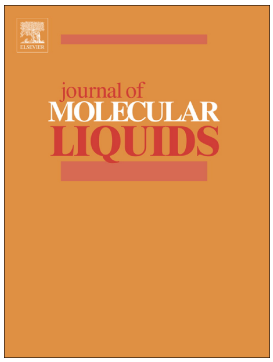

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The assessment of intramolecular hydrogen bonding in ortho-substituted anilines by an NMR method.

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ABSTRACT

We describe the Δlog *P* method for the assessment of intramolecular hydrogen bonds (IMHBs), and show that it is not a very general method of distinguishing between molecules in which there is an IMHB and molecules in which there is no IMHB. The 'double' Δlog *P* method of Shalaeva *et al* is a much more reliable method for the assessment of IMHB but requires the synthesis of a model compound and the determination of no less than four water-solvent partition coefficients. In addition, it is difficult to apply to compounds that contain more than one hydrogen bond acidic group capable of IMHB. We then describe our NMR method of assessing IMHB, based on ^{1}H NMR chemical shifts in solvents DMSO and $CDCl_3$. We have determined ^{1}H NMR chemical shifts for a number of ortho-substituted anilines and show that the only compound we have studied that forms an IMHB is methyl 2-methylaminobenzoate though there is no IMHB present in methyl 2-aminobenzoate. This apparently anomalous result is supported by both MM and ab initio calculations.

The NMR method is much simpler and less time consuming than other methods for the assessment of IMHB. It provides a quantitative assessment of IMHB and can be applied to molecules with more than one hydrogen bond acidic group.

Keywords: Intramolecular hydrogen bonding; hydrogen bond acidity; water-solvent partition coefficients; linear free energy relationship; ^{1}H NMR chemical shifts

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1. Introduction

The identification and assessment of IMHBs is an important area in drug discovery. The presence of an IMHB can considerably influence the physicochemical and biochemical properties of a molecule, as pointed out on numerous occasions. [1, 2] The Cambridge structural data base has been surveyed [3] in order to investigate the propensity of various structures to form IMHBs. It was shown [3] that the highest frequency of IMHBs occurs with planar six-membered rings, followed by five-membered rings and some way back by seven-membered rings. Although this is a very valuable contribution to IMHBs, it does not deal with the assessment of IMHBs especially in compounds for which no crystallographic data exists.

Several methods have been employed for the assessment of IMHB, mostly based on the measurement of water-solvent partition coefficients, and particularly the difference between a water-octanol partition coefficient, *Poct*, and a water-non-polar solvent partition coefficient, *Pnon*, see Eq. 1. The first formulation of Δlog *P* used cyclohexane as the nonpolar solvent, [4] Eq. 2. The Δlog *Pcyc* property was later analysed [5] using the linear free energy relationship shown in Eq. 3, where *SP* is a solute/compound property such as a series of values of Δlog *Pcyc*

$$\Delta\log Pnon = \log Poct - \log Pnon \quad (1)$$

$$\Delta\log Pcyc = \log Poct - \log Pcyc \quad (2)$$

$$SP = c + e\,\mathbf{E} + s\,\mathbf{S} + a\,\mathbf{A} + b\,\mathbf{B} + v\,\mathbf{V} \quad (3)$$

In Eq. 3, the coefficients *c*, *e*, *s*, *a*, *b* and *v* characterize a given system and the independent variables **E**, **S**, **A**, **B** and **V** are properties or descriptors of the solutes used.[6] There have been numerous reviews of the application of Eq. 3, [6-11] and so we shall just define the solute descriptors as follows. **E** is the solute excess molar refractivity in units of $(cm^3\ mol^{-1})/10$, **S**

is the solute dipolarity / polarizability, **A** and **B** are the overall or summation hydrogen bond acidity and basicity of the solute and **V** is the solute McGowan characteristic volume in units of (cm^3 mol^{-1})/100. In Table 1 we give the coefficients for Δlog *Pnon* for a number of nonpolar solvents: hexane, [12] cyclohexane and benzene, [13] toluene [14] and chloroform. [15] That is Δlog *Phex* for hexane solvent is (log *Poct* – log *Phex*).

Table 1. Analysis of the coefficients in the LFER, Eqn 3, for Δlog *Pnon*

Solvent	Δ*c*	Δ*e*	Δ*s*	Δ*a*	Δ*b*	Δ*v*
Hexane	-0.245	0.002	0.656	3.612	1.479	-0.649
Cyclohexane	-0.071	-0.222	0.624	3.774	1.469	-0.763
Benzene	-0.054	0.098	-0.466	3.133	1.165	-0.677
Toluene	-0.037	0.131	-0.410	3.036	1.288	-0.710
Chloroform	-0.103	0.457	-0.651	3.146	0.054	-0.581

For all the Δlog *Pnon* systems in Table 1, the most important solute parameter is the **A**-descriptor, and it is not surprising that Δlog *Pchl*, that is with chloroform as the nonpolar solvent, has been used as a method of estimating the **A**-descriptor.[16] However, other solute parameters also make substantial contributions, and Δlog *Pchl* has also been used to obtain the hydrogen bond basicity for a series of substituted pyridines [17] for which **A** = 0.

2. Experimental Methods

Methyl 2-aminobenzoate and 2-aminoacetophenone were gifts from Professor J. C. Anderson (University College London), and methyl 2-methylaminobenzoate was a gift from Dr Boris Schilling (Givaudan Schweiz AG, Switzerland). 2-Chloroaniline and 2-methoxyaniline were purchased from Sigma Aldrich (Germany). 2-Methylaniline, 2-nitroaniline and 2-aminophenol were purchased from Sigma Aldrich (UK).

Proton nuclear magnetic resonance (1H NMR) spectra were recorded at 298K using Bruker Avance 400 spectrometer (BRUKER) operating at 400 MHz. The deuterated chloroform (CDCl3) and dimethyl sulfoxide (DMSO-d6) used as solvents were purchased from Sigma Aldrich (UK) and Cambridge Isotope Laboratories Inc respectively. ^{1}H NMR chemical shifts (δ, ppm) are reported relative to an internal reference tetramethylsilane (TMS). The chemical shifts were obtained over a range of concentration, from 200 mM down to 5 mM, and we checked in this range there was no dependence on concentration.

3. The assessment of IMHB

The most recent study on the use of Δlog *Pnon* for the assessment of IMHB used Δlog *Ptol* with toluene as the nonpolar solvent. [18] It was suggested that if Δlog *Ptol* is nearly zero, then this indicates the presence of an IMHB. However, in practice assessment of an IMHB is not so straightforward, and if more than one IMHB is present, then Δlog *Ptol* could be as high as 2.00. [18] The disadvantage of the Δlog *Ptol* method is that there is no mathematical relationship between Δlog *Ptol* and IMHB, and so any analysis of Δlog *Ptol* is just subjective. Instead of using the simple Δlog *Ptol* method a more rigorous method was then used in which a 'control' molecule was synthesized that was a model of the molecule under investigation but with no propensity to form an IMBH. [19] Log *Poct* and log *Ptol* were then determined both for the investigated and the control model, so that four water-solvent partitions have to be experimentally obtained, and a control molecule has to be synthesized. Two situations were considered:

I) Δlog *Ptol* of the control is larger than Δlog *Ptol* of the investigated compound. This indicates that the investigated compound has a high propensity to form an IMHB.

II) Δlog *Ptol* of the control is smaller than Δlog *Ptol* of the investigated compound. This indicates that the investigated compound has a low propensity to form an IMHB.

Results for the ortho-substituted anilines, compounds 6, 8 and 10, are given in Table 2 together with an assessment of IMHB. [19]

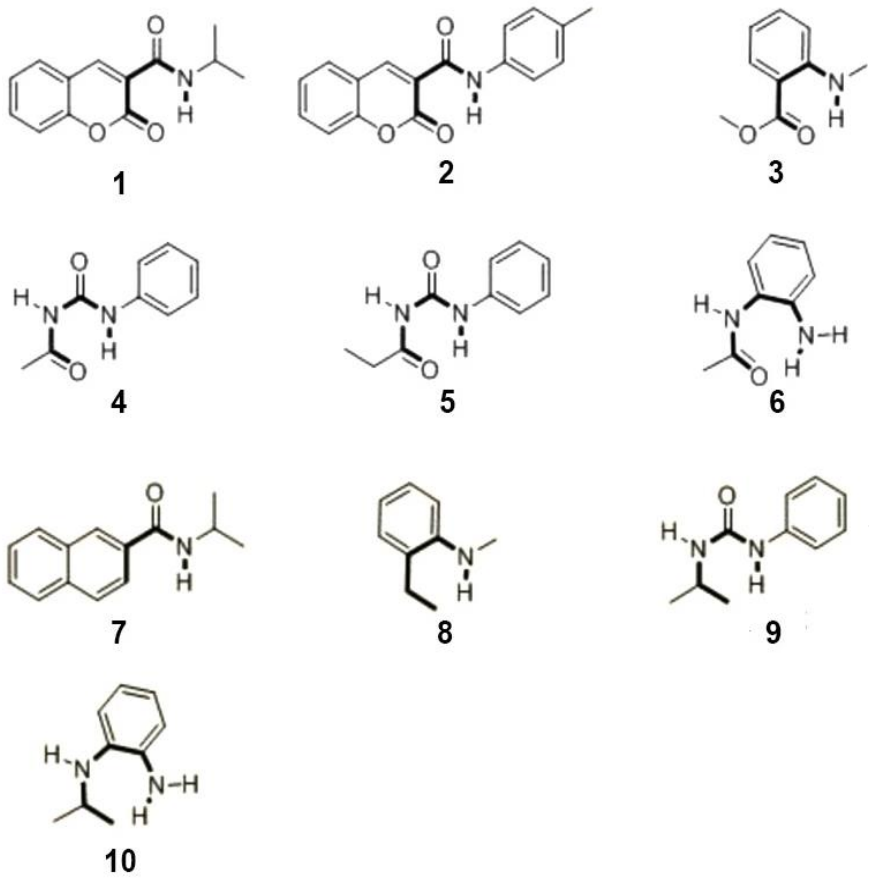

Figure 1. Compounds studied. [19]

(**1:** N-isopropyl-2-oxo-2H-chromene-3-carboxamide, **2:** 2-oxo-N-(p-tolyl)-2H-chromene-3-carboxamide, **3:** methyl 2-(methylamino)benzoate, **4:** N-(phenylcarbamoyl)acetamide, **5:** N-(phenylcarbamoyl)propionamide, **6:** N-(2-aminophenyl)acetamide, **7:** N-isopropyl-2-naphthamide, **8:** 2-ethyl-N-methylaniline, **9:** 1-isopropyl-3-phenylurea, **10:** N-1-isopropylbenzene-1,2-diamine)

Table 2. Results of using the "double Δlog *P*" method for the assessment of IMHB in ortho-substituted anilines. [19]

Solute	Δlog *Ptol*			IMHB [19]
	Compound	Control	Difference	
Compound 3	-0.76	-0.59 (8)	0.17	Yes
Compound 6	0.64	-0.32 (10)	-0.96	No
Compound 8	-0.59			(No)
Compound 10	-0.32			(No)

The "double Δlog *P*" method [19] seems to be a much sounder procedure than the simple Δlog *P* method. However, the "double Δlog *P*" is now requires the synthesis of a control molecule and the determination of four water-solvent partitions, two for the molecule under consideration, and two for the control molecule. In addition, the 'double Δlog *P'* method for the assessment of IMHB becomes very difficult to apply if the studied molecule contains more than one OH/NH group that could possibly be involved in an IMHB. Caron et al. [20] have used a new HPLC method to assess IMHB in a number of compounds, including the o-substituted aniline, No 11, Fig. 2, which was suggested to possess an IMHB.

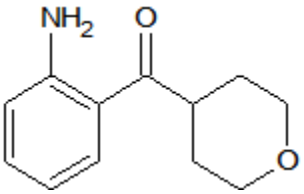

Figure. 2. Compound 11, studied by Caron *et al* [20]

Our NMR method for the assessment of IMHB is directly connected [6-11] to the solute descriptors shown in Eq. 3, where **A** is the hydrogen bond acidity of a given solute. Values of **A** are known for some 8,000 compounds (these are non-zero values) and software is available for the calculation of **A**, if necessary. [21, 22] The Helmholz data base and calculations [21] are freely available. We first showed [23] that NMR could be used to estimate the solute hydrogen bond acidity, **A**, in Eq. 3 through the difference in ^{1}H NMR chemical shifts of a protic hydrogen atom in solvents DMSO and $CDCl_3$, Eq. 4.

$$\Delta\delta = \delta(\text{DMSO}) - \delta(CDCl_3) \quad (4)$$

$$\mathbf{A} = 0.0066 + 0.133\ \Delta\delta - 0.128\ \text{IS} \quad (5)$$

These shifts were shown [23] to be linearly related to **A**-values for compounds that contained only one hydrogen bond acidic group through Eq. 5. In this equation, IS is an indicator variable for –SH groups, IS = 1 for an SH group and IS = 0 for OH and NH groups. The great

advantage of the NMR method is that Δδ can be determined for each OH, NH or SH group in a molecule separately, so that Eq. 5 can then be applied to each OH or NH group in order to assess the IMHB of that particular group. A study of 55 compounds containing an OH group and 60 compounds containing an NH group led to an assessment of IMHB in terms of the **A**-descriptor as shown in Table 3. [23, 24]

Table 3. Values of the **A**-descriptor in IMHB sites and in non-IMHB sites

Hydrogen bond acid	**IMHB**	**No IMHB**
Aromatic OH	< 0.1	> 0.50
Aliphatic OH	< 0.1	> 0.30
NH [a]	< 0.05	> 0.15

[a] Exclude aliphatic amines

An example of IMHB involving an NH group is the application [25] of the NMR method to a new hydrogen bond motif in peptides, [26] see Fig. 3. In Table 4 are details of the observed NMR chemical shifts, and our deduction as to whether the motif includes any IMHB, and if so, then how strong is the IMHB.

Table 4. Assessment of IMHB in the motif, Fig. 3, R = Me, R_1 = Et.

δ(DMSO)	10.56
δ(CDCl3)	10.44
Δδ (NH)	0.12
A	0.02
Assessment	Strong IMHB

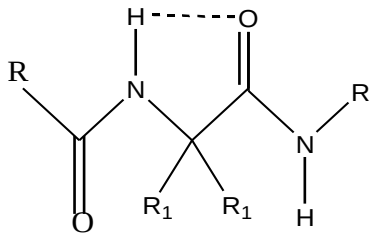

Figure. 3. A new hydrogen bond motif in peptides. [26]

In an interesting development, it has been shown [27] that it is not necessary to determine partition coefficients in two solvent systems to obtain an assessment of IMHB. A parameter denoted as H_M (obs) is obtained from an experimental determination of a water-alkane partition coefficient. Then a value of H_M is calculated from the hydrogen bonding capability of the polar atoms in the molecule, without considering any IMHBs. This gives H_M (calc) which is in effect a water-alkane partition coefficient if the molecule has no IMHB. It was then shown that H_M (calc - obs) was less than 2 units for a range of molecules that had no tendency to form IMHBs. H_M (calc - obs) was then taken as a measure of IMHB. If H_M (calc - obs) is large, say about 20 units, then a strong IMHB is present. If H_M (calc – obs) has an intermediate value of around 6 units then a weak IMHB is present, And if H_M (calc – obs) is near 2 units, then no IMHB is present. In Table 5 are summarized the chemical shifts that we have determined, with the observed NMR shifts in DMSO and in $CDCl_3$ together with the differences, Δδ. In Table 6 are given the assessments made from H_M (calc – obs), [27] together with assessments made from our NMR method, using the NMR shifts in Table 5.

Table 5. NMR shifts of some anilines in DMSO and in $CDCl_3$

Compound [a]	δ(DMSO)	δ($CDCl_3$)	Δδ
Aniline [b]	4.94	3.61	1.33
2-Methylaniline	4.75	3.58	1.17
2-Chloroaniline	5.29	4.02	1.27
2-Methoxyaniline	4.64	3.77	0.87
2-Aminoacetophenone	7.18	6.27	0.91
Methyl 2-aminobenzoate	6.64	5.71	0.93
Methyl 2-methylaminobenzoate	7.54	7.63	-0.09
2-Aminophenol (NH2)	4.45	3.61	0.84
2-Aminophenol (OH)	8.91	4.77	4.14

2-Nitroaniline	7.40	6.06	1.34
2-Aminoacetanilide (NH) [b]	4.85	3.85	1.00

[a] This work, see Experimental methods. [b] Ref. 24

Our NMR method, Table 5 and Table 6, shows that, with one exception, none of the ortho-substituted anilines that we have examined form IMHBs. Even 2-aminoacetanilide, with a potential 6-membered IMNB ring, does not form an IMHB. The exception is methyl 2-methylaminobenzoate that forms a strong IMHB, as found also before (Compound 3, Fig. 1). [19] This leaves a situation in which methyl 2-methylaminobenzoate forms an IMHB but methyl 2-aminobenzoate does not (see Table 6) even though they can both form the same 6-membered ring system. This apparently anomalous result is however supported by detailed inspection of the geometries of the two molecules. In both MM and ab initio calculations the C=O...H-N distance in the six-membered ring is significantly *shorter* in the 2-methylamino compound, see Figure 4, than in the 2-amino compound. (MM calcs 1.893 vs 1961 Å, ab initio 1.890 vs 1.945 Å), thus supporting our result.

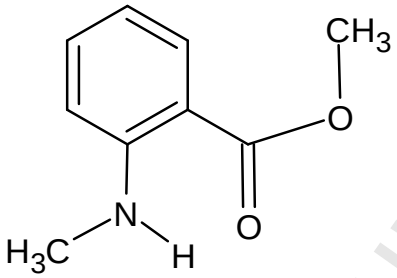

Figure 4. Methyl 2-methylaminobenzoate

The compounds studied by Chen et al. [27] have either no IMHB or have only one IMHB, and it is not clear how their method can be extended to the very important class of molecules that have more than one IMHBA. In Table 6 are given **A**-values for the $–NH_2$ and –OH groups in 2-aminophenol, as obtained from the chemical shifts given in Table 5, through Eqn. 4 and Eqn. 5. We can conclude that neither the NH_2 group nor the OH group in 2-aminophenol forms an IMHB.

Table 6. Assessments of IMHB made from the H_M method [27] and our NMR method

Compound	**H_M (calc – obs)**	**IMHB**	**A(NMR)**	**IMHB**
Aniline			0.18	None
N-Methylaniline			0.25	None
N-Phenylaniline			0.33	None
2-Methylaniline	-0.6	None	0.16	None
2-Nitroaniline	5.8	Weak	0.18	None
2-Chloroaniline	2.3	None	0.18	None
2-Methoxyaniline	3.8	None	0.12	None/weak
2-Aminoacetanilide			0.14	None
Methyl 2-aminobenzoate			0.13	None
Methyl 2-methylaminobenzoate			-0.01	Strong
2-Aminoacetophenone			0.13	None
2-Aminoacetamide (NH)			0.18	None
2-Aminophenol (NH2)			0.12	None/weak
Compound 11, Fig. 2				Medium [20]
2-Aminophenol (OH)			0.56	None

Conclusions

Both the simple Δlog *P* method, the double Δlog *P* method [19] and the H_M method [27] are more complicated, more time consuming and much less convenient than the NMR method that uses **A**-values for the assessment of the presence of intramolecular hydrogen bonds. [6-11] We show, just from the NMR shifts, that in several ortho-substituted anilines there is no IMHB present, but that there is a strong IMHB in methyl 2-methylaminobenzoate. In addition, the NMR method has a clear advantage in that it can be applied to molecules that contain several hydrogen bond acidic groups all of which may be capable of forming intramolecular hydrogen bonds.

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Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

We have no financial interests nor personal relationships that may be considered to be potential competing interests

Author Statement

Michael Abraham initiated the project and wrote the first draft of the manuscript, Raymond Abraham carried out the NMR calculations and was joint author of subsequent drafts, Xiangli Liu supervised the NMR work and was joint author of subsequent drafts, Amin Aghamohammadi and Kamyar Afarinkia carried out the NMR experiments.

Highlights

- NMR shifts in DMSO and CDCl3 determined
- Information on intramolecular hydrogen bonds, IMHBs, obtained
- ortho-Substituted anilines investigated
- Only methyl 2-methylaminobenzoate has an IMHB
- NMR method easier than methods based on partition coefficients