CONTRIBUTION TO THE CORRELATION OF STERIC STRUCTURE WITH DISSOCIATION CONSTANTS IN ORGANIC COMPOUNDS. I. BASES

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The correlation of steric hindrance with basic strength has been established in »α«-substituted aryl and alkyl amines. Solvent effect, indicating primary steric effect has been determined in the field of o-substituted anilines on the basis of increased steric compression. A method was offered for the detection of H bonds. Steric effects acting from α and β positions in aliphatic amines have been discussed and in connection with that conformational analyses of some saturated amines were carried out as well.

Organic chemists studied since long the correlation of steric structure with the stage of dissociation in organic compounds. In the course of investigations of molecular structure two effects were taken into account, i. e. the correlation of dissociation constants with polar effect and that of steric with dissociation constant, resp. The comparison of the values of dissociation constants of various organic acids and bases contributed markedly to the development of the electron displacement theory. LUCAS studied the changes of dissociation constants in the field of differently substituted derivatives of acetic acid [1a] and benzoic acid [1b], which led to the numerical expression of the inductive effects of various groups. Early efforts directed at the determination of the acid strength of o-, m-, p- substituted benzoic acids were made by FLÜRSCHEIM [2], in 1909, according to which considerable steric effects were suggested. Recently THOMSON [3], DIPPY [4, 5, 6], INGOLD [9] and BROWN [7, 8] investigated the correlation of electro-kinetic forces with steric effects; further experiments on this subject are carried out in the same way as well.

According to INGOLD the steric effect of a certain group in the case of a one-molecular dissociation is due to three factors:
1) *a primary steric effect*, that is steric compression exerted in different degrees in the conjugated acid and base. 2) *a secondary steric effect*, that is, a pressure-produced twisting of the acidic or basic group, with a consequent breakdown of conjugation, and therefore a modification of the mesomeric effect on acid strength; 3) *chemically specific interactions* of groups near to the acidic or basic centre, for example: hydrogen bridge or coordination.

The published investigations refer mostly to aromatic or doublebond systems. Saturated systems were, however, scarcely studied so far, excepting that of c-hexane-carboxylic acid. The possibility of different corformations makes difficult the close examination of the steric effect, while just the knowledge of

the interrelation of steric effect to dissociation constants renders possible the elucidation of the fine structure of the molecule. Investigations on the correlation of β-substituted compounds with dissociation constants including saturated systems not yet discussed, are the main subject of the present work.

I. The ortho-effect in the field of aromatic amines

In connection with the dissociation of aniline compounds FLÜRSCHEIM pointed out that in the case of *ortho*-substitution basicity is significantly decreasing. This effect was explained with the overlap exerted by the *ortho*-positioned alkyl group, which corresponds to the more up to date interpretation of the primary steric effect [1]. This may have risen from two causes, 1.) in the aniline-anilinium equilibrium the ionic form is hydrated at a larger scale and equilibrium has been shifted towards the »non-protonated« form due to the increased compression energy, 2.) the effect of steric restriction caused by an *ortho*-substituent, hindering the proton uptake on the amino group. Both effects weaken the basicity of arylamines. In the field of carboxylic acids the dissociation constant is explained independently of steric effects — in terms of proton activity, that is of solvation differences between ionic and non ionic form, resp. [11]. FLÜRSCHEIM's overlapping effect is to be considered as one of the factors of proton activity.

Table 1 gives the values K for differently substituted *o-*, *m-*, *p*-aniline derivatives.

Table 1

Basicity of aniline and substituted aniline derivatives in water at $25°$ C

Compound	$\log K_b$	$K_b . 10^{12}$
Aniline	9,42	381
o-Fluoroaniline	11,04	9,13
o-Chloroaniline	11,38	4,17
o-Bromoaniline	11,40	3,99
o-Toluidine	9,62	240
o—t-Butil-aniline	10,22	61
o-Anisidine	9,51[1]	310
o-Phenetidine	9,53[1]	296
m-Chloroaniline	10,68	21
m-Bromoaniline	10,49	32
p-Chloroaniline	10,19	65
p-Bromoaniline	10,09	81
p-Anisidine	8,71[1]	1950
p-Phenetidine	8,75[1]	1780

The figures unlabelled are due to different authors, values are cited by *McDaniel* and *H. C. Brown.*: J. Amer. Chem. Soc., **77**, 3756 (1955).

[1] *Hall N. F., M. S. Sprinkle:* J. Amer. Chem. Soc., **54**, 3469 (1932).

Thus, according to the data of Table 1, the *ortho*-effect — as the outcome of proton activity and solvent effect — causes the basic strength to fall gradually with the increased number of *o*-methyl groups in methyl substituted derivatives, though the inductive effect of the methyl group should increase

basicity. Since no steric effect seems to be operative, the basic strengths of p-toluidine increase with the inductive effect, when compared to that of aniline. Whereas the dissociation constant of *ortho*-substituted compounds — independently of the inductive effect of various *ortho* substituents — show a decrease on basic strength — the values K for *para*substituted derivatives are governed by inductive effects. This shows unequivocally that the correlation of the *ortho*-effect with dissociation constants is very largely responsible for the above mentioned findings.

Solvent effect. Solvent effects regarding steric compression in primary steric effects are of considerable interest. The size of solvatation shell varies according to the solvatation abilities of different solvents. The size of the solvatation molecule together with the dielectric moment constitute the major factor of this effect, in the case of a given ion. Dissociation constants, depending upon dielectric moments and steric features represent different values. Solvent effect, in *ortho*-substituted compounds arises from two factors: 1.) General solvent-effect, depending conclusively on the specific nature of solvent, 2.) Specific solvent- effect, being in connection with the electronic and steric nature of the substituent. A numerical expression for the correlation of the dielectric constant with ionotropy was given by BORN [12]. In the case of two differently polar solvents having various molecular bulks, — the larger solvation shell bound by the same energy will be found in the most polar solvent — provided that the molecular volume of the solvent does not exert conclusive effects on polarity differences.

If the increase of size arising from the molecular bulk of the less polar solvent, exceeds the decrease of solvation shell, which may be regarded as the consequence of lower polarity, then the bulk of the solvation shell will be approximately in proportion to molecular dimensions. Obviously, in the case of a sterically hindered solvatation ion, the larger solvation shell enhances steric restrictions. This, in turn, increases the compression energy, which leads to the decreasing of solvation shell belonging to the sterically hindered ion. As the result of this interaction an equilibrium between solvatation and compression energy takes place. Since compression energy is, in general, of a lower

Table 2

$K_b 10^{12}$ data of aniline and its substituted derivatives by variation of the percentage of aqueous ethanol

Compound	30 % aqueous EtOH	50 % aqueous EtOH
Aniline	126 [1]	175 [2]
o-Fluoroaniline	2,95 [1]	—
o-Chloroaniline	1,35 [1]	—
o-Bromoaniline	1,00 [1]	—
o-Toluidine	—	96,5 [2]
m-Chloroaniline	8,51 [1]	—
p-Chloroaniline	28,8 [1]	—

[1] *Benneth, G. M., G. L. Brooks, S. Glastone:* J. Chem. Soc., 1821 (1935).
[2] *Thomson G.:* J. Chem. Soc., 1113 (1946).

value than that of solvatation, the bulk of solvation shell — of a given ion, will be by no means, equivalent, according to the different solvents applied, but exhibits some sort of solvent effect. Data of dissociation constants, measured in aqueous alcohol are compiled in Table 2.

The data of Table 2 show that, for example, in water and water-alcohol relations, the solvation shell of aqueous alcohol raises steric compressions stronger than pure water, thus the increased quantity of alcohol results in a larger ammonium solvation shell, which, in turn, strengthens steric compression. The rise of steric compression relating to aniline-anilinium equilibrium dominates in those cases, where ortho-situated groups are of larger size. Consequently, the dissociation constants of aniline and o-substituted aniline derivatives are showing smaller differences in pure water, than in aqueous alcohol, in which solvent the solvation shell induces more powerful compression energies.

Table 3 shows how $K_{aniline}$ / $K_{substituted\ aniline}$ values, evaluated from Tables 1 and 2, vary in pure water and water-ethanol, resp.

Table 3

The values and the corresponding quotients of
$K_{aniline}$ / $K_{substituted\ aniline}$ evaluated from Tables 1 and 2

$K_{substituted\ aniline}$	H_2O (A)	Aqueous ethanol (B)	B/A
o-Toluidine	1,59	1,81	1,14
o-Fluoroaniline	41,7	42,7	1,02
o-Chloroaniline	91,4	93,3	1,02
o-Bromoaniline	95,5	126,0	1,33
m-Chloroaniline	18,1	14,8	0,82
p-Chloroaniline	5,9	4,37	0,74

The quotients clearly demonstrate that in the field of o-methyl and o-bromo anilines, the steric effects caused by solvatation are more powerful in water-alcohol medium. $K_{aniline}$ / $K_{subst.\ aniline}$ values for o-fluoro- and o-chloro derivatives, measured in water and in aqueous alcohol, resp. are rather close to each other. The deviation exhibited, however, is due to hydrogen bonds and will be discussed more extensively later on. Quotients of m-chloro and p-chloro aniline show reverse variations, which arise largely from differently polar solvents in the absence of steric effect. This points also to the conclusion that in o-substituted derivatives the specific solvent effect is due to steric hindrances. The method discussed may be applied at least qualitatively to detection of the mentioned steric effect, mainly in the field of -I groups, where basic strength is weakened by polar and steric effects as well.

Other factors affecting dissociation constants

The basicity of o-substituted amino-derivatives was explained so far in terms of primary steric effect. It was mentioned, however, already in the introduction that apart from the latter also other effects, that is: a secondary steric effect and a specific chemical one exist.

In the field of o-fluoro and o-chloro aniline also hydrogenbonding exerts influence on dissociation constants that is, increases basicity [8]. Since the formation of an intramolecular hydrogen bridge is less probable in a less polar solvent, i. e. in water, an intramolecular hydrogen bridge increases stronger basic strengths in water-alcohol solvent. Furthermore as the probability of the formation of a hydrogen bridge is greater in a »solvation shell forming« solvent, consequently $K_{aniline}$ / $K_{substituted\ aniline}$ values measured in water and water-alcohol approximate each other, because of the contrasting influences. Attempts to distinguish the chloro- and fluoro-compounds by considering the probability of a hydrogen bridge formation failed due to the limited exactness of experimental data. The method of measuring dissociation constants in different solvents offers some informations apart from the primary steric effect on hydrogen bridge.

Considering the above examples, the existence of a secondary steric effect may be presumed in the case of o-t-butyl-aniline to certain extent. The secondary steric effect operating in the field of Ṅ-dimethyl-aniline derivatives is, however, of major significance.

II. The basic strengths of β-substituted acridine derivatives

β-substituents decrease the basic strength also in compounds containing hetero nitrogen atoms. The discussion of steric effects is simpler since in these cases secondary steric effects may be disregarded and further because the formation of a hydrogen bridge is probable only in the field of β-hydroxyl compounds. The effect of β-substituents on carbazol derivatives has been scarcely studied. CRAIG [13], on dealing with the problem of the proton uptake of 1,9 diamino-acridine and 1-amino-9-methyl-acridine, confirmed that the ionization of ring nitrogen decreased stronger by comparison with that of acridine. This is due to overlapping effect of the ring-nitrogen on 1- and 9-groups, as illustrated below.
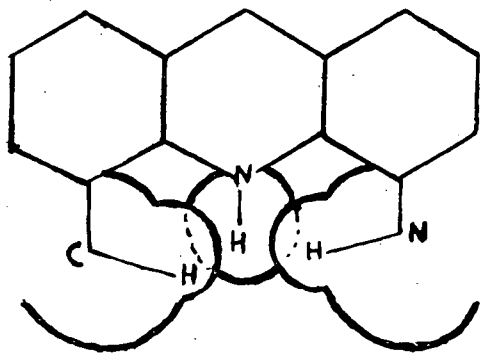

Fig. 1.

III. Basic strengths of saturated bases

The correlation of basicity with the order of different alkylamines has been studied extensively. It was confirmed that when an alkyl substituent is introduced into ammonia, the basicity increases according to the sequence of primary, secondary amines, whereas it decreases in tertiary amines [14]. This may be explained in terms of steric effect dominating over inductive effect. If the steric effect is of such a great importance even in the substitution of amino group, as it has been revealed in the case of tertiary amines, then it may expected, that α-, or β-situated groups

increase steric effects more effectively on account of decreasing inductive effect.

As can be seen in Table 4 the conformations of the methylamine derivatives referred are of no determinative importance. The basic strength of tertiary butylamines weakens when compared to that of propylamines, indicating clearly the effect of steric hindrances exerted by α-situated alkyl substituents. This is in contrast to earlier conclusions of VEXLEARSCHI [15] according to which the steric effects of β-substituents may be neglected. In the field of β-substituted amines, steric interaction becomes more evident, because of the decreasing inductive effect.

Table 4

$10^5 K_b$ values of methylamine derivaties, substituted at α—C atom at 25°C in water

Compound	$10^5 K_b$
CH_3—NH_2	43,7
$CH_3CH_2NH_2$	46,8
CH_3—CH—NH $\mid$ CH_3	42,7
CH_3 $\mid$ CH_3—C—NH_2 $\mid$ CH_3	28,2

Table 5

$10^5 K_b$ values of β-substituted alkylamines in water at 25°C

Compound	$10^5 K_b$
$CH_3H_2CNH_2$	46,8 [1]
$CH_3CH_2CH_2NH_2$	38,1 [1]
$CH_3CHCH_2NH_2$ $\mid$ CH_3	26,4 [1]
CH_3 $\mid$ CH_3—C—CH_2NH_2 $\mid$ CH_3	24,0 [2]

[1] Hall, N. F., M. R. Sprinkle: J. Amer. Chem. Soc., 54, 3469 (1932).
[2] Vexlearschi, G.: Compt. rend., 233, 1630 (1951).

The configuration and constellation of the amino group and the β-substituent, respectively, proved to determine steric hindrance and hereby the basic strenght of the molecule as well. The stronger effect of this type is exhibited by the β-alkyl substituted derivatives of amino-c-pentane, but experimental data are not yet available.

The correlation of the steric hindrance of β-substituents with basic strength makes possible, in the knowledge of basicity, a certain distinction of the various steric positions. This is in connection with conformational analysis quite important, since the ground state of molecule is not influenced energetically by the method discussed. For example, on the ground of basicity, the conformation of i-butylamine may be determined, as follows. The rotational isomers of neopentylamine are identical with themselves, thus only one conformation may be ascribed to the molecule.

In the field of i-butylamines two steric structures may be considered. In one of the cases the (b) configuration of both methyl and amino groups are identical with that of ne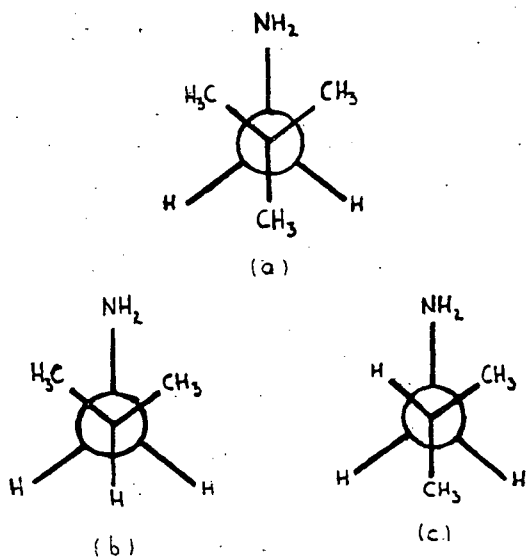opentylamine. As to the other »c« conformation, only one methyl is situated in the vicinity of amino group. The decrease of this type of steric hindrance must result in an enhanced basicity. On comparing the dissociation constant of neopentylamine with that of i-butyl-amine, the »c« conformation of the latter seems to be supported. Conclusions regarding the conformation of propylamine, may be drawn from that of i-butylamine. Of the two possible configurations that may dominate in a solution in which the terminal methyl and amino groups form a 180.° angle i. e. in this case steric hindrance exerted by the only methyl group, becomes irrevelant. Consequently the basic strength has been found to increase.

Fig. 2

Whereas the falling basicity of propylamine in comparison to that of ethylamine is attributed largely to steric effects — an increase of size in methyl, ethyl sequence as »basicity weakening factor« may be explained only by the presence of an »a« configuration to a considerable degree. The determination of the numerical proportions of various conformations requires exact measurements of dissociation constants at different temperatures. Activation energies of the transition state may be calculated from the latter as well.
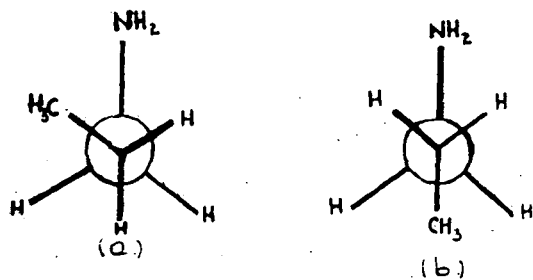
Fig. 3.

Dissociation constants of 2–amino-cyclohexanol are:

K cis = 9,6, K trans = 9,5 [16].

Conformational alternatives of this compound will be seen from the following figure. K values — as it has been shown above — lie rather close to each other, consequently amino and hydroxy groups are equatorial in the *trans* compound, wich is in full agreement with the experimental data. In the equilibrium of *cis* compounds, the conformation will dominate in which an equatorial amino group is preferred. Namely, in the case of an axial amino group basicity should decrease, owing
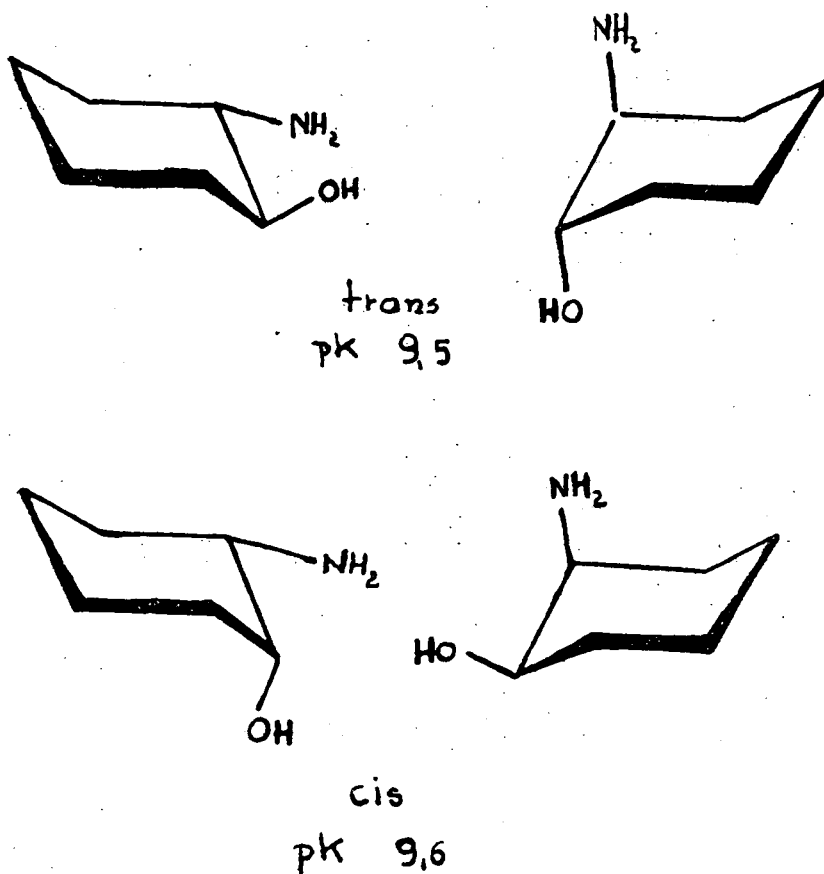
NH₂ trans pk 9,5

HO

NH₂ cis pk 9,6

OH

Fig. 4

to the operative steric hindrance between the amino and the two adjacent methylen groups. The effect of the steric hindrance of axially placed methylen groups may be seen below:
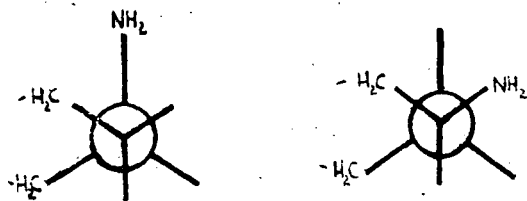
Fig. 5

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