^+$	5.30	4.95[e]	+0.35
4–Cl–2–$NO_2C_6H_3NH_3^+$	4.36	4.2[e]	+0.16
2,3,5-tricyanocyclopentadiene	4.16	3.00[f]	+1.16

[a]ref 40. [b]ref 41. [c]ref 42. [d]ref 13. [e]ref 43. [f]ref 6.

VII

Acid–Base Equilibria in Nonpolar Media. 1. A Spectrophotometric Method for Acidity Measurements in Heptane

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A UV–vis spectrophotometric method for measurements of relative acidities in heptane has been developed. The phosphazene base *t*-BuP_4 is used as the deprotonating agent. Its protonated form is a good counterion for the anions of the acids because it is bulky, has delocalized charge, and therefore does not have specific interactions with the anions. A self-consistent scale of relative acidities in heptane spanning for 3 pK_a units has been constructed.

Introduction

Acidity measurements of organic compounds have a long history dating back to the end of the 19th century, when the first pK_as were measured.[1] Since then a vast body of data on acidities in various solvents has been collected.[2–5] The measurements have mostly been limited to polar solvents however, water being by far the most exploited medium, followed by alcohols and dipolar aprotic solvents.

Acidity data in solvents of low polarity are also very valuable for many reasons. (1) The acidity of a compound in a given medium is influenced by both electronic effects of the substituents and the solvent effects of the medium. In polar solvents the solvent effects are strong and analysis of the acidity data in terms of electronic effects is difficult. In nonpolar solvents the medium has less influence on the acidities and the acidities are better differentiated. (2) Systems of extremely high acidity can be studied in nonpolar solvents. (3) Acidities of very weak acids can be measured in nonpolar solvents. (4) Many processes in organic synthesis and in the chemical industry involving acids and bases are carried out in nonpolar media, and acidity data in nonpolar media are needed to be able to understand and to quantitatively describe these processes.

The first ion-pair acidity scales in low-polarity media were set up by Conant et al.[6] in diethyl ether (dielectric constant $D = 4.20$) and McEwen[7] in benzene ($D = 2.27$). Since then several others have been created: in cyclohexylamine[8] ($D = 4.73$), in 1,2-dimethoxyethane[9] ($D = 7.20$), and in tetrahydrofuran[10] ($D = 7.58$). All these scales were built using metalation with alkali metals for deprotonation of the acids under study. This approach has been criticized by Konovalov et al.,[11] who state that because the ions in nonpolar media exist as ion-pairs (or larger associates), the alkali metal cations in nonpolar solvents will have strong specific interactions with the anions of the acids studied. The extent of the interaction is dependent on the anion as well as the cation, and therefore these scales lack the significance necessary for carrying out accurate analysis of substituent effects. These authors propose use of the lithium [2.1.1]cryptate as the counterion. The interactions between this ion and the anions are limited to electrostatic and van der Waals forces. The specific interactions are eliminated because the metal cation is coordinatively saturated and the cryptate ion is large (radius 5 Å).[11] Using this technique the Russian authors have built acidity scales in tetrahydrofuran[12] ($D = 7.58$), *N*-methylmorpholine[13] ($D = 4.3$), and benzene[14] ($D = 2.27$).

The least polar solvent in which a scale of acidity has been set up is benzene.[14] It would be of considerable interest to perform acidity measurements also in media with $D < 2$. This is because the $D = 2$ medium is halfway between polar solvents and the gas phase.

When measuring acidities in polar solvents, equilibrium (1) is studied usually:

$$HA + S \rightleftharpoons A^- + SH^+ \quad (1)$$

where S refers to the solvent. This equilibrium is also used to define the term "acidity of a compound", which is usually expressed as pK_a, where K_a is the equilibrium

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constant:

$$K_a = \frac{a(SH^+)a(A^-)}{a(HA)} \quad (2)$$

where a is the activity of the corresponding species. In nonpolar (and particularly in nonbasic) solvents the equilibrium (1) is shifted strongly to the left. In these solvents it is almost impossible to study the equilibrium directly. It is common to study the following equilibrium instead:

$$HA_2 + A_1^- \rightleftharpoons A_2^- + HA_1 \quad (3)$$

The pK of this equilibrium is the relative acidity (ΔpK_a) of the acids HA_1 and HA_2:

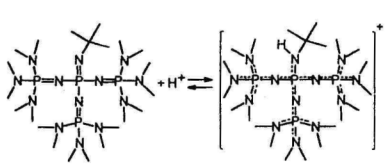
$$\Delta pK_a = pK_a(HA_2) - pK_a(HA_1) = \log\frac{a(A_1^-)a(HA_2)}{a(A_2^-)a(HA_1)} \quad (4)$$

Analyzing real systems according to eq 1 and eq 3 is certainly a simplification. In reality various association processes between ions (ion pairing), between ions and neutrals, and between neutrals occur as well. The less polar the solvent, the more complicated the picture.

Alkanes are solvents with very weak solvating power toward polar and especially ionic species. To prevent extensive aggregation and eventually precipitation of ionic compounds in such solvents, the ions should have the following properties: (1) The charge of the ion should be as delocalized as possible (the ion should have no well-defined ionic centers, such as $-O^-$ or $-NH_3^+$). (2) The ion should be as large as possible.

The neutral acids themselves should also be as nonpolar as possible and should not have polar centers, such as $-OH$. This restricts both the number of acids that can be studied in heptane and the choice of the method of deprotonation of the acids and the counterion. To the best of our knowledge, no systematic acidity measurements have been performed in alkanes to date.

An ideal deprotonating agent would be a very strong base, which is soluble in heptane and able to deprotonate acids in nonpolar medium, and the protonated form of this base would meet all the criteria setup for ions above. There are bases—phosphazenes[15,16]—which meet all these requirements. We use phosphazene t-BuP_4 [the systematic name of t-BuP_4 is 3-(*tert*-Butylimino)-1,1,1,5,5,5-hexakis(dimethylamino)-3-{[tris(dimethylamino)phosphoranylidene]amino}-1λ^5,3λ^5,5λ^5-1,4-triphosphazadiene] for our work. It is a very strong base [pK_a(DMSO) = 30.2[16]] which upon protonation gives a bulky cation (its radius has been estimated to about 7 Å[17]) with strongly delocalized charge:



t-Bu-P$_4$ (5)

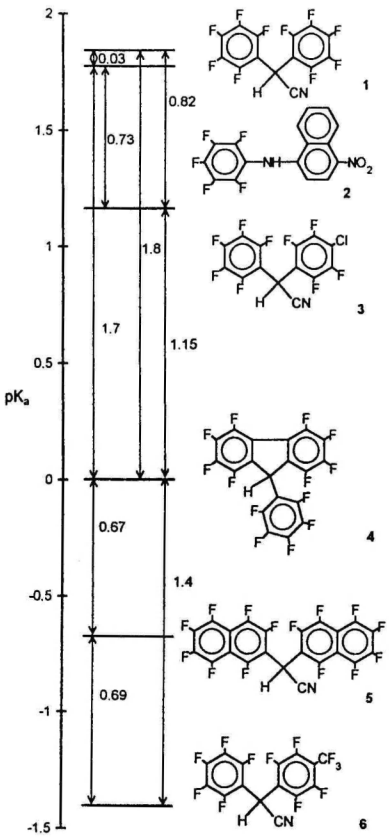


Figure 1. Interlocking ladder of relative acidities in heptane. The ladder is anchored to arbitrarily chosen reference compound 4.

It is also important to note that the protonated basicity center of this phosphazenium ion is sterically strongly hindered and has, therefore, a low ability to specifically interact (e.g., hydrogen bonding) with the anions of the acids, which are very bulky too and devoid of well-defined charged centers. An additional advantage of t-BuP_4 is that its cation is transparent practically across the entire UV spectral range.

In this paper we report a method for determining relative acidities in heptane (D = 1.92) utilizing t-BuP_4 as the deprotonating agent. The acids studied in this work form extensively delocalized anions and are presented in Figure 1. As a result of our measurements we have set up a continuous, self-consistent acidity scale in heptane.

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Experimental Section

Method of pK_a Determination. The relative acidities were measured using a UV–vis spectrophotometric titration technique: a solution containing two acids, HA_1 and HA_2, was titrated with a solution of t-BuP_4 in heptane. A spectrum was recorded after each addition of the titrant. The number of titration points per experiment ranged from 10 to 30. Both of the acids were also titrated separately to obtain the spectra of the neutral and the ionized forms of both acids. All titrations came to a point where further addition of the titrant did not change the spectrum. This was considered the equivalence point of the titration. From the spectra the relative acidity of the two acids could be calculated. The calculation methods are presented below.

The calculations assume constant analytical concentrations of the acids. The spectra were corrected for the dilution due to titrant addition.

We assume that the ratio of the activity coefficients of the anion and the neutral $f(A^-)/f(HA)$ in heptane is constant for all acids, so that the ratios of activities in eq 4 can be replaced by the ratios of concentrations. These ratios (indicator ratios) were measured from the absorbance spectra of the compounds. The prerequisite for this is that the two compounds must have different spectra in the UV–vis region and the spectrum of the acid must be different from that of the anion. These criteria are met by all the acids under study.

When two partially ionized acids HA_1 and HA_2 are in the same solution, their UV–vis spectra usually overlap and the following equation holds for absorbance A^λ at wavelength λ:

$$A^\lambda = [HA_1]\epsilon^\lambda_{HA_1} + [A_1^-]\epsilon^\lambda_{A_1^-} + [HA_2]\epsilon^\lambda_{HA_2} + [A_2^-]\epsilon^\lambda_{A_2^-} \quad (6)$$

The ϵ values are molar absorption coefficients of the respective species; the optical path length is equal in all cases and can be included in A. If we use the concentrations of the acids as normalized to 1, we may write $[HA_1] = 1 - [A_1^-]$ and $[HA_2] = 1 - [A_2^-]$ and the equation can be rewritten:

$$A^\lambda = \epsilon^\lambda_{HA_1} + \epsilon^\lambda_{HA_2} + [A_1^-](\epsilon^\lambda_{A_1^-} - \epsilon^\lambda_{HA_1}) + [A_2^-](\epsilon^\lambda_{A_2^-} - \epsilon^\lambda_{HA_2}) \quad (7)$$

And finally:

$$\frac{A^\lambda - \epsilon^\lambda_{HA_1} - \epsilon^\lambda_{HA_2}}{(\epsilon^\lambda_{A_2^-} - \epsilon^\lambda_{HA_2})} = [A_1^-]\frac{(\epsilon^\lambda_{A_1^-} - \epsilon^\lambda_{HA_1})}{(\epsilon^\lambda_{A_2^-} - \epsilon^\lambda_{HA_2})} + [A_2^-] \quad (8)$$

This expression represents a linear equation with slope $[A_1^-]$ and intercept $[A_2^-]$. All the ϵ values are constants at a fixed wavelength, and they can be determined from spectra containing only one acid in entirely ionized or neutral form. If we take a spectrum of a solution containing both acids in partially ionized form and vary the λ, the terms containing absorbance and the extinction coefficients are variables and the $[A_1^-]$ and $[A_2^-]$ are constants, which can be determined from regression analysis and the relative acidity can be calculated as follows:

$$\Delta pK_a = \log\frac{[A_1^-](1 - [A_2^-])}{[A_2^-](1 - [A_1^-])} \quad (9)$$

This general calculation method is universal, but it has the drawback that the concentration of the acids HA_1 and HA_2 in the solutions (or at least the ratio of the concentration in the mixture and in the solution from which the ϵ values were found) must be known precisely. Even small errors in concentrations tend to introduce large errors in ΔpK_a values. The errors are the larger the bigger the ΔpK_a.

The spectra of most of the compounds studied contain features which allow simpler methods of calculation to be used. There are isosbestic points in the spectra, and often one of the acids absorbs at a longer wavelength than the other and its indicator ratio can be determined from the spectrum of the mixture in the presence of that other acid. A couple of simple methods will be outlined below.

If for both acids HA_1 and HA_2 a wavelength can be found at which the absorbance of the other acid (that is HA_2 and HA_1, respectively) does not change in the course of titration, the indicator ratios $[A^-]/[HA]$ of both acids in the same solution can be directly determined from the spectra of the mixture without using spectra of solutions of pure compounds. A very simple relationship holds for the indicator ratio:

$$\frac{[A^-]}{[HA]} = \frac{A^\lambda - A_n^\lambda}{A_i^\lambda - A^\lambda} \quad (10)$$

where A_n^λ and A_i^λ are the absorbances of solution containing both acids in neutral and ionized forms, respectively. The wavelength λ is one at which the absorbance of the other acid does not change during the titration. When the indicator ratios are known, the ΔpK_a can be calculated using eq 4. This is a very simple and accurate method since the spectra from only one titration are involved and the values of the concentrations of the acids in the solution are unimportant.

For carbon acids such as those studied in this work, it is very common that the anions absorb at long wavelengths where the neutrals are transparent. If a range of wavelengths can be found at which both anions absorb and both neutrals are transparent, then an elegant calculation method can be applied. Absorbance A^λ of the mixture at any wavelength λ in that wavelength region can be expressed as a linear combination of the absorbances of the anions A_1^λ and A_2^λ:

$$A^\lambda = b_1 A_1^\lambda + b_2 A_2^\lambda \quad (11)$$

where b_1 and b_2 are constants for a given mixture within that wavelength range and are determined using a least-squares method. For each spectrum of the titration, b_1 and b_2 can be found and ΔpK_a can be calculated as follows:

$$\Delta pK_a = \log\frac{b_1(b_2^i - b_2)}{b_2(b_1^i - b_1)} \quad (12)$$

where b_1^i and b_2^i are the coefficients of the mixture in which both acids are fully ionized. Again, the concentrations of the acids in solutions are unimportant with this method.

For each measurement the most appropriate calculation method was chosen. The simpler methods were preferred over the general one because of their higher accuracy. In difficult cases several methods were used.

Solvent. The solvent suitable for our work must be very dry and be low in any acidic and basic impurities and those that absorb UV radiation. Heptane (Reakhim, "pure") (1.75 L) was stirred three times, 4 h each time, with 15 mL of concentrated sulfuric acid. The last portion of sulfuric acid was only slightly yellowish after stirring. Then the solvent was stirred twice with 20 mL of of 0.5 N solution of potassium permanganate (Reakhim, analytical grade) in 5 N sulfuric acid for 4 h each time. The solvent was washed with 200 mL of water and then with 200 mL of a 10% solution of sodium hydroxide and then stirred with solid potassium hydroxide for 4 h. Finally it was distilled through a 1.2 m column packed with Teflon chips from P_2O_5 (Reakhim, analytical grade) with magnetic stirring (to avoid possible decomposition processes at the bottom of the distillation flask). The first and last 10% portions of the solvent were discarded. A stream of dry argon was passed through the solvent during the distillation. The solvent was stored over anhydrous magnesium perchlorate in airtight bottles. The absorbance values of the middle fraction (1 cm cell, vs H_2O) at 207, 210, 220, 230, and 260 nm are 1.0, 0.85, 0.16, 0.07, and 0.03, respectively.

Acids. The acids were prepared at the Institute of Organic Chemistry in Novosibirsk, and their preparation has been previously described: **1**, **3**, **6**;[18] **2**;[19] **4**;[20] **5**.[21]

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Phosphazene *t*-BuP$_4$. This compound was prepared according to the procedures described in the literature.[15,16,22,23]

Experimental Setup. The solutions were prepared in 10 mL vials. Care was taken to prevent air getting into contact with the solutions. All operations were performed using standard syringe techniques. All the glassware used was dried at 150 °C and cooled in a desiccator over P_2O_5.

The titration was carried out directly in the spectrophotometer cell. The cell contained a small Teflon-coated stirring bar for mixing the solution. The amount of titrant added was measured by weighing the cell.

The concentrations of the acids were chosen as low as possible to prevent precipitation and association of ions during titration. The average values were in the range 1 to 5 × 10^{-5} M. The concentrations of the titrant were around 1 × 10^{-3} M. The solutions of the acids and the solution of the titrant were made fresh daily.

Spectrophotometry. A Perkin-Elmer Lambda 2S UV–vis spectrophotometer equipped with cell holders thermostated to 25 °C was used for all the measurements. The spectrophotometer was controlled from a PC, and the spectra were stored in digital form. Fused silica cells with an optical path length of 1 cm were used. The reference cell contained pure heptane.

Results and Discussion

The results of the measurements are presented in Figure 1. The compounds as well as their salts with *t*-BuP$_4$ are sufficiently soluble in heptane. In some cases, however, precipitation occurred during the titration as the concentration of the salt increased. This was recognized by opalescence of the solution and shift of the base line of the spectrum away from zero. This problem was remedied by reducing the concentration of the acid.

Beer's law was found to hold for the acids and their anions at the low concentrations (1 to 5 × 10^{-5} mol/L) used. Sharp isosbestic points were observed with all compounds. At higher concentrations the spectra sometimes changed in an odd way. This was often caused by precipitation, but in some cases the solution remained clear and the shape of the spectrum changed. This can probably be attributed to some aggregation process, but further investigations are needed to give a conclusive answer.

Each arrow on Figure 1 represents one measurement of relative acidity. To make the results more reliable and to be able to estimate the consistency of the results, we carried out multiple overlapping measurements. The entire range from **1** to **6** involves two independent pathways of measurements, and the relative acidity of any two acids can be obtained by combining at least two independent sets of measurements. The uncertainties of the results are best estimated from Figure 1 by observing how good the agreement is between different pathways of measurements. The most uncertain measurements are those of the pairs **1**–**4**, **2**–**4**, and **4**–**6**. These pairs of acids have large ΔpK_as, and this is the reason for the low precision of these results. We estimate the uncertainties of these three measurements as large as 0.2 pK_a unit and the uncertainties of the rest of the measurements 0.05–0.1 pK_a unit. Taking into account that the large ΔpK_a values cannot be measured with high precision, the agreement between different pathways is good and the scale can be considered self-consistent.

The method used lets us obtain only relative acidities. Compound **4** has been taken as an arbitrary reference compound, and the acidities of all others are expressed relative to that of **4**. We assign the following ΔpK_a values (all relative to **4**) to the acids investigated: **1** 1.8; **2** 1.8; **3** 1.1_5; **4** 0; **5** -0.6_7; **6** −1.4. No attempt is made in this paper to convert the relative acidities to absolute numbers.

The actual state of the ions in solution is an important issue. It is well-known that ions in nonpolar media exist as ion pairs or higher aggregates. Depending on the ions involved and the solvating properties of the medium, two types of ion pairs can be distinguished: contact ion pairs and solvent-separated ion pairs.[24] It has been shown that as the ions get larger, the spectral properties of contact ion pairs approach those of solvent-separated ion pairs and that the spectral properties of solvent-separated ion pairs and free ions generally do not differ.[24] Konovalov et al.[11] have carried out detailed spectrophotometric and conductometric investigations of the state of lithium [2.1.1]cryptate ion in solvents of low polarity. These investigations are particularly relevant to our case because the phosphazenium ion present in our solutions is similar in size to that of the cryptate ion used by Konovalov et al. These investigators varied the solvent polarity (ranging from DMSO to hexane) as well as the degree of charge delocalization of the anions. It was found that the cryptate ion and the anion exist as ion pairs in all the solvents studied (except DMSO in which the ion pairs dissociate) and that in all the media the spectral characteristics of the ion pair are indistinguishable from those of solvent-separated ion pairs. The authors proposed the term "cryptate-separated ion pair" for this type of ion pair. The results of conductometric investigations showed that if the concentration of the cryptate ion in solution is less than 1 × 10^{-4} mol/L, then the ion pairs in a solvent with $D < 15$ do not associate significantly into larger aggregates.[11]

Taking into account the structural properties of the compounds involved in the equilibria, the results of Konovalov et al., and the very low concentrations of the acids used in this work, we predict that the ions exist as "loosely bound" ion pairs, analogous to the cryptate-separated ion pairs described by Konovalov et al. This means that although neither of the two ions in the ion pair is solvated in heptane to an appreciable extent, there are no specific interactions between the ions because they are bulky and have delocalized charge.

Some support for this prediction can also be drawn from the fact that Beer's law holds for the salts and that isosbestic points are observed. This means that under our experimental conditions the state of the ion pair in terms of specificity of interactions between the ions does not change with increasing concentration of the salt relative to the neutral acid. On the other hand, as the spectral properties of the distant ion pairs and free ions do not differ, these results do not say anything about the extent to which the ion pairs dissociate into free ions as well as about possible aggregation of the loosely bound ion pairs.

It is not possible to thoroughly discuss substituent effects or correlations of the results with measurements

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in other media because at present our scale contains too few compounds and these are not very common. However, acidities of compounds **1**, **3**, **4**, and **6** have been measured in the gas phase (ΔG_{acid} = 312.4,[25] 311.8,[26] 301.8,[25] and 307.5[25] kcal/mol, respectively) and in DME solution[27] (pK_a = 6.4, 5.4, 5.3, and 3.9, respectively).

The correlation of pK_a(heptane) vs pK_a(DME) is not very good: r^2 = 0.91, slope 0.70 (pK_a in heptane is on abscissa) and standard error s = 0.38. No obvious outlier was detected. It must be noted that these pK_a values in DME have been obtained using Li^+ as the counterion and the anions exist in DME solution as contact ion pairs with Li^+.[27] Specific interactions between ions cannot be neglected here, but there are too few data to draw far-reaching conclusions.

In the gas phase the correlation is good: r^2 = 0.993 and slope 0.92 (ΔG_{acid} values are transformed to pK_a scale prior to the correlation analysis) if the compound **4** is excluded from the correlation analysis. This compound severely deviates from the correlation line. If we take that one of the measurements (that is pK_a in heptane or ΔG_{acid} in the gas phase) is correct, then the other one must be in error by approximately 5 orders of magnitude (!) in order to fit into the correlation. Compound **4** is of a different family from compounds **1**, **3**, and **6**, and this can be partially the reason for the enormous deviation. It can be expected that charge in the deprotonated **4** is more delocalized than that in **1**, **3**, and **6**, which have CN groups attached directly to the acidic center. This CN group will carry significant negative charge in these anions, and they are more strongly solvated in the liquid phase than the deprotonated **4**. The three anions are also expected to interact more strongly with traces of water and with counterions than the deprotonated **4**. Thus one can expect that going from the gas phase to the liquid phase the increase in acidity of **1**, **3**, and **6** is larger than that of **4**. This is really the case: the pK_a of **4** in heptane (and in DME too) relative to the other three compounds is about 5 units higher than that predicted from the gas phase measurements. Nevertheless, neither heptane nor DME has strong ability to solvate anionic centers and this difference in solvation cannot be the only reason for this phenomenon. Further experiments are necessary.

Work is in progress in our laboratory to further extend the acidity scale. Also the actual state of the ions in solution needs to be further studied by other methods.

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MAIN SCIENTIFIC PUBLICATIONS

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TÄHTSAMAD TEADUSPUBLIKATSIOONID

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