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Lipophilicity of the Nitrophenols

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The lipophilicity of the nitrophenols, expressed as a water−solvent partition coefficient, *P*, has been investigated using the solvation equation, $\log P = c + eE + sS + aA + bB + vV$. It is shown that this equation accounts quantitatively for lipophilicity in a selection of water−solvent systems, viz: octanol, 1,2-dichloroethane, and cyclohexane. In the latter two systems, the major factor in the increased lipophilicity of 2-nitrophenol over 3- and 4-nitrophenol is the lack of hydrogen bond acidity of 2-nitrophenol. The water−octanol system differs in that the *a* coefficient is effectively zero, so that hydrogen bond acidity of solutes plays no part, and the three mononitrophenols then have similar lipophilicities. The dinitrophenols and picric acid are similarly discussed. The hydrogen bond acidity of 2,3-dinitrophenol (0.67) is very much larger than that of 2,4- or 2,5-dinitrophenol (0.09 and 0.11), indicating a very much reduced internal hydrogen bonding. A similar but much smaller effect occurs with 2,6-dinitrophenol ($A = 0.17$). Picric acid has a moderate hydrogen bond acidity (0.46) so that the phenolic OH is still available for external hydrogen bonding. These results are confirmed by ab initio calculations which show that 2,3- and 2,6-dinitrophenol and picric acid are significantly distorted away from planarity, which apparently disrupts their internal hydrogen bonding.

Introduction

The lipophilicity of a compound may be defined as log *P*, where *P* is a water−solvent partition coefficient. The first such solvent to be used was olive oil,[1,2] but later workers [3−6] used a variety of solvents such as oleyl alcohol.[3] Following the work of Hansch and Leo,[7−11] octanol became the standard solvent,[12] although, again, partition coefficients in several other water−solvent systems have been suggested as providing scales of lipophilicity or as model solvents.[13,14] Girault et al.[15] have recently measured log *P* values for phenol and the mononitrophenols in the water−1,2-dichloroethane (DCE) system and have shown that 2-nitrophenol is much more lipophilic than the 3- or 4-nitrophenol, see Table 1. This is the case for most aprotic solvents, for example, cyclohexane,[16] but is not so for octanol; the value of $\log P_{\mathrm{OCT}}$ is almost the same for the three nitrophenols. Girault et al.[15] rather carefully analyzed the $\log P_{\mathrm{DCE}}$ values for nitrophenols using a solvatochromic equation that includes descriptors for solute hydrogen bond acidity, α, and solute hydrogen bond basicity, β. They concluded that nitrophenols with intramolecular hydrogen bonding deviate from the solvatochromic equation and suggested that "...the hydrogen bond donor capacity for these compounds is not expressed in the water−DCE system."

Table 1. Coefficients in Eq 1 for Partition between Water and Solvents

solvent	*c*	*e*	*s*	*a*	*b*	*v*
octanol	0.088	0.562	−1.054	0.034	−3.460	3.814
1,2-dichloroethane	0.277	0.278	−0.167	−2.816	−4.324	4.205
cyclohexane	0.159	0.784	−1.678	−3.740	−4.929	4.577

Since lipophilicity is such an important property, and since equations that use hydrogen bond acidity and basicity as solute descriptors are in common use, it seemed very important to ascertain if these equations do or do not yield any insight into the factors that influence lipophilicity.

Rather than use the solvatochromic system favored by Girault et al.,[15] we much prefer to use our "solvation equation",[17]

$$\log P = c + eE + sS + aA + bB + vV \qquad (1)$$

for a number of reasons. First, the solvatochromic parameters were originally obtained from solvatochromic shifts of indicators in solvents,[18] and so solvent parameters are being used as surrogate solute parameters.

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[1] Overton, E. *Studien uber die Narkose*; Fischer: Jena, Germany, 1901.

[2] Meyer, H. *Arch. Exp. Pathol. Pharmakol. (Nauyn-Schmiedebergs)* **1899**, *42*, 109−118. Meyer, H. *Arch. Exp. Pathol. Pharmakol. (Nauyn-Schmiedebergs)* **1901**, *46*, 338−346.

[3] Meyer, K.H.; Gottlieb-Billroth, H. *Z. Physiol. Chem.* **1920**, *112*, 55−79.

[4] Collander, R.; Barlund, H. *Acta Bot. Fenn.* **1933**, *11*, 1−112.

[5] Collander, R. *Acta Physiol. Scand.* **1947**, *13*, 363−381.

[6] Collander, R. *Physiol. Plantarum* **1954**, *7*, 420−445.

[7] Hansch, C.; Maloney, P. P.; Fujita, T.; Muir, R. M. *Nature* **1962**, *194*, 178−180.

[8] Hansch, C.; Fujita, T. *J. Am. Chem. Soc.* **1964**, *86*, 1616−1626.

[9] Hansch, C. *Acc. Chem. Res.* **1969**, *2*, 232−229.

[10] Leo, A.; Hansch, C.; Elkins, D. *Chem. Rev.* **1971**, *71*, 525−616.

[11] Leo, A.; Hansch, C. *J. Org. Chem.* **1971**, *36*, 1539−1544.

[12] Buchwald, P.; Bodor, N. *Curr. Med. Chem.* **1998**, *5*, 353−380.

[13] Dearden, J. C. *Environ. Health Perspect.* **1985**, *61*, 203−228.

[14] Leahy, D. E.; Taylor, P. J.; Wait, A.R *Quant. Struct.−Act. Relat.* **1989**, *8*, 17−31.

[15] Chopineaux-Cortois, V.; Reymond, F.; Bouchard, G.; Carrupt, P.-A.; Testa, B; Girault, H. H. *J. Am. Chem. Soc.* **1999**, *121*, 1743−1747.

[16] Abraham, M. H.; Chadha, H. S.; Whiting, G. S.; Mitchell, R. C. *J. Pharm. Sci.* **1994**, *83* 1085−1100.

[17] Abraham, M. H. *Chem. Soc. Rev.* **1993**, *22*, 73−83.

[18] Kamlet, M. J.; Doherty, R. M.; Abboud, J.-L. M.; Abraham, M. H.; Taft, R. W. *CHEMTECH* **1986**, *16*, 566−576.

10.1021/jo000840w CCC: $19.00

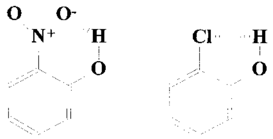

Figure 1. Intramolecular hydrogen bonding in 2-nitrophenol and 2-chlorophenol

Table 2. Descriptors in Eq 1 for Phenol, Nitrophenols, and Chlorophenols

solute	E	S	A	B	V
phenol	0.805	0.89	0.60	0.30	0.7751
2-nitrophenol	1.015	1.05	0.05	0.37	0.9493
3-nitrophenol	1.050	1.57	0.79	0.23	0.9493
4-nitrophenol	1.070	1.72	0.82	0.26	0.9493
2,3-dinitrophenol	1.200	1.48	0.67	0.42	1.1235
2,4-dinitrophenol	1.200	1.49	0.09	0.56	1.1235
2,5-dinitrophenol	1.260	1.45	0.11	0.54	1.1235
2,6-dinitrophenol	1.220	2.04	0.17	0.48	1.1235
3,4-dinitrophenol	1.320	2.25	1.14	0.16	1.1235
3,5-dinitrophenol	1.320	2.18	1.05	0.16	1.1235
2,4,6-trinitrophenol	1.430	2.66	0.46	0.42	1.2977
2-chlorophenol	0.853	0.88	0.32	0.31	0.8975
3-chlorophenol	0.909	1.06	0.69	0.15	0.8975
4-chlorophenol	0.915	1.08	0.67	0.20	0.8975

Second, the solvatochromic parameters reflect spectroscopic energies; since log P values are free-energy related, it is more correct to use free-energy related properties as descriptors. Third, there is no protocol for the determination of further solvatochromic “solute” parameters. In eq 1, the descriptors S, A, and B are all derived from equilibrium measurements,[17] and so are rigorously free-energy related. The independent variables in eq 1 are solute descriptors as follows:[17] we use a simplified terminology and give the original symbols in parentheses. E (R_2) is the solute excess molar refractivity, S (π_2^{H}) is the solute dipolarity/polarizability, A ($\Sigma\alpha_2^{H}$) and B ($\Sigma\beta_2^{H}$) are the overall or summation hydrogen bond acidity and basicity, and V is the McGowan characteristic volume[19] in units of (mol dm^{-3})/100.

The aim of this paper is to apply eq 1 to log P values for the mononitrophenols in water−solvent systems, including DCE, to ascertain whether the equation can account quantitatively for the values of log P and then to deduce exactly the role of hydrogen bonding in the lipophilicity of the nitrophenols.

Results and Discussion

The coefficients in eq 1 are given in Table 1 for partitions between water and octanol,[16] cyclohexane,[16] and DCE.[20] As pointed out previously,[15−17] the a-coefficient for the water−octanol system is effectively zero, in contrast to the large a-coefficients for log P_{CYC} and log P_{DCE}. Descriptors for phenol and nitrophenols[17] are in Table 2, together with those for the monochlorophenols.[17] The values for 2-nitrophenol are interesting in that intramolecular hydrogen bonding, as in Figure 1, reduces the ability to donate a hydrogen bond to an external base almost to zero. In addition, the dipolarity/polarizability of 2-nitrophenol is much less than that of the 3- or 4-nitrophenols, as expected from the comparatively low dipole moment of 2-nitrophenol. More unexpected is the increase in hydrogen bond basicity of 2-nitrophenol over the 3- or 4-nitrophenols. Because our method provides estimates of the overall hydrogen bond basicity of a compound, and not estimates of the individual functional group basicities, we cannot attribute the increase in basicity to any particular functional group. However, by comparison with the three chlorophenols (Table 2), where the increase in basicity of 2-chlorophenol over 3- and 4-chlorophenol can only arise from the phenolic oxygen, we suggest that the effect in 2-nitrophenol is also the result of the increased basicity of the phenolic oxygen due to internal hydrogen bonding.

Table 3. Observed and Calculated Lipophilicity of Phenols and Nitrophenols as Values of log P

solvent	phenol	2-	3-	4-	2,3-	2,4-
octanol log P(obs)[a]	1.50	1.79	2.00	1.91	2.08	1.55[b]
octanol log P(calc)	1.54	1.89	1.88	1.63	2.06	1.54
DCE log P(obs)[c]	0.61	2.81	0.92	0.72		2.46
DCE log P(calc)	0.58	2.59	1.03	0.80	1.34	2.36
cyclohexane log P(obs)[d]	−0.80	1.51	−1.44	−1.86	−0.81	0.54[e]
cyclohexane log P(calc)	−0.89	1.54	−1.44	−1.94	−0.82	0.64

solvent	2,5-	2,6-	3,4-	3,5-	2,4,6-
octanol log P(obs)	1.75	1.25	2.23[f]	2.36	1.64[g]
octanol log P(calc)	1.69	1.25	2.23	2.30	1.60
DCE log P(obs)	2.49				
DCE log P(calc)	2.42	2.40	1.04	1.31	2.53
cyclohexane log P(obs)	0.71[f]	−0.17[f]	−2.48[f]	−2.07[f]	
cyclohexane log P(calc)	0.78	−0.17	−2.49	−2.04	−1.03

[a] log P^* values from ref 21. [b] This work; log $P^* = 1.67$, but other recorded values are 1.51, 1.54, 1.55, 1.56, 1.59, and 1.79.[21] [c] Reference 15. [d] Reference 21; average value where more than one value is recorded. [e] Average value of 0.46 (this work), 0.46,[21] and 0.76[21]. [f] This work. [g] See Table 5.

These intramolecular interactions have marked influences on the lipophilicity of the phenols. Values of log P in three water−solvent systems are in Table 2, some from Girault et al.,[15] some from the MedChem database, [21] and some we have determined by the “shake flask” method at pH 2.6 to suppress ionization. The corresponding calculated log P values can be obtained from the equation coefficients in Table 1 and the descriptors in Table 2 and are also in Table 3. There is excellent agreement between calculated and observed values of log P in all three systems. It should be noted that the equation coefficients and the descriptors (for the mononitrophenols) have all been previously published, so that the log P(calc) values for the mononitrophenols in the DCE system are predictions. The solvation equation, eq 1, provides a very good quantitative account of the numerical values of lipophilicity of the mononitrophenols in all three water−solvent systems.

Having ascertained that eq 1 can account quantitatively for the various log P values, it is now possible to analyze the terms in eq 1 and so deduce the factors that influence lipophilicity. Details are in Table 4. In the case of water−octanol partition coefficients, the increased hydrogen bond basicity of 2-nitrophenol is counterbalanced by its decreased dipolarity/polarizability, and since the aA term is zero for all the phenols the lipophilicity of the three mononitrophenols is almost the same. The situation is not the same for water−DCE partitions, where solute hydrogen bond acidity plays a substantial role. The aA term is now 2 log units more positive for

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(19) Abraham, M. H.; McGowan, J. C. *Chromatographia* **1987**, *23*, 243−246.

(20) Abraham. M. H.; Green, C. E.; Platts, J. A. Unpublished work.

(21) Leo, A. J. MedChem Software, BioByte Corp., P.O. 517, Claremont, CA 91711-0157.

Table 4. A Term-by-Term Analysis of Lipophilicity through Eq 1

solute	*eE*	*sS*	*aA*	*bB*	*vV*
		log P_{OCT}			
phenol	0.45	−0.94	0.02	−1.04	2.96
2-nitrophenol	0.57	−1.11	0.00	−1.28	3.62
3-nitrophenol	0.59	−1.65	0.03	−0.80	3.62
4-nitrophenol	0.60	−1.81	0.03	−0.90	3.62
		log P_{DCE}			
phenol	0.22	−0.15	−1.70	−1.30	3.26
2-nitrophenol	0.28	−0.18	−0.14	−1.60	3.99
3-nitrophenol	0.29	−0.26	−2.22	−0.99	3.99
4-nitrophenol	0.30	−0.29	−2.31	−1.12	3.99
		log P_{CYC}			
phenol	0.66	−1.54	−2.27	−1.47	3.60
2-nitrophenol	0.83	−1.82	−0.19	−1.81	4.41
3-nitrophenol	0.86	−2.72	−2.98	−1.13	4.41
4-nitrophenol	0.87	−2.98	−3.10	−1.28	4.41

Table 5. Comparison of Calculated log *P* Values for Picric Acid in Water/Solvent Systems with Observed Values

solvent	calc	taken	obs[21]
octanol	1.564	1.64 [a]	−0.97, 0.84, 0.89, 1.44, 1.46, 2.03
pentanol	1.896	1.85	1.85, 2.94
hexanol	1.641	1.72	1.72
decanol	1.613		1.24
dichloromethane	2.738		2.04, 2.04, 2.07
trichloromethane	2.095	1.62[b]	1.20, 1.23, 1.47, 1.49, 1.50, 1.80
tetrachloromethane	0.174	0.23[b]	0.22, 0.49, 1.98
1,2-dichloroethane	2.558		1.76
hexane	−1.365		0.22
octane	−1.057		0.20
nonane	−1.264		0.18
decane	−1.338		0.14
cyclohexane	−1.004		0.32
benzene	1.729	2.05[c]	1.64, 1.69, 2.03, 2.25, 2.37
toluene	1.491	2.06[c]	0.88, 1.56, 1.71
nitrobenzene	3.232	3.28[b]	1.90
diethyl ether	1.709	1.73[c]	
ethyl acetate	1.338		2.75
butyl acetate	2.893		2.10
CS_2, dry	0.827	0.25[b]	
methanol, dry	2.125	2.22[b]	
ethanol, dry	1.869	1.80[b]	
propanol, dry	1.603	1.47[b]	
butanol, dry	1.373	1.37[b]	
pentanol, dry	1.268	1.29[b]	
propan-2-ol, dry	1.653	1.84[b]	
acetone, dry	3.138	3.07[b]	

[a] CLOGP value. [b] Ratio of solubilities, corrected for ionization in water. [c] Average of ratio of solubilities and direct partition, both corrected for ionization, see text.

2-nitrophenol than for 4-nitrophenol. Although there are other minor effects, it is this term that accounts for the much greater lipophilicity of 2-nitrophenol over 3- or 4-nitrophenol. There is no difficulty in reaching this conclusion—it follows quite logically from the solute descriptors and the system coefficients. In the case of the water−cyclohexane system, the difference in lipophilicity of the 2-nitrophenol and the 3- and 4-nitrophenols is even larger than for water−DCE, with 2-nitrophenol being some 3.5 log units more lipophilic than 4-nitrophenol. The *aA* term contributes 2.9 log units, but the *sS* term cannot be disregarded and contributes 1.2 log units. The increased basicity of 2-nitrophenol counteracts these to some extent, leaving a net increase of 3.5 log units.

In conclusion, the solvation equation, eq 1, leads to a quantitative account of lipophilicity for the mononitrophenols and enables the origin of the differences between the nitrophenols to be accounted for. Internal hydrogen bonding in 2-nitrophenol leads to a marked decrease in hydrogen bond acidity, and this is the major factor in the increase in lipophilicity in DCE and cyclohexane. The decrease in dipolarity/polarizability in 2-nitrophenol also leads to an increase in lipophilicity, as shown by log *P* values in the water−cyclohexane system.

Having successfully explained the lipophilicity of the mononitrophenols, we now examine the dinitrophenols as well. The solvation descriptors are in Table 2. Those for 2,4-, 2,5-, 3,4-, and 3,5-dinitrophenol are as expected. Internal hydrogen bonding in the 2,4- and 2,5-dinitrophenols greatly reduces the hydrogen bond acidity, which is only slightly more than that in 2-nitrophenol. The 3,4- and 3,5-dinitrophenols are strong hydrogen bond acids, with the -OH now free for external hydrogen bonding. There is a pronounced peculiarity in 2,3-dinitrophenol; the value of 0.67 for *A* is not far short of that for 3- or 4-nitrophenol, which suggests that there cannot be substantial internal hydrogen bonding. Possibly, the 2-nitro group is twisted out of the plane of the aromatic ring by steric effects and is then not in a favorable position for internal hydrogen bonding. A similar, but much smaller, effect seems also to apply to 2,6-dinitrophenol, where *A* is a little larger than that for 2,4- or 2,5-dinitrophenols.

The effect of internal hydrogen bonding leads to remarkable changes in lipophilicity. If log P_{OCT} is used as an index of lipophilicity, the order of increasing lipophilicity is 2,6- < 2,4- < 2,5- < 2,3- < 3,4- < 3,5-dinitrophenol, but if log P_{CYC} is taken as the index, the order is completely different: 3,4- < 3,5- < 2,3- < 2,6- < 2,4- < 2,5-dinitrophenol. All this can be explained through eq 1, in the same way as for the mononitrophenols.

The usual method of obtaining solvation descriptors is through the analysis of partition coefficients.[22] The only trinitrophenol for which considerable partition data exists is 2,4,6-trinitrophenol or picric acid. However, the literature data on partition coefficients, as carefully recorded by Leo,[21] is completely inconsistent, see Table 5. We therefore reanalyzed data on partition coefficients given by Seidell,[23] who lists the original water and solvent concentrations, to take into account ionization in water; the pK_a of picric acid is 0.22.[21] This led to direct log *P* values for the following solvent systems: benzene (2.13), toluene (2.06), wet ether (1.81), and trichloromethane (1.63). We also converted the experimental aqueous solubility of picric acid (0.0553 ± 0.0031 mol dm^{-3} from nine recorded[23] values) into the aqueous solubility of the neutral form (0.0043 mol dm $^{-3}$) and combined the latter with solubilities in solvents to obtain a set of "indirect" partition coefficients, as described previously.[24,25] Where there is an overlap with direct partitions, see above, the indirect partition coefficients are in good agreement: benzene (1.98), toluene (2.06), wet ether (1.66), and trichloromethane (1.63). The various log *P* values, both direct and indirect, are in Table 5, together with the calculated values using the descriptors for picric acid in

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(22) Abraham, M. H.; Kumarsingh, R.; Cometto-Muniz, J. E.; Cain, W. S.; Roses, M.; Bosch, E.; Diaz, M. L. *J. Chem. Soc., Perkin Trans. 2* **1998**, 2405−2411.

(23) Seidell, A. *Solubilities of Organic Compounds*, 3rd ed., Vol. II, Van Nostrand: New York, 1941.

(24) Abraham, M. H.; Green, C. E.; Acree, W. E., Jr.; Hernandez, C. E.; Roy, L. E. *J. Chem.* Soc., *Perkin Trans. 2* **1998**, 2677−2681.

(25) Abraham, M. H.; Green, C. E.; Acree, W. E., Jr. *J. Chem. Soc., Perkin Trans. 2* **2000**, 281−286.

Table 6. Comparison of Values of *A* with Those Calculated from pK_a Values

substituent	*A*(calc)	*A*(obs)	ratio[a]
2-nitro	0.95	0.05	0.95
2,3-dinitro	1.18	0.67	0.43
2,4-dinitro	1.29	0.09	0.93
2,5-dinitro	1.17	0.11	0.91
2,6-dinitro	1.33	0.17	0.87
2,4,6-trinitro	1.73	0.46	0.73
2-fluoro	0.74	0.61	0.18
2-chloro	0.76	0.32	0.58
2-bromo	0.77	0.35	0.55
2-iodo	0.76	0.40	0.47
2-cyano	0.92	0.78	0.15
2-methoxy	0.58	0.22	0.62

[a] $[A(\text{calc}) - A(\text{obs})]/A(\text{calc})$.

Table 2 and the known[20,24,25] coefficients in eq 1. The *A* value for picric acid is much lower than expected from its pK_a (0.22) and suggests that there is considerable internal hydrogen bonding. Because of the various solute properties that influence log *P* values in different solvents, the relative lipophilicity of picric acid depends greatly on the particular water−solvent system.

We can attempt to put the extent of internal hydrogen bonding on a quantitative (or semiquantitative scale) by estimating what the *A* value would be in the absence of any internal hydrogen bonding at all. It is known[26] that within a family of compounds there is a correlation between 1:1 hydrogen bond complexation constants (as log *K*) and pK_a values. We find that for 32 3- and 4-substituted phenols there is a good correlation between the overall or effective hydrogen bond descriptor and pK_a,

$$A = 1.76 - 0.118\ \mathrm{p}K_a \qquad (2)$$

with $r^2 = 0.946$, $F = 521$, and a standard deviation, sd, = 0.033; considering that the error in *A* values is around 0.03 unit, this sd value is quite good. Equation 2 can then be used to assess the *A* value in the absence of internal hydrogen bonding, with results as shown in Table 6. Of course, this can only be an approximate calculation, because effects such as nonplanarity that affect *A* may also affect pK_a. If we proceed by estimating the fraction of internal hydrogen bonding as the ratio $[A(\text{calc}) - A(\text{obs})]/A(\text{calc})$, we obtain the values given in Table 6 for nitrophenols and also for various 2-substituted phenols.

From the rather low ratio for 2,3-dinitrophenol, we can deduce that internal hydrogen bonding is very much less than for the 2,4- or 2,5-substituted phenols. The 2,6-dinitrophenol is not quite as hydrogen bonded as the 2,4- or 2,5-dinitrophenols. The expected *A* value for picric acid is very large (1.73), and so the observed *A* value of 0.46 suggests that there is considerable internal hydrogen bonding.

Results for other 2-substituted phenols are given in Table 6 for comparison. 2-Nitrophenol is very much more internally hydrogen bonded than any other 2-phenol in Table 6. Interestingly, we calculate that 2-cyanophenol is only weakly hydrogen bonded, in stark comparison to 2-nitrophenol.

We have optimized the geometries of each nitrophenol discussed in Table 6 at the HF/6-31G** level [28] using Gaussian98[29] and confirmed each structure as a true minimum by means of harmonic frequency calculations. Selected geometrical details are reported in Table 7: the three mononitrophenols are completely planar, as are 2,4- and 2,5-dinitrophenol (and phenol itself). However, those compounds that appear experimentally to have disrupted internal hydrogen bonding do not have this C_s symmetry but instead are distorted away from this ideal geometry. This effect is largest for 2,3-dinitrophenol in which the H−O−C−C torsion angle is 11.0°, see Table 7. Smaller deviations of 1.7° and 1.5° are found in 2,6-dinitrophenol and picric acid, respectively—in these compounds the 6-nitro group is almost orthogonal to the ring, but the phenol and 2-nitro groups are roughly coplanar.

Table 7. Some Calculated Properties of Nitrophenols

substituent	r(O···H) (Å)	H−O−C−C (°)	ρ(O···H) (e·bohr^{-3})	calc *A*[a]
2-nitro	1.822	0.00	0.037	0.67
2,3-dinitro	1.877	11.04	0.032	0.80
2,4-dinitro	1.817	0.00	0.038	0.83
2,5-dinitro	1.833	0.00	0.036	0.80
2,6-dinitro	1.788	1.66	0.040	0.81
2,4,6-trinitro	1.782	1.48	0.040	0.96

[a] Calculated from eq 3.

The O···H hydrogen bond distance is much longer (1.877 Å) in 2,3-dinitrophenol than in all other molecules considered here (average 1.815 Å). Another measure of hydrogen bond strength is ρ O···H, the electron density at the H-bond critical point;[30] the larger this value, the stronger the H-bond. All six values in Table 7 are of a similar magnitude and are typical of hydrogen bonding at around 10^{-2} e·bohr^{-3}. However, it is apparent that 2,3-dinitrophenol has a much weaker internal H-bond than the others, supporting the experimental deduction above. In contrast, 2,6-dinitrophenol and picric acid have shorter, stronger internal H-bonds than the average, which may suggest that their low *A* values are due more to their nonplanarity than to any disruption of internal H-bonding.

We have recently demonstrated[31] that *A* is closely correlated with the value of the electrostatic potential evaluated at the donor H nucleus according to eq 3:

$$A = 6.562 + 6.102\ \mathrm{EP}_{\mathrm{NUC}} \qquad (3)$$

which reproduced *A* values of 40 diverse acids with sd = 0.07. Predictions of *A* based on eq 3 are reported in Table 7 and should be directly comparable to the calculated values in Table 6. In general, eq 3 predicts lower *A* than eq 2, but the overall trend is similar in that the four dinitrophenols in Table 7 have roughly equal calculated *A*, with 2-nitrophenol lower and picric acid much higher. Thus, the same conclusions as above can be drawn, i.e., that 2,3-dinitrophenol's *A* value is due to disruption of its internal H-bond but that picric acid's is more due to its very large intrinsic acidity.

A plot of *A* vs either −pK_a or EP$_{\mathrm{NUC}}$ illustrates the effects of internal hydrogen bonding in substituted phenols (Figure 2). The 3- and 4-substituted phenols form a roughly straight line, as discussed above. Most of the

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(26) Abraham, M. H.; Grellier, P. L.; Prior, D. V.; Duce, P. P.; Morris, J. J.; Taylor, P. J *J. Chem. Soc., Perkin Trans. 2* **1989**, 699−711.

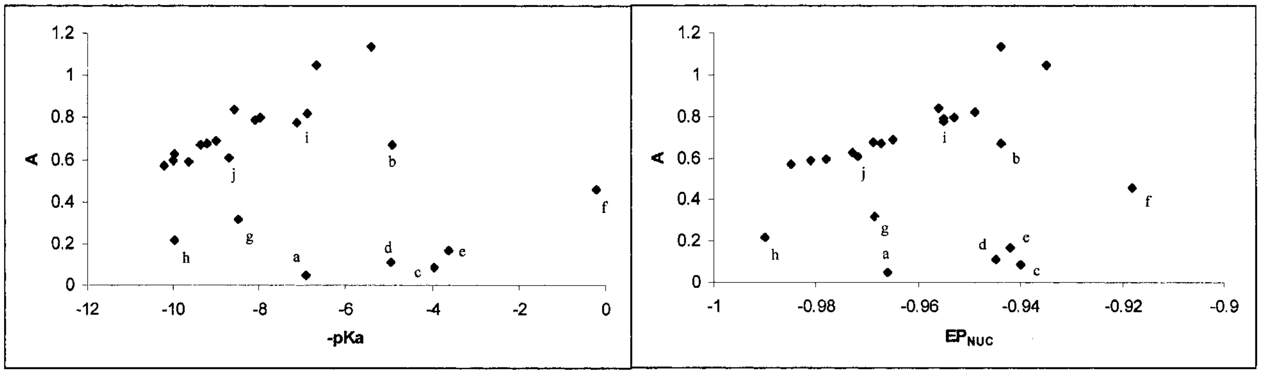
(27) Abraham, M. H.; Duce, P. P.; Prior, D. V.; Barrett, D. G.; Morris, J. J.; Taylor, P. J *J. Chem. Soc., Perkin Trans. 2* **1989**, 1355−1375.

(28) (a) Ditchfield, R.; Hehre, W. J.; Pople, J. A. *J. Chem. Phys.* **1971**, *54*, 724−728. (b) Gordon, M. S. *Chem. Phys. Lett.* **1980**, *76*, 163−168.

(29) Frisch M. J.; et al. *Gaussian98 Rev. A.6*, Gaussian Inc., Pittsburgh, PA, 1998.

(30) Boyd, R. J.; Choi, S. C. *Chem. Phys. Lett.* **1985**, *120*, 80−85.

(31) Platts, J. A. *Phys. Chem. Chem. Phys.* **2000**, *2*, 973−980.



(a) **A** vs –pKa

(b) **A** vs. EP_{NUC}

Figure 2. Plots of A vs $-pK_a$ and EP_{NUC} for 23 phenols· Legend: a, 2-nitro; b, 2,3-dinitro; c, 2,4-dinitro; d, 2,5-dinitro; e, 2,6-dinitro; f, 2,4,6-trinitro; g, 2-chloro; h, 2-methoxy; i, 2-cyano; j, 2-fluorophenol.

2-substututed phenols, on the other hand, fall well below this line: by this criterion 2-nitro, 2,4-, 2,5-, and 2,6-dinitro, and 2,4,6-trinitro (and to a lesser extent 2-chloro and 2-methoxy) have strong internal H-bonds. The disrupted internal H-bond of 2,3-dinitrophenol means this molecule is found much closer to the reference line than 2,4-, 2,5-, and 2,6-dinitrophenols. In this respect 2,3-dinitrophenol is more like 2-cyano- or 2-fluorophenol, which do not appear to have any significant H-bonding.

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