Scales of Hydrogen-bonding

Workshop

London, 1st - 3rd July 1987

Sponsored by the Office of Naval Research Branch Office, London

Final Report
About 25 chemists took part in the ONRL-sponsored workshop, "Scales of Hydrogen-bonding," held in London from 1 through 3 July 1987. The purpose of the gathering was to discuss current activities in setting up scales of both solute and solvent hydrogen-bond strength. The importance of solute hydrogen-bond scales in the understanding and prediction of effects in such diverse areas as solubilities in water and in blood, water-solvent partition coefficients, toxicological studies, and the response of chemical microsensor coatings to vapors. Work on scales of solute hydrogen-bond acidity and basicity is well advanced. Most of these scales are based on log K values for hydrogen-bond complexation in dilute solution—that is, they are nearly always Gibbs energy related scales. Theoretical work by I.H. Hillier (University of Manchester, UK) has demonstrated that such scales are likely to be more easily handled than scales based on enthalpies of complexation. Not so much work is ongoing in the area of solvent scales, and what work there is seems to be exclusively oriented to solvent hydrogen-bond basicity. P.-C. Maria and J.-F. Gal (University of Nice, France) described their multivariate analysis that leads to an angle δ, descriptive of the electrostatic:covalent ratio in the base:reference acid complex. M.H. Abraham (University of Surrey, UK) showed that it was possible to demonstrate the virtual equivalence of a solute scale and a solvent scale of hydrogen-bond basicity for nonassociated compounds, provided that the reference acids in each case led to δ values that were almost the same—around 65°.
WORKSHOP
SCALES OF HYDROGEN-BONDING

LONDON, 1st - 3rd July 1987

Sponsored by the Office of Naval Research Branch Office, London

FINAL REPORT
by

Dr. Michael H. Abraham

The Department of Chemistry
University of Surrey
Guildford, Surrey, GU2 5XH, U.K.
ACKNOWLEDGEMENTS

It is a pleasure to acknowledge the support of the Office of Naval Research Branch Office, London, without whose help the workshop could not have been held, and especially the contribution of the Scientific Director, Dr. David L. Venezky. The help of the secretarial staff at the Office of Naval Research Branch Office, London, over the organisation of the workshop in London, and of the secretarial staff at the University of Surrey in the general administration of the workshop is gratefully acknowledged.

Finally, I would like to thank all the participants for their individual contributions that helped to make the workshop so successful.

Michael H. Abraham
INTRODUCTION

Over the past few years, a large amount of work has been carried out on the correlation and prediction of solvent effects and, more recently, on solute effects. One of the most powerful methods used in this work has been that of multiple regression analysis, in which some solvent effect, or solute effect, is correlated with a number of parameters. In the case of a solvent effect, the most widely applicable and successful multiple regression equation is that based\(^1,2\) on the solvatochromic parameters of Kamlet and Taft:

\[
XYZ = XYZ_0 + s. \pi^* + a. a_1 + b. \delta_1 + h. \delta_H^2
\]  

(1)

Here, \(XYZ\) is some property to be correlated, and \(\pi^*, a_1, \delta_1, \) and \(\delta_H\) are the solvent dipolarity, hydrogen-bond acidity, hydrogen-bond basicity, and Hildebrand solubility parameter respectively. The constants \(XYZ_0\), \(s\), \(a\), \(b\), and \(h\) are found by multiple regression analysis. Although the \(\delta_H\) parameter is available through calorimetric enthalpies of vaporisation of solvents, or alternatively from vapour pressures, the so-called solvatochromic parameters \(\pi^*, a_1, \) and \(\delta_1\) need to be determined. By now, numerous values have been obtained, but there is still need for new values and for re-evaluation of already determined values of these parameters.

A similar situation exists in the correlation of a solute property, \(SP\), with parameters characteristic of the solute (the solvent now being a fixed quantity). Two general equations are currently in use, one being used for processes in condensed phases, equation \(2\)\(^3,4\) and the other for processes involving solute vapour + solute in a condensed phase, equation \(3\)\(^5\):

\[
SP = SP_0 + s. \pi^* + a. a_2 + b. \delta_2 + m. V_2
\]  

(2)

\[
SP = SP_0 + s. \pi^* + a. a_2 + b. \delta_2 + l. \log L
\]  

(3)

Now \(\pi^*, a_2, \delta_2, \) and \(V_2\) denote the solute dipolarity, hydrogen-bond acidity, hydrogen-bond basicity, and volume, and \(L\)\(^6\) is the solute Ostwald solubility coefficient on \(n\)-hexadecane at 298K. For general application of equations \(2\) or \(3\), these parameters must be available for a wide range of solutes. It is already the case that many such applications cannot be carried out fully because of lack of data especially in connection with the very important solute hydrogen-bond acidity and basicity scales, \(a_2\) and \(\delta_2\).
The aim of the present workshop was to draw together workers who were active in the construction of solute scales of hydrogen-bond acidity and basicity, or in the improvement of the already existing solvent scales, in the hope that some general agreement or co-operation could be achieved that would enable progress in these areas to be made. In addition to those chemists engaged on the various scales as such, a number of workers who were concerned with the use of hydrogen-bond scales were invited in order that their views could also be aired at the workshop.

A list of lectures follows, together with summaries kindly supplied by the lecturers. There was a considerable amount of discussion after each lecture, as well as an extended general discussion on the last day of the workshop. Much of the discussion after some of the lectures, especially those devoted to the detailed construction of hydrogen-bond scales, was repeated and extended in this general discussion. Hence a brief summary of the main discussion points is given for five lectures that were rather self-contained (those of Kamlet and Doherty, Morris and Taylor, Grate, Hillier and Gould, and Abboud), and the entire discussion following the remaining four lectures (those of Maria and Gal, Laurence and Nicolet, Prior, and Abraham, Grellier and McGill) is contained in the general discussion that follows the lecture summaries.


LECTURES

MORTIMER J. KAMLET AND RUTH M. DOHERTY
Parameter estimation rules for LSER

PIERRE-CHARLES MARIA AND JEAN-FRANCOIS GAL
Multivariate analysis of different kinds of basicity scales: contribution to the understanding of the hydrogen-bond interaction.

JEFFREY J. MORRIS AND PETER J. TAYLOR
Hydrogen-bonding scales for use in QSAR

CHRISTIAN LAURENCE AND PIERRE NICOLET
Hydrogen-bond basicity of alcohols

DAVID V. PRIOR
Construction of scales of solute hydrogen-bond acidity and basicity

JAY W. GRATE
The relevance of solute solubility properties to the absorption of vapours into chemical microsensor coatings

IAN H. HILLIER AND I.R. GOULD
Ab-initio MO calculations of hydrogen-bonding: comparison with experimental measurements

JOSE-Louis M. ABBoud
The hydrogen-bonding basicity of oxygen and sulphur compounds

MICHAEL H. ARRAHAN, PRISCILLA L. GRELLIER AND R ANDREW McGILL
A scale of solvent basicity, using only solvatochromic measurements
PARAMETER ESTIMATION RULES FOR LINEAR SOLVATION ENERGY RELATIONSHIPS

Mortimer J. Kamlet
Advanced Technology and Research, Inc., Burtonsville, MD, 20707, USA

Ruth M. Doherty
Naval Surface Weapons Center, White Oak Laboratory, Silver Spring, MD, 20910, USA

We have recently devised a set of rules for estimation of \( V_i \), \( \pi^* \), \( \delta_m \), and \( a_m \) of polycyclic aromatic hydrocarbons, polychlorinated benzenes and biphenyls, alkyl and halo-substituted phenols, anilines, and benzoic acids, and aliphatic carboxylic acids. These are consistent with earlier published experimental solvatochromic parameters, and have significantly expanded the data base of solubility, partition, HPLC, and toxicological properties that can be correlated by equation (1).

\[
XYZ = XYZ_0 + mV_i/100 + \pi^* + \delta + \beta_m + a_m [\pm \omega(mp - 25)] \tag{1}
\]

Recent correlations of the expanded data sets by equation (1) are summarized in Table 1; underlined values are not statistically significant at the 95% confidence level.

Some examples of the parameter estimation rules are given below, and an illustration of the effectiveness of these rules, used with equation (1), in correlating the aqueous solubility of a large number of environmentally important liquids and solids is shown in the Figure, where \( S_w \) is the molar solubility.

In equation (1), \( V_i \) is the solute intrinsic volume, \( \pi^* \) is the solute dipolarity, \( \delta \) is a polarisability correction term, and \( a_m \) and \( \beta_m \) are the solute monomeric hydrogen-bond acidity and basicity. The latter are sometimes denoted as \( a_m \) and \( \beta_m \).
SIMPLE PARAMETER ESTIMATION RULES

Polychlorobenzenes

- Chlorobenzene: \( V_I = 58.1, \pi^* = 0.71, \beta = 0.07 \)
- 1,2-Dichlorobenzene: \( V_I = 67.1, \pi^* = 0.80, \beta = 0.03 \)
- Other polychlorobenzenes: Add 9.0 to \( V_I \) for each chlorine. If additional chlorine increases dipole moment, add 0.05 to \( \pi^* \); if it decreases dipole moment, subtract 0.05. Subtract 0.04 from \( \beta \) for each addition Cl to minimum of 0.0

Polychlorobiphenyls

- \( V_I = 92.0 \) for biphenyl, add 9.0 to \( V_I \) for each chlorine.
- Calculate \( \pi^* \) and \( \delta \) separately for each ring, and use summation of \( \pi^*, \delta, \) and \( \beta \) values; i.e., \( \delta = 2.0 \) for biphenyl derivatives

Polycyclic Aromatic Hydrocarbons

- Naphthalene: \( V_I = 75.3, \pi^* = 0.70, \beta = 0.15 \)
- Add 6.55 to \( V_I \) for each additional C or CH in fused ring, e.g., add 26.2 for naphthalene to anthracene or phenanthrene; add 52.4 for naphthalene to triphenylene; add 36.3 for naphthalene to chrysene.
- For each additional fused aromatic ring, add 0.10 to \( \pi^* \); add 0.05 to \( \beta \).
- For addition of methyl, add 9.8 to \( V_I \); add 0.01 to \( \beta \); subtract 0.04 from \( \pi^* \)
TABLE 1. APPLICATION OF EQUATION (1) TO A NUMBER OF SOLUTE PROPERTIES

<table>
<thead>
<tr>
<th>Property</th>
<th>X</th>
<th>Y</th>
<th>Z</th>
<th>o</th>
<th>m</th>
<th>s</th>
<th>d</th>
<th>b</th>
<th>a</th>
<th>w</th>
<th>n</th>
<th>r</th>
<th>sd</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aqueous solubility, liquid aliphatic solutes (ex strong HBD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.05</td>
<td>-5.85</td>
<td>+1.09</td>
<td>+5.23</td>
<td></td>
<td></td>
<td>115</td>
<td>0.9944</td>
<td>0.153</td>
</tr>
<tr>
<td>Aqueous solubility, liquid and solid aromatic solutes (ex strong HBD)</td>
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<td></td>
<td></td>
<td></td>
<td>0.24</td>
<td>-5.30</td>
<td>+0.08</td>
<td>+3.99</td>
<td>-0.0096</td>
<td>147</td>
<td>0.9903</td>
<td>0.337</td>
<td></td>
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<tr>
<td>Octanol/water partition</td>
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<td></td>
<td>0.32</td>
<td>+5.35</td>
<td>-1.04</td>
<td>+0.35</td>
<td>-0.10</td>
<td></td>
<td>245</td>
<td>0.9959</td>
<td>0.131</td>
</tr>
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<td>Cyclohexane/water partition</td>
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<td></td>
<td></td>
<td></td>
<td>0.27</td>
<td>+6.73</td>
<td>-1.89</td>
<td>+0.64</td>
<td>-3.88</td>
<td></td>
<td>70</td>
<td>0.9932</td>
<td>0.187</td>
</tr>
<tr>
<td>CCl₄/water partition</td>
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<td></td>
<td></td>
<td></td>
<td>0.36</td>
<td>+6.35</td>
<td>-0.65</td>
<td>-0.01</td>
<td>-5.26</td>
<td>-3.26</td>
<td>50</td>
<td>0.9950</td>
<td>0.140</td>
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<td></td>
<td></td>
<td></td>
<td>0.11</td>
<td>+6.18</td>
<td>+0.03</td>
<td>+0.04</td>
<td>-3.61</td>
<td>-3.26</td>
<td>57</td>
<td>0.9934</td>
<td>0.163</td>
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<td></td>
<td></td>
<td></td>
<td>0.13</td>
<td>+6.27</td>
<td>-0.17</td>
<td>+0.29</td>
<td>-4.93</td>
<td>-3.02</td>
<td>54</td>
<td>0.9955</td>
<td>0.131</td>
</tr>
<tr>
<td>Diethyl ether/water partition</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.33</td>
<td>+5.79</td>
<td>-0.55</td>
<td>+0.24</td>
<td>-4.90</td>
<td>-0.29</td>
<td>46</td>
<td>0.9923</td>
<td>0.131</td>
</tr>
<tr>
<td>Tadpole narcosis</td>
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<td>-4.87</td>
<td>-0.48</td>
<td>+4.57</td>
<td>-0.65</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>39</td>
<td>0.9899</td>
<td>0.168</td>
</tr>
<tr>
<td>Nerve blocking, frog muscle</td>
<td>+4.04</td>
<td>-5.09</td>
<td>-0.56</td>
<td>+1.32</td>
<td>-0.28</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>20</td>
<td>0.9907</td>
<td>0.163</td>
</tr>
</tbody>
</table>
BENZENE DERIVATIVES

PYRIDINE AND BENZOPYRIDINE DERIVATIVES

POLYCYCLIC AROMATICS

EXPERIMENTAL log $S_w$

$\log S_w$ (CALC'D, eq. 1)
Laurence asked if results using the general solvatochromic equations had been compared to results using other possible combinations of parameters. Doherty replied by stating that for the correlation of solute effects there was almost no comparison to be made, but that in terms of solvent effects a few comparisons have been published (J. Org. Chem., 1981, 46 3053). Doherty stressed, however, that in comparing results from one set of parameters with those from another set, the general interpretation of the correlation was probably more important than minor statistical differences in the goodness-of-fit.
MULTIVARIATE ANALYSIS OF DIFFERENT KINDS OF BASICITY SCALES: CONTRIBUTION TO THE UNDERSTANDING OF THE HYDROGEN-BOND INTERACTION

Pierre-Charles Maria and Jean-Francois Gal

Laboratoire de Chimie Physique Organique, Universite de Nice - Parc Valrose 06034 Nice Cedex, France

Different kinds of basicity scales related to hydrogen bonding, proton transfer and interactions with hard and soft Lewis acids, including our - \( \Delta \text{H}_\text{AHC} \) scale, have been analysed by use of Principal Component Analysis. The first two factors account for about 95% of the total variance of the data, and may be used to quantify electrostatic/covalent contributions to the acid-base interaction.

In the first instance, these contributions depend on the studied physical property: \( \Delta \text{H}^\circ, \Delta \text{H}^\circ, \Delta \text{S}^\circ, \) spectroscopic shifts ... and on the nature of the reference acid.

For a particular physical property, even when we focus on hydrogen-bonding interactions, significant variations in the electrostatic/covalent behaviour arise from changes in the reference acid/solvent system. The medium effect shows up as a small electrostatic contribution.

Our multivariate analysis, based on Principal Component Analysis and Information Theory, allowed us to sort out many basicity scales, including various measures of the hydrogen-bond acceptor affinities, and to shed light on their relationships.

1. For molecules commonly used as solvents see:
   A more comprehensive list of about 300 \( -\Delta \text{H}^\circ \) is available from the authors.

**FA of the BASICITY**

- **The Data Matrix**
  - Objects: Weak to Strong Bases
  - Properties: Thermodynamic and Spectroscopic
  - Data: Reference Acids

- **Implicit Constraints**
  - Model: Linear

---

**SOLUTION/GAS PHASE RELATIONSHIPS**

- **Significance of $F_1$ and $F_2$**
  - $F_1$ is linear with Proton Affinities
    - Corrected for polarizability
  - COVALENT + ELECTROSTATIC contribution
  - $F_2$ is linear with $X^+$ Affinities
  - ELECTROSTATIC contribution

---

**Properties**

- Tolerable loss of information
- $n$ Principal Components (in CH)
- $n$ is the Dimensionality of the problem

---

**Data Matrix**

<table>
<thead>
<tr>
<th>Factors</th>
<th>$F_1$</th>
<th>$F_2$</th>
<th>$F_3$</th>
<th>$F_4$</th>
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</thead>
<tbody>
<tr>
<td>$F$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>62.14</td>
<td>17.19</td>
<td>4.54</td>
<td>1.00</td>
</tr>
<tr>
<td>2</td>
<td>69.35</td>
<td>99.85</td>
<td>100.00</td>
<td></td>
</tr>
</tbody>
</table>

---

**Correlation Coefficients**

<table>
<thead>
<tr>
<th>Variable</th>
<th>$r$</th>
<th>$r'$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$-\Delta H\text{H}_{\text{mix}}$</td>
<td>0.82</td>
<td>0.02</td>
</tr>
<tr>
<td>$\Delta H\text{H}_{\text{mix}}$</td>
<td>0.04</td>
<td>0.72</td>
</tr>
<tr>
<td>$X_{\text{pro}}$</td>
<td>0.65</td>
<td>0.01</td>
</tr>
<tr>
<td>$-\Delta H\text{H}_{\text{mix}}$</td>
<td>0.96</td>
<td>0.39</td>
</tr>
<tr>
<td>$X_{\text{elec}}$</td>
<td>0.57</td>
<td>0.13</td>
</tr>
</tbody>
</table>
How to use $F_1$ and $F_2$ for the study of H-Bonding

$$BDP = BDP_0 \cdot \sigma \cdot F_1 \cdot F_2$$

If a BDP is known for only a few bases, $S_1$ and $S_2$ are significant as long as $F_1$ and $F_2$ are orthogonal.

**H-BONDING SCALES**

Different Properties — Wide different behaviours evidenced by $\Theta$

- NO GENERAL SCALE

One Property
- Different Reference Acids

One Property
- Different Reference Acid
- Different Media

Small variations of $\Theta$

- ONE-PROPERTY SCALE

- Comprehensive Scale: "Wide range, low resolution"

- Restricted Scale: "High resolution"
HYDROGEN BONDING SCALES FOR USE IN QSAR

J.J. Morris and P.J. Taylor

(ICI Pharmaceuticals Division, Alderley Park, Macclesfield, Cheshire, SK10 4TG, UK)

In the multi-parameter Hansch equation (1) as used in QSAR, the electronic term is commonly modelled by Hammett's $\sigma$. This is entirely appropriate when varying the substituent affects either some general molecular property, eg. $pK_a$, or interaction with the receptor through a remote functional group. It is not appropriate when the substituent itself interacts with the receptor, eg. by formation of a hydrogen bond.

$$\log 1/C = a \log P - b(\log P)^2 + c(\text{electronic}) + d(\text{steric}) + \ldots \ (1)$$

We have therefore attempted to generate substituent scales of hydrogen bonding for use in QSAR. At the time this work began, in about 1979, it had no precedent and four chief problems quickly became apparent. Firstly, an unequivocal free energy scale is required to allow congruence with equation (1); it is not altogether clear from their derivation whether the Taft-Abboud-Kamlet (TAK) solvent $a$ and $b$ scales are true free energies or some blend of $\Delta H$ with $\Delta G$. Hence we need to measure equilibrium constants, though because of arguments which suggest that $\Delta S$ may be nearly a constant for the replacement of one (small) substituent by another, the ability simultaneously to generate enthalpy-based quantities could be an advantage. Secondly, we have to avoid solute self-association, since it is abundantly clear that, for example, $a$ and $b$ for bulk alkanols is no guide to the likely behaviour of OH in isolation. Thirdly, a single donor probe (for acceptors) and acceptor probe (for donors) is required that will place all members of each class on a common scale; it is inconvenient and could be misleading to use a range of standards. And fourthly, we need to work in a medium whose polarity is realistic in a biological context and that will dissolve the highly polar molecules that interest us; previous standard solvents, eg. CCl$_4$ and cyclohexane, fail in both respects. This problem has been solved by the use, for the first time in such studies, of 1,1,1-trichloroethane (TCE); the high polarity ($D=7.53$) of this otherwise totally inert solvent is on a par with octanol, has helped to
minimise solute self-association, and has allowed us to examine a much wider range of highly polar molecules than has hitherto been possible.

Proton acceptor strength (log K = pK_B) has been measured using p-nitrophenol (PNP) as standard probe. At the same time, we have derived a solute $S$ ($E_{sm}$) scaled to TPPO as unity. This methodology possesses features, therefore, derived both from TAK and the earlier Taft-Schleyer pK_{HB} scale. There was no useful precedent for a proton donor methodology. Here we use N-methylpyrrolidinone (NMP) in excess over the proton donor (this will generally destroy any residual self-association), measuring $K_0$ (log K = pK_A) either from the change in free $A_{OH}$ or $A_{NH}$ or by a titrational calorimetric technique (Drs M H Abraham and P P Duce, University of Surrey). Simultaneously we measure $\Delta u_c^{\circ}$ as a putative enthalpy-based quantity. In each series, the results are derived by a rigorous non-linear fitting procedure.

Many results for acceptors parallel previous investigations, though it is encouraging, for example, that alcohols and ethers now possess similar pK_B values. However, there are many new results: for example, sulphones are much weaker than sulphoxides and imides than amides, both being roughly on a level with esters. The known range of hetero-cycles has been greatly extended; here there is a partial correlation with basicity but with positive deviations due, at least in some cases, to the "a effect".

Among proton donors, most NH acids are weak, but the triazoles are as strong as phenol while tetrazole possesses the highest pK_A value yet to be measured. Unexpectedly, simple carboxylic acids are no stronger than phenol; while anion resonance in CO$_2^-$ may contribute to the explanation, the anomalous weakness of sulphonamides where this cannot be important suggests that the crucial factor may be lone pair repulsion between CO or SO$_2$ and the incoming proton acceptor. For OH or heterocyclic NH, this will be absent. These anomalies apart, pK_A relates much more simply than pK_B to pK_A, with alkanols and most NH donors lying close to a single line. Phenols however behave quite differently - the two lines cross; so far, this is not understood.

There is no single relation between pK_B and the general pK_{BH} scale of Abraham et al.; dipolar acceptors ($P = 0$ and $S = 0$), carbonyl, and heterocyclic N lie on three lines of increasing relative pK_B value and possibly
increasing slope (Figure 1). We regard this as an example of "solvent-induced partial ionisation" as identified by Taft in 1972, and since analysed as due to a solvent-dependent balance between electrostatic and covalent forces. Its effect is to make results in TCE unique so that our biochemically-targetted scales are not, except within limited series, interchangeable with others. There is even less of a single relation between $pK_B$ and $\theta_{sm}$ or between $pK_A$ and $\Delta u_{c=O}$. In the former (Figure 2), $pK_B$ for a given $\theta_{sm}$ is much less favourable for $sp^2$-nitrogen than for $sp$-oxygen. Since heterocycles possess a single, highly directional lone pair whereas the stereochemistry for the latter class is much less demanding, this strongly suggests an entropic origin for the difference, in which case $\theta_{sm}$ may be a measure of internal enthalpy. Deviations within series also suggest an entropic explanation. Similarly, while unhindered OH and NH donors fall on lines of different slope (Figure 3), negative deviations from either (lower $pK_A$ for a given $\Delta u_{c=O}$) appear to be associated with severe steric hindrance or stereoelectronic repulsion. Within series, therefore, $\Delta u_{c=O}$ may also be a measure of internal enthalpy. The difference in the lines may relate to the expected difference in bond length between any NH...B and OH...B pair (B=base); the latter should be the shorter, hence the greater responsiveness of $\Delta u_{c=O}$.

Finally we show a plot of $pK_A$ and $pK_B$ vs. $\theta$ (Figure 4): the result, a scattergram, may help to explain why the electronic term has appeared in so few successful correlations according to equation (1). We believe that its replacement by $pK_A$ or $pK_B$ may open up new possibilities for the medicinal chemist.
DISCUSSION ON MORRIS AND TAYLOR'S LECTURE

Gal asked if there was any complication from proton transfer when using 4-nitrophenol in TCE. Morris replied that no phenoxide ion can be seen, but if the solvent is made rather more polar, for example CH₂Cl₂, then phenoxide is indeed formed. Gal also enquired why the existing pK_HB scale was not used by Taylor, rather than developing a new pK₈ scale, but Taylor indicated that the use of a solvent such as TCE meant that many more interesting compounds of use to the medicinal chemist could be studied than with CCl₄, and that TCE is probably a better measure of receptor environment than is CCl₄. However, because of the solvent dependence of logK values, ICI would need to continue to use their pK₆ and pK₈ scales as distinct scales of solute hydrogen-bonding from those set up by Prior, for example.

Both Gal and Laurence were concerned with problems over polyfunctional compounds and multisite bases. Morris felt that there must be a new initiative set up to deal with the specific problem of what happens to the hydrogen-bond tendency of one site in a molecule after hydrogen-bonding to another site in the same molecule.

During his lecture, Taylor had shown a plot of pK₆ vs ν_C=O for complexation of acids with NMP in TCE. Abraham asked if such a plot showed family dependencies, and Morris replied in some detail indicating that within families where there was no steric hindrance, very good linear plots were obtained that could be used for the estimation of pK₆ values. Morris also noted that pyridines and ethers were much more susceptible to steric hindrance to hydrogen-bond complexation than were ketones, for example. Taylor followed this up by noting a very important set of results by Hine et al. (J. Org. Chem., 1986, 51, 577) that suggested that whereas ketones could form two hydrogen-bonds, pyridines, trialkylamines, and (very surprisingly) ethers formed only one hydrogen bond, in dilute solution in CCl₄.
HYDROGEN BONDING BASICITY SCALE OF ALCOHOLS

Christian Laurence and Pierre Nicolet

Lab. Spectrochimie Moleculaire University of Nantes

Water and alcohols are probably the most important of all solvents and their basicities are of great importance from practical viewpoints. There are, however, few thoroughly acceptable values for the basicities of the alcohols and water in solution. For example, by using hydrogen bonding to study basicity, Kamlet, Taft and co-workers have defined a $\beta$ scale of hydrogen bond acceptor basicity of a great number of organic solvents, but are particularly uncertain about the $\beta$ values for the alcohols and water. The differing $\beta$ values in the 1976-1986 literature are summarized in table I.

Table I. $\beta$ values of alcohols and water

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>$t$-BuOH</td>
<td>0.95 (0.91)</td>
<td>-1.01</td>
<td>-1.0</td>
<td>0.95</td>
<td>0.95</td>
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<td>(CF$_3$)$_2$CHOH</td>
<td>0.00</td>
<td>0.0</td>
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</table>

1 M.J. Kamlet and R.W. Taft, JACS, 1976, 98, 377. The first value refers to p-nitroaniline and the second to p-nitrophenol (vide infra).
The reasons for these unprecise values are (i) that the determination of these parameters involves unraveling three types of effects (polarity, acidity, and basicity) and (ii) that the HBA basicity of water and alcohols depends on the extent of their self-association. It is well known that monomeric alcohols (existing in dilute solutions in an inert solvent) are much less basic than polymeric alcohols existing in the bulk solvent. Kamlet, Taft and co-workers have defined a $\beta_m$ scale for monomeric alcohols as solutes while the $\beta$ scale is valid for alcohols as solvents.

We have first measured the HBA basicity of monomeric alcohols in very dilute solution in $CCl_4$ from the frequency shift $\Delta v(\text{OH})$ of MeOH.

In the presence of a hydrogen bond acceptor stronger than MeOH, the MeOH probe behaves as a hydrogen bond donor in the equilibrium:

$$CCl_4 + CH_3OH \rightleftharpoons CH_3OH + \text{ROH}$$

$$\Delta \nu(\text{OH}) = 3644 - \nu(\text{OH})$$

The $\Delta \nu(\text{OH})$ values are in the order expected from the inductive and polarizability effects of the R group, except for phenylethanol and glycol where intramolecular hydrogen bonding seems to increase the HB basicity. They agree well with (i) a $\Delta \nu(\text{OH})$ phenol scale in $CCl_4$ (M.H. Aslam, G. Collier, J. Shorter, J.C.S. Perkin II, 1981, 1572), (ii) a $\Delta \nu(\text{HF})$ scale in the gas phase (A.C. Legon, D.J. Millen, O. Schrems, J.C.S. Faraday, 1979, 592), and (iii) a thermodynamic logK scale for the association of 3,4-dinitrophenol with monomeric alcohols in cyclohexane (J.L.M. Abboud, K. Sraidi, G. Guiheneuf, A. Negro, M.J. Kamlet and R.W. Taft, J. Org. Chem. 1985, 50, 2870).

For the measurement of HBA basicity of alcohols less basic than methanol, we have chosen perfluoro-t-butanol, a very strong HBD alcohol, and a very inert medium (a perfluorinated compound, FC-75), hoping to attain the basicity of $CF_3CH_2OH$ and $(CF_3)_2CHOH$. The frequency shifts of the 3618 cm$^{-1} \nu(\text{OH})$ band of perfluoro-t-butanol, $\Delta \nu(\text{OH})$ pFtB, are significantly correlated with the $\sigma^*$ Taft's constant, and show clearly that $CF_3CH_2OH$ and $(CF_3)_2CHOH$ keep a residual HBA basicity.
The HBA basicity of pure alcohols has been measured by Kamlet and Taft by means of their solvatochromic comparison method (results in table I). We have revisited their results and measured new alcohols, with the following homomorphs:

![Chemical Structures](image)

Three types of hydrogen bonding, A (bathochromic), B (bathochromic) and C (hypsochromic) can be considered \((X = O, NH)\):

![Thermosolvatochromic Comparison Plots](image)

The thermosolvatochromic comparison plots for 1-2 (fig. 1) and 3-4 (fig. 2) show that 1-2 are better indicators of type B hydrogen bonding than 3-4: \(-\Delta\nu(1-2) < \Delta\nu(3-4)\).
lower than \(-\Delta A\nu(3-4)_{OH}^{H_2O}\) for \((CF_3)_2CHOH\) and \(-\Delta A\nu(1-2)_{H_2O}^{H_2O}\) values are less underevaluated for \(CF_3CH_2OH\) and \(H_2O\) than \(-\Delta A\nu(3-4)_{OH}^{H_2N}\). Another factor detrimental to the choice of 3-4 is the occurrence of type C hydrogen bond in 3 with \(CF_3CH_2OH\) and \((CF_3)_2CHOH\). However \(-\Delta A\nu(1-2)_{H_2O}^{H_2O}\) are certainly underevaluated for weakly basic alcohols because of the electron-releasing order:

\[
0^- > OMe > OH...\left(O\hat{C}^{R}_{H}n\right) > OH
\]

It is possible that for strongly basic alcohols this order becomes:

\[
0^- > OH...\left(O\hat{C}^{R}_{H}n\right) > OMe > OH
\]

which causes \(-\Delta A\nu(1-2)_{H_2O}^{H_2O}\) to be overevaluated for these alcohols.

These over and underevaluations of \(-\Delta A\nu(1-2)_{H_2O}^{H_2O}\) might explain the curvature of the \(-\Delta A\nu(1-2)\) vs. \(\sigma^+\) correlation (fig. 3).

These imperfect evaluations of HBA basicity of alcohols originate in the amphoteric nature of indicators 1 and 3. Since we want to reveal the basicity of alcohols, we have turned to a very acidic and very weakly basic indicator, trichloroacetic acid 5, which we have compared to methyl trichloroacetate 6 to unravel polarity from basicity effects of alcohols. In fact the carbonyl stretching wavenumber of 5 is lowered by type B hydrogen bonding \(CCl_3COOH...\left(O\hat{C}^{R}_{H}n\right)\). The infrared carbonyl stretching absorption of 5 and 6 in alcohols (examplified in figs. 4 and 5) can be understood on the basis of the following equilibria for solutions of 5 and 6 in pure alcohols:

\[
CCl_3C\equiv^O + (ROH)_n \rightarrow CCl_3C\equiv^O...\left(O\hat{C}^{R}_{H}n\right)
\]

\[
CCl_3C\equiv^O + (ROH)_n \rightarrow CCl_3C\equiv^O \rightarrow CCl_3C\equiv^O \hat{O} \ldots HO\hat{O}
\]

\[
CCl_3C\equiv^O \hat{O} \ldots \hat{O}(OH) \ldots \hat{O}(ROH)_{n} \rightarrow CCl_3C\equiv^O \hat{O} \ldots \hat{O}(ROH)_{n}
\]
An "infrared comparison method" allows to calculate the wavenumber shift 
$\Delta \nu(\text{CO})_{B-HO}$ from the equation (P. Nicolet, C. Laurence, M. Luçon, 
J.C.S. Perkin II, 1987, 483)

$$\Delta \nu(\text{CO})_{B-HO} = (1.1715 \nu_0 - 292.8) - \nu_B$$

They are satisfactorily correlated to $\sigma_B^*$. Unfortunately the 
CCl$_3$COOH probe does not allow to study (CF$_3$)$_2$CHOH (only 
7 and 10 are observed) and H$_2$O (because of decarboxylation and proton transfer).

**Acknowledgements**: We are indebted to Professor M. Berthelot for 
providing us with unpublished results and Mrs Luçon, Helbert and Sraïdi 
for assistance in the measurements.
CONSTRUCTION OF SCALES OF SOLUTE HYDROGEN-BOND ACIDITY AND BASICITY

David V. Prior
The Department of Chemistry, University of Surrey, Guildford, Surrey, GU2 5XH, UK

Although the hydrogen-bonding ability of solutes is known to be of vital importance in numerous physiochemical and biochemical processes,¹ no scale of hydrogen-bond strength has been constructed, for acids. We now find that hydrogen-bond complexation constants, as log K values, of a series of acids against reference bases in solvent CCl₄ can be used to define a scale of hydrogen-bond acidity. If log K values for a series of acids against a given base are plotted vs log K values for a series of acids against any other reference base, there results a set of lines that intersect at a point corresponding to log K = -1.1, when complexation constants are defined in terms of concentration in mol dm⁻³. An exactly similar result is obtained when a scale of hydrogen-bond basicity is constructed from log K values for a series of bases against reference acids in solvent CCl₄. We then generate a number of equations (1), where log Kᴵ represents hydrogen-bond complexation constants of a series of acids against a reference base in CCl₄.

\[ \log K^I = L_B \cdot \log K^{Hi}_A + D_B \] (1)

The constants L_B and D_B are characteristic of the reference base, and the log K^{Hi}_A values characterise the acids. These latter values thus constitute a scale of solute hydrogen-bond acidity. Forty-five equations of type (1) were constructed in which log K^I values for 89 acids against 45 reference bases were used. The forty-five equations contained a total of 738 data points (log K^I values): only acids that appeared in at least two equations were used in this primary set. All the 45 equations were constrained to intersect at the magic point with log K^I = log K^{Hi}_A = -1.1, and the resulting equations reproduced the 738 data points with a standard deviation of only 0.089 log units. The set of 45 equations and the 89 primary log K^{Hi}_A values define a reasonably general scale of solute hydrogen-bond acidity. A quite large number of secondary log K^{Hi}_A values may be obtained, usually from single point det-
erminations, giving a total of over 150 available log $K^H_A$ values. Certain combinations of acids and reference bases are excluded from the present analysis, specifically acids with Maria-Gal $^2 \theta$ values greater than about 75 degrees in combination with pyridines, aliphatic amines, and aliphatic ethers. These acids are usually weak acids such as pyrrole, indole, 5-fluoroindole, $\text{Ph}_2\text{NH}$, $\text{CHC}_3$, etc.

In order to develop a hydrogen-bond basicity scale, we now set up a series of equations (2), where $\log K^i$ is the complexation constant for a series of bases (i) against a reference acid in $\text{CCl}_4$. The constants $L_A$ and $D_A$ characterise the reference acid, whilst the $\log K^H_B$ values characterise the bases and thus represent a reasonably general scale of solute hydrogen-bond basicity.

$$\log K^i = L_A \log K^H_B + D_A \tag{2}$$

The scale is not completely general, because of the exclusion of certain acid-base combinations, as specified above. Using literature data on $\log K$ values in $\text{CCl}_4$ we set up a system of 32 equations (2), containing 937 $\log K$ values pertaining to no less than 194 bases (only bases that appeared in two or more equations were allowed in this primary set). As found for the corresponding equations leading to an acidity scale, all the 32 generated equations intersect at a given point, with $\log K = -1.1$ units. On forcing (slightly) all the equations through this magic point ($\log K = \log K^H_B = -1.1$) the 937 $\log K^i$ values could be reproduced with a standard deviation (sd) of only 0.079 log units. From the set of 32 equations, it is possible to obtain a large number of secondary $\log K^H_B$ values for bases that appear in only one equation, giving a total of over 500 $\log K^H_B$ values. Together with the 32 equations (2), it is now possible to predict some 16,000 $\log K$ values in $\text{CCl}_4$ to around 0.08 log units. The 500 $\log K^H_B$ values represent the first scale of solute hydrogen-bond basicity for which the generality is well-defined (c.f. the p$K_{\text{HB}}$ scale of Taft et al. $^3$).

We can show also that our acidity and basicity scales are fully compatible by noting that $L_B$ in equation (1) is related to $\log K^H_B$ in equation (2), and that $L_A$ in equation (2) is related to $\log K^H_A$ in equation (1), a clear demonstration of the importance of setting up general solute hydrogen-bond acidity and basicity scales along the same lines.


THE RELEVANCE OF SOLUTE SOLUBILITY PROPERTIES TO THE SORPTION
OF VAPORS INTO CHEMICAL MICROSENSOR COATINGS

Jay W. Grate

Naval Research Laboratory, Washington, D.C. 20375

A key component of many gas sensors is the chemical coating material which absorbs and concentrates the gas to be detected. Absorption of the gas can be modeled as a solute-solvent interaction, where the gas is the solute and the sensor coating is the solvent. This model has been very useful in understanding the behavior of surface acoustic wave (SAW) vapor sensors, which detect the mass of vapor absorbed into a soft polymeric stationary phase coating.

The solute hydrogen bonding properties, in particular, have been indicated as an important factor in determining the sensitivity and selectivity of SAW vapor sensors. Using pattern recognition techniques, the data from a variety of coating materials on SAW devices exposed to vapors with a full range of solubility properties were examined. Hierarchical cluster analysis demonstrated that vapors which could accept or donate hydrogen bonds were distinguished from non-hydrogen bonding vapors.

A better understanding of the factors influencing the sorption of gases and vapors into sensor coating materials would facilitate the development of gas sensors for specific applications. Indeed, one of the attractive features of sensors employing thin absorbent films is their potential to be adapted to a wide variety of gas phase analytical problems by strategic design or selection of the coating material. However, full realization of this potential will require methods to quantify, understand, and ultimately, to predict, the vapor/coating interactions responsible for vapor sorption.

Quantification of the equilibrium distribution of vapor between the gas phase and a sensor coating (stationary phase) can be achieved using a partition coefficient, $K$, which gives the ratio of the concentration of the vapor in the stationary phase, $C_s$, to the concentration of the vapor in the gas phase, $C_v$ (equation 1).
\[ K = \frac{C_s}{C_v} \] 

(1)

Partition coefficients are a particularly useful concept for thinking about SAW sensor responses because the sensor's response, a frequency shift, can be directly related to the partition coefficient by equation 2.

\[ f_v = f_s \frac{C_v K}{p} \] 

(2)

In this equation, \( f_v \) is the frequency shift caused by vapor absorbed into the coating, \( f_s \) is the frequency shift caused by the application of the coating to a bare device (and provides a measure of the amount of coating applied), \( C_v \) is the concentration of the vapor in the gas phase, \( K \) is the partition coefficient, and \( p \) is the coating material density. With this simple equation, partition coefficients can be calculated from SAW sensor data. Alternatively, if \( K \) is known from GLC measurements or solvatochromic correlation equations, then SAW sensor responses can be predicted.

The relationship between partition coefficients and SAW sensor responses was experimentally tested using the coating material 'fluoropolyol', which has proven in repeated testing to be a very well behaved and reproducible sensor coating. Polymer/gas partition coefficients calculated from sensor responses were compared with the same partition coefficients determined independently by GLC measurements, using fluoropolyol as the column stationary phase. The results are in good agreement, confirming the solubility model above.

The importance of solute solubility properties can be easily seen simply by examining the magnitudes of the partition coefficients for the vapors examined. The lowest \( K \) values were those of isooctane, a solute which is not dipolar, and cannot accept or donate hydrogen bonds. Somewhat more strongly sorbed are vapors such as dichloroethane and toluene, which are polarizable. However, these solutes are still incapable of hydrogen bonding. The vapors with the largest partition coefficients are exclusively those which are capable of hydrogen bonding.

Sorption isotherms can also be used to investigate solubility interactions. For the vapor dimethyl methylphosphonate, the sorption isotherm provides strong evidence for site-specific sorption of this
hydrogen bond acceptor vapor at hydrogen bond donating sites on the polymer.

A more complete and quantitative understanding of the solubility interactions responsible for vapor sorption into sensor coatings requires a numerical scale of vapor solubility properties, which is the subject of this workshop, and a means to quantitatively characterize the solubility properties of the coating materials. The latter problem is being addressed using equations of the form in equation (3).

\[
\log K = \text{constant} + s \pi^2 + a a + b b + l \log L
\]  

(3)

The equation correlates partition coefficients with vapor solubility properties. The coefficients \( s, a, b, \) and \( l \) characterize the solubility properties of the stationary phase. The individual terms in the equation allow individual solubility interactions to be sorted out and evaluated. In addition, these types of equations allow partition coefficients, and hence SAW sensor responses, to be predicted.

Full characterization of fluoropolyol and a variety of other sensor phases by equations of the form shown in equation (3) is well underway, and we hope to report more on this work soon. The final numerical values will be dependent on the establishment of standard scales for solute hydrogen bond donor strength and solute hydrogen bond acceptor strength. Thus, the subject of this workshop is very important to the full characterization and prediction of the behavior of gas-absorbing coating materials used on chemical microsensors.

Acknowledgements

The GLC measurements and development of correlation equations are carried out at the University of Surrey by Michael Abraham, R. Andrew McGill, and Pnina Sasson. SAW sensor research is carried out through the Naval Research Laboratory, and includes work by Arthur Snow, Susan Rose-Pehrsson, David Ballantine, and Hank Wohltjen.
DISCUSSION ON GRATE’S LECTURE

Morris asked if anything was known about the conformation of polymers used as sensor and GLC phases - are all polymer sites available for hydrogen-bonding on absorption of vapours? Abraham suggested that -OH groups in a polymer, for example, might act independently or might still be associated in some way in the polymer. In reply, Grate noted that both sensor and GLC results were obtained at low solute concentration (approx. zero for the GLC results) and that for the polymers studied probably nearly all the sites were available, since the experimental temperature was always above the polymer T_G value; the polymers might usefully be studied by FTIR to determine the nature of the -OH group. McGill suggested that many of the materials used by Grate would offer advantages as selective GLC phases. Grate agreed, saying that GLC phases now used were not very selective.
Ab initio molecular orbital (MO) calculations can now be used to study an increasing range of molecular systems and to predict, to a chemical accuracy, microscopic properties of such systems. In the case of hydrogen-bonding studies, these theoretical methods may be used

i) to determine the structure and energetics of hydrogen-bonded complexes;

ii) to determine spectroscopic properties of hydrogen-bonded complexes, particularly vibrational frequencies

and

iii) to provide data to allow for the inclusion of solvent effects using suitable models.

We have studied, from a theoretical viewpoint the system

\[ \text{XH} + \text{C} < XH \ldots \text{O} < \]

The proton donors (XH) studied include phenols, alcohols, carboxylic acids and anilides. The proton acceptor used here, formaldehyde, is taken to model N-methylpyrrolidinone. Calorimetric data for reaction (1) for these systems have been obtained by Abraham et al., using 1,1,1-trichloroethane and tetrachloromethane as solvent.

For the simplest example of reaction (1), (XH = H₂O), experimental data have been obtained for the vibrational frequencies of the hydrogen-bonded complex in an inert gas matrix at low temperature. In Table 1 we show the shifts in the frequencies of the vibrational modes of the proton donor and acceptor which occur on complex formation, obtained from ab initio MO calculations using various basis sets, together with the corresponding experimental values. Although the overall agreement between theory and
experiment is improved by basis set expansion, at the minimal basis level (STO-3G), the shift in the C=O stretching frequencies is well produced. With a range of proton donors of varying strengths, complexing with formaldehyde, we find, at the STO-3G level, that there is a linear relationship between the calculated intrinsic hydrogen bond strength and the calculated shift in the C=O frequency (see Figure 1) thus giving theoretical support for the use of this spectroscopic quantity as a measure of intrinsic hydrogen bond strength.

Turning now to the influence of solvent on the predicted enthalpy of the reaction (1), we use the reaction field continuum model\(^4\) to estimate the solvation energy of the proton donor (HX) and of the hydrogen bonded complex. We ignore the solvation of the common proton-acceptor, since this will not affect the relative values of \(\Delta H\), for different proton donors. In this simple model, the interaction energy (G) is given as

\[
G = \frac{-f^2}{2(1-fa)}
\]

Where

\[
f = \frac{2(\epsilon-1)}{(2\epsilon+1)a_s^3}
\]

Here \(a\) is the solute polarizability (estimated from atom additivity values\(^5\)), \(\mu\) the solute dipole moment (obtained from the MO calculation), \(\epsilon\) the solvent dielectric constant, and \(a_s\), the radius of the cavity in the solvent containing the solute (estimated from molecular dimensions).

The combination of solvation energies, calculated in this way, with the intrinsic hydrogen-bond strengths from the \(ab\) \(initio\) MO calculations, leads to the results shown in Figure 2. Here, pKa is \(\log_{10}\) of the experimental equilibrium constant for reaction (1). The trends shown in Figure 2 are in good agreement with the experimental data and help to rationalize data, which at first sight, are apparently somewhat random. These calculations have been further extended to explain the differing behaviour of measured enthalpies\(^1\) for reaction (1) in the two solvents \(\text{CCl}_4\) and \(\text{CH}_3\text{CCl}_3\).
This work was carried out in collaboration with ICI (Pharmaceuticals Division). We are particularly grateful for numerous discussions with Mr. P.J. Taylor, who suggested a theoretical investigation of the systems studied herein.

References


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SOLVENT - CH₃CCl₃

Figure 2
DISCUSSION ON HILLIER AND GOULD'S LECTURE

Taylor pointed out that the results of Hillier show that on transfer from a solvent such as CCl$_4$ to a solvent like 1,1,1-trichloroethane (TCE), measured enthalpies of hydrogen-bond complexation no longer have the same meaning. And this obtains even when calorimetrically determined $\Delta H^\circ$ values are used, let alone van't Hoff enthalpies. Hence it must be very much more difficult to generate a general hydrogen-bond acidity scale based on $\Delta H^\circ$ than on $\Delta G^\circ$.

The results of Hillier indicated that polar solvents interact with the proton donors (i.e. the phenols) producing large effects on $\Delta H^\circ$. Prior then referred to work carried out jointly by ICI Pharmaceuticals and the University of Surrey that confirmed experimentally the theoretical results of Hillier - on transfer from CCl$_4$ to TCE there were large changes in enthalpies of transfer of the phenols themselves with change in substituent, but little such effect on the phenol/NMP complexes.
THE HYDROGEN BONDING BASICITY OF OXYGEN AND SULPHUR COMPOUNDS

Jose-Luis M. Abboud


The hydrogen-bonding (H.B.) basicity parameters, $B_m$, for various "monomeric" alcohols and thiols as well as for a variety of carbonyl and thiocarbonyl amphiprotic bases have been determined. Also determined were the H.B. basicity parameters, $B$, for a series of aprotic carbonyl and thiocarbonyl bases ($B_m = 8$ for these materials). The analysis of the data for a set of 62 compounds provides the basis for a comparison of structural effects on the H.B. basicity of oxygen and sulphur bases.

In general, the H.B. basicity of sulphur bases is lower than that of their oxygen homologues. Within families, structural effects on the basicity of oxygen and sulphur bases are proportional. Our results show the contributions from polarizability, field/inductive and resonance effects to the basicity of these compounds. Also, some differential contributions from steric hindrance and hybridization changes have been singled out.

The $B_m$ values have been obtained from the equilibrium constants, $K_c$, pertaining to the formation of 1:1 complexes between these bases and phenols (ArOH):

$$K_c \text{ ArOH } + B \leftrightarrow \text{ ArOH...B}$$

in $CCl_4$ and/or cyclohexane.

The relationship between $B_m$ and $K_c$ is as follows:

$$\log K_c = a + bB_m + c\mu$$

where $a$, $b$ and $c$ are constants and $\mu$ stands for the molecular dipole moment of the base. Data for 3,4-dinitrophenol (1) in $cC_6H_{12}$ at 23.3°C, phenol (2), 4-fluorophenol (3) and p-chlorophenol (4) in $CCl_4$ at 25°C have been used.
The analysis of the $\beta_m$ values shows that in the case of amphiprotic thioamides, cyclic 1:1 complexes between these bases and p-chlorophenol can be formed. It is then possible to decompose the apparent $\beta_m$ values in two terms: one, $\beta_{tr}$, reflects the "true" (intrinsic) basicity of the thiocarbonyl group, while the other, $\beta_{cyc}$, provides a measure of the relative stability of the cyclic structures.
DISCUSSION ON ABOUD'S LECTURE

In the lecture, Abboud had shown that complexing constants in CCl₄, as logK, could be correlated through a simple plot against $\alpha_2 \cdot \beta_2$, where the latter represent the solute hydrogen-bond acidity and basicity. Prior noted that the plot seemed to include acid/base combinations such as pyridine/chloroform that were now known through the work of Maria and Gal to lie outside the general applicability of such plots. Abboud replied that the error in the predicted logK values was only around 0.07 log units, but Prior felt that in any extended application of the $\alpha_2 \cdot \beta_2$ equation, careful attention must be given to acid/base combinations that are known to be irregular.
A SCALE OF SOLVENT HYDROGEN-BOND BASICITY USING ONLY SOLVATOCHROMIC MEASUREMENTS

Michael H. Abraham, Priscilla L. Grellier, and R. Andrew McGill

The Department of Chemistry, University of Surrey, Guildford, Surrey GU2 5XH

The original solvent solvatochromic \( \beta \) scale of Kamlet and Taft\(^1\) has been used in the correlation and prediction of a large number of solvent effects. More recently, \( \beta \) values for nonassociated compounds have been used in the construction of a solute hydrogen-bond basicity scale, it being assumed that for such nonassociated compounds solute and solvent hydrogen-bond basicity can be put on the same (\( \beta \)) scale\(^2\). In order to test such an assumption it is necessary to compare two separate sets of hydrogen-bond basicities, (a) derived only from solvent properties, and (b) derived only from solute properties. Although a set of solute hydrogen-bond basicities is now available, obtained from log \( K \) values for hydrogen-bond complexation of monomeric solutes with reference bases in \( \text{CCl}_4 \),\(^3\) there is no set of solvent values that has been obtained only from solvent properties. It should be noted that the original \( \beta \) scale was constructed from five properties, two of which were solvatochromic solvent properties, and three of which were actually solute properties.\(^1\) It seemed therefore useful to attempt to construct a solvent \( \beta_1 \) scale based entirely on solvatochromic solvent properties, and then to compare such a scale with the already available solute hydrogen-bond basicity scale (denoted as \( \beta_2^H \)).

Following the work of Maria and Gal,\(^4\) it is evident that two basicity dependent properties will only show a family independent relationship if their Maria and Gal \( \beta \)-values are the same, or nearly the same. Hence a match between any solvent \( \beta_1 \) solvatochromic scale and the solute \( \beta_2^H \) scale is only possible if the \( \beta_1 \) scale leads to a value of around 68° (the value corresponding to the general solute \( \beta_2^H \) scale). Now it is already known\(^4\) that the solvatochromic indicator (4-nitrophenol/4-nitroanisole) leads to a value of only 2°, whereas the indicator (4-nitroaniline/4-nitrodimethyl-aniline) gives rise to a \( \beta \) value of 66°. Hence for the purpose of matching solute and solvent \( \beta \) scales, the technically better indicator 4-nitrophenol cannot be used. Rather than basing our solvent scale on just one aniline indicator, we used a double regression method based on equation (1).
We start with known values of $\pi^*$ for the solvents concerned, and set up $n$ equations of type (1), one for each indicator (note that results from two different workers using the same indicator are used to set up two separate equations). Results were available to yield $\beta_1$ values for 45 non-associated solvents using eleven equations for $\text{ArNH}_2$ indicators, and to give $\beta_1$ values for 39 non-associated solvents using seven equations for $\text{ArNHR}$ indicators. In all cases, our $\beta_1$ scale was set with reference compounds cyclohexane (0.00), acetone (0.48), and HMPT (1.00). For consistency we calculated $\pi^*_1$ values using only the results of Laurence and Nicolet on 4-nitroanisole and 4-nitrodimethylaniline. Values of $\pi^*_1$ obtained using 4-nitroanisole gave extraordinary $\beta_1$ values from equation (1), and these $\pi^*_1$ values were not further used. However, $\pi^*_1$ values calculated from the indicator 4-nitrodimethylaniline yielded reasonable values of $\beta_1$ via equation (1) and we shall discuss only results using this latter indicator.

Our first finding is that $\beta_1$ values obtained using the $\text{ArNH}_2$ indicators differed from those using the $\text{N}$-alkylated $\text{ArNHR}$ indicators. We analysed both sets of results using the Maria-Gal equation (2),

$$BDP = (BDP)_0 + S_1 F_1 + S_2 F_2$$

For the same fourteen non-associated solvent $\beta_1$ values, the resultant $S_1$ and $S_2$ values yielded $\beta$ values as follows: 71° (from $\text{ArNH}_2$ indicators), and 49° (from $\text{ArNHR}$ indicators), as compared to a value of 68° using the same fourteen compounds as solutes in $\beta_2^H$. Hence there is little point in comparing $\beta_1$ ($\text{ArNHR}$) with $\beta_2^H$, but it is possible the $\beta_1$ ($\text{ArNH}_2$) is essentially the same scale as $\beta_2^H$. Some comparisons are made in Table 1.

It can be seen from these, and other values that the two $\beta$ scales are, indeed, virtually identical - thus demonstrating that for non-associated compounds the solvatochromic $\beta_1$ ($\text{ArNH}_2$) solvent scale can be matched to the hydrogen-bond $\beta_2^H$ solute scale. However, there are a number of exceptions, the most outstanding being acetonitrile (0.30, 0.44) and tri-$n$-butylamine (0.42, 0.59). Even granted an error in $\beta_1$ ($\text{ArNH}_2$) of around 0.05, these $\beta_1$ ($\text{ArNH}_2$) values are much too low.
Table 1. A COMPARISON OF SOLVENT \( \beta_1 (ArNH_2) \) AND SOLUTE \( \beta^H_2 \) VALUES

<table>
<thead>
<tr>
<th>compound</th>
<th>( \beta_1 (ArNH_2) )</th>
<th>( \beta^H_2 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>chlorobenzene</td>
<td>0.09</td>
<td>0.13</td>
</tr>
<tr>
<td>toluene</td>
<td>0.15</td>
<td>0.15</td>
</tr>
<tr>
<td>1-bromobutane</td>
<td>0.14</td>
<td>0.20</td>
</tr>
<tr>
<td>anisole</td>
<td>0.23</td>
<td>0.27</td>
</tr>
<tr>
<td>diethylether</td>
<td>0.42</td>
<td>0.44</td>
</tr>
<tr>
<td>acetone</td>
<td>0.48</td>
<td>0.49</td>
</tr>
<tr>
<td>DMSO</td>
<td>0.76</td>
<td>0.77</td>
</tr>
<tr>
<td>HMPT</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>pyridine</td>
<td>0.63</td>
<td>0.62</td>
</tr>
<tr>
<td>triethylamine</td>
<td>0.54</td>
<td>0.66</td>
</tr>
</tbody>
</table>


GENERAL DISCUSSION

Throughout the discussion, considerable use was made of the results of Maria and Gal et al.\textsuperscript{1,2} who had analysed various basicity dependent properties, BDP, in terms of the principal component parameters $F_1$ and $F_2$, obtained from multivariate analysis of different kinds of basicity.

$$\text{BDP} = (\text{BDP})_0 + S_1 F_1 + S_2 F_2$$  (1)

Here, $F_1$ and $F_2$ characterise a number of bases, and the constants $(\text{BDP})_0$, $S_1$ and $S_2$ are obtained by multiple linear regression of some BDP against $F_1$ and $F_2$. Then $S_1$ and $S_2$ are used to define an angle $\theta = \tan^{-1} \left( \frac{S_2}{S_1} \right)$ that reflects the relative electrostatic: covalent ratio in the complexes of the series of bases against the reference acid used to establish the BDP. The importance of the angle $\theta$ is that two BDP's will only be linear with each other (i.e. will show family independent characteristics) if their respective $\theta$ values are the same, or nearly the same. Some values of $\theta$ for various BDP's are given in Table 1.

Table 1. Maria - Gal $\theta$ values

<table>
<thead>
<tr>
<th>$\Delta \Delta \nu$</th>
<th>4-nitroaniline, 4-nitrodimethylaniline</th>
<th>66</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\Delta \Delta \nu$</td>
<td>4-nitrophenol, 4-nitroanisole</td>
<td>2</td>
</tr>
<tr>
<td>$\log K$ against 4-nitrophenol in CCl\textsubscript{4}</td>
<td>67</td>
<td></td>
</tr>
<tr>
<td>$\log K$ against 4-fluorophenol in CCl\textsubscript{4}</td>
<td>70</td>
<td></td>
</tr>
<tr>
<td>$\log K$ against phenol in CCl\textsubscript{4}</td>
<td>67</td>
<td></td>
</tr>
<tr>
<td>$\log K$ against ethanol in CCl\textsubscript{4}</td>
<td>67</td>
<td></td>
</tr>
<tr>
<td>$\log K$ against water in CCl\textsubscript{4}</td>
<td>69</td>
<td></td>
</tr>
</tbody>
</table>

Another topic that influenced the general discussion considerably was that of methodology. Laurence argued that the best method of setting up any particular scale was to select a given reference compound as a primary standard. Thus if a solute scale of hydrogen-bond basicity is to be constructed, one given acid (suggested to be 4-fluorophenol) should be used as the primary standard. Both Prior and Abraham replied against this view. Prior pointed out that if such a method was adopted, any errors in the initial results with the primary standard could not be rectified.
Abraham claimed that such a method did not make use of all the available data, and that a much better method was the matrix method, in which a series of equations using (in the present example) results for bases against a number of acids is solved by an iterative method.

A possible resolution of this argument is as follows. If it is quite clear that for some technical reason one particular reference compound is much better than any other reference compound, then the methodology preferred by Laurence should be used. On the other hand, if there is no technical reason for choosing one particular reference compound out of a number of possible reference compounds, then the methodology advocated by Prior and by Abraham should be used.

Scales of solute hydrogen-bond acidity and basicity

Three scales of solute hydrogen-bond acidity were described at the workshop, (1) the general matrix-generated scale of the University of Surrey/ICI Group described by Prior, (2) the special scale of Abboud using the reference system pyridine-N-oxide/cyclohexane, and (3) the special scale of Taylor and Morris using the reference system NMP/TCE. Taylor pointed out that the latter scale ($pK_a$) was used exclusively in QSAR work, and that the relationship between $pK_a$ and Prior's scale had yet to be worked out; there should be no confusion between the two scales and, indeed, ICI would use Prior's scale for general (non-QSAR) purposes.

Unlike the construction of a solute hydrogen-bond acidity scale, that of a solute hydrogen-bond basicity scale can logically be based on the results of Maria and Gal.1,2 Nearly all the use of multiple regression analysis via equations (2) and (3) in the introduction is concerned with solute bases hydrogen-bonded to oxygen acids, for example water, octanol, octanol/water, ethylene glycol, etc. Now all these acids give rise to Maria-Gal $\theta$ values of around 60-70°, and hence the reference acid or acids used in the construction of a solute hydrogen-bond basicity scale should lead also to a similar $\theta$ value. If not, then some extra parameter will be needed to match up the derived scale to the experimental values to be analysed - an inconvenient procedure, to say the least. In the event, two scales were described, each giving rise to suitably useful $\theta$ values. Laurence advocated a scale tied exclusively to 4-fluorophenol as a reference.
acid in CCl₄, using logK values for hydrogen-bond complexation a θ value of 70° is found. Prior put forward a general scale, again using logK values for hydrogen-bond complexation in CCl₄, but now generated from a large number of reference acids by the matrix method. This scale gives rise to a θ value of 68° so that for practical purposes, as pointed out by Abraham, the two scales are almost equivalent.

It was agreed that Laurence and Abraham would investigate the possibility of setting up just one solute hydrogen-bond basicity scale, using logK values for complexation in CCl₄. Following any firm decision would be subsequent possible work on secondary (non-thermodynamic) processes that might conceivably be matched to the above solute scale.

Scales of solvent hydrogen-bond acidity and basicity

There was practically no discussion on solvent acidity scales, but considerable argument over solvent basicity scales. Abraham, McGill, and Grellier had shown by the matrix method that it was possible to construct a purely solvatochromic solvent hydrogen-bond basicity scale for nonassociated compounds using aniline (ArNH₂) indicators. This scale gave a θ value of 71°, quite close to the θ value for the solute scale described by Prior (68°). Although there were rather large error limits for the solvent scale, the solvent and solute scales could be reasonably well matched and, indeed, could be matched to the θ scale used by Kamlet for nonassociated compounds.

Laurence argued strongly that any solvent θ scale should be based on 4-nitrophenol indicator and not on aniline indicators, since 4-nitrophenol was technically by far the best indicator to use (because there is less fine structure, the peak maximum is much easier to locate, and the peak shape is more Gaussian). Furthermore, use of 4-nitrophenol indicator enables much more accurate θ values to be obtained for solvents water and alcohols. Of course, use of only 4-nitrophenol means that the homomorphism method has to be used, using 4-nitroanisole, but Laurence argued that this "one-indicator" method was still technically the best method.

Abraham pointed out that because the 4-nitrophenol indicator gives rise to θ = 2° (see Table), whereas ArNH₂ indicators lead to a θ value of 71°, a solvent basicity scale using 4-nitrophenol indicator would show family dependencies against a solvent basicity scale using
$\text{ArNH}_2$ indicators (and for nonassociated compounds similar family dependencies against the general solute scale described by Prior). Sasson asked whether the difference in the two solvent scales was large enough to reverse the order of solvent basicity, and Prior replied that that was indeed the case. McGill pointed out that because of overlapping peaks, 4-nitrophenol could not be used with all solvents, so that $\text{ArNH}_2$ indicators would still have to be used as secondary standards. Shuely suggested that in future, solvent basicity scales with $\theta = 2^\circ$ and with $\theta = 70^\circ$ might both be needed, depending on the process to be studied; Gal agreed, citing proton transfer as a case in point. Abboud then attempted to resolve the problem by the suggestion that if a primary solvent basicity scale was constructed using the homomorphism method with 4-nitrophenol/4-nitroanisole, transfer rules could be set up (e.g. by use of the Kamlet-Taft $\xi$ parameter) to convert this scale with $\theta = 2$ to the secondary solvent basicity scale with $\theta = 68^\circ$. It was agreed that Laurence would set up such a primary scale and that Abboud and Abraham in conjunction with Kamlet, Doherty, and Taft would attempt to convert the scale, through transfer rules as outlined above, to a solvent basicity scale giving rise to $\theta$ around 70°.

Finally, it should be noted that indicators of type $\text{ArNHR}$ give rise to a solvent basicity scale with $\theta$ of about 49°. Abboud suggested that $\text{ArNHR}$ indicators were technically better than $\text{ArNH}_2$ indicators. Abraham pointed out that a solvent hydrogen-bond basicity scale using $\text{ArNHR}$ indicators would still show family dependences against the $\text{ArNH}_2$ established scale, and Laurence noted again that 4-nitrophenol indicator was to be preferred over the $\text{ArNHR}$ indicators so that use of the $\text{ArNHR}$ indicators would still give rise to the difficulties mentioned previously with the $\text{ArNH}_2$ indicators.


PARTICIPANTS

Dr David L Venezky
Office of Naval Research
223/231 Old Marylebone Road
London
NW1 5TH

Dr Michael H Abraham
Dr Priscilla L Gellatly (ne Grellier)
Dr Gabriel J Buist
Dr Graham Webb
Dr Pnina Sasson
Mr R Andrew McGill
Mr David V Prior

Dr Jeffery J Morris
Mr Peter J Taylor
ICl Pharmaceuticals Division
Mereside Alderley Park
Macclesfield
Cheshire
SK10 4TG
U.K.

Dr Ian H Hillier
The Department of Chemistry
University of Manchester
Manchester
U.K.

Dr Christian Laurence
Laboratoire de Spectrochimie Moleculaire
Ex-Faculte des Sciences
2 Rue de la Houssiniere
44072 Nantes cedex 03
FRANCE

Dr Pierre-Charles Maria
Dr Jean-Francois Gal
Laboratoire de Chimie Physique Organic
Universite de Nice
Parc Valrose
06034 Nice cedex
FRANCE

Dr Jose-Louis M Abboud
Consejo Superior de Investigaciones Cientificas
Instituto de Quimica Fisica Rocasolano
Serrano 119-28006
Madrid
SPAIN
Dr Ruth M. Doherty
Naval Surface Weapons Centre
White Oak Laboratory
Silver Spring
Maryland, 20910
U.S.A.

Dr Jay W. Grate
Chemistry Division
Naval Research Laboratory
Washington DC
20375-5000
U.S.A.

Dr Wendel J. Schuely
U.S. Army Chemical Research
Development and Engineering Center
Aberdeen Proving Ground
Maryland 21010
U.S.A.

Dr Mortimer J. Kamlet
Advanced Technology and Research Inc.
3933 Sandy Spring Road
Burtonsville
Maryland 20866
USA

Dr N. F. Franks
Dr W. R. Lieb
The Blackett Laboratory
Prince Consort Road
London
SW7 2BZ

Dr John C. Dearden
School of Pharmacy
Liverpool Polytechnic
Byrom Street
Liverpool
L13 AF

Dr David Brooke
Princes Risborough Laboratory
Building Research Establishment
Department of the Environment
Princes Risborough
Aylesbury
Bucks
U.K.