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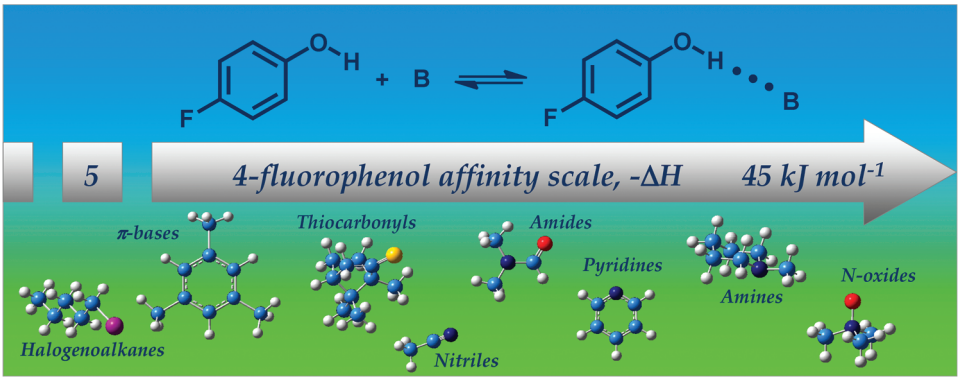
An Enthalpic Scale of Hydrogen-Bond Basicity. 4. Carbon π Bases, Oxygen Bases, and Miscellaneous Second-Row, Third-Row, and Fourth-Row Bases and a Survey of the 4-Fluorophenol Affinity Scale

Christian Laurence,* Jérôme Graton,* Michel Berthelot, François Besseau, Jean-Yves Le Questel, Maryvonne Luçon, Carole Ouvrard, Aurélien Planchat, and Eric Renault

Laboratoire CEISAM, UMR CNRS 6230, Faculté des Sciences et des Techniques, Université de Nantes, 2, rue de la Houssinière, BP 92208, 44322 Nantes, Cedex 3, France

christian.laurence@univ-nantes.fr; jerome.graton@univ-nantes.fr.

Received March 12, 2010



The thermodynamics of the O−H···B hydrogen bond (HB) has been determined in CCl_4 by FTIR spectrometry for a wide variety of carbon π bases, oxygen bases, and miscellaneous first- to fourth-row bases, using 4-fluorophenol as a reference hydrogen-bond donor (HBD). After inclusion of previously studied nitrogen, sulfur, and halogen bases, this 4-fluorophenol affinity scale contains 314 varied organic bases and ranges over 40 kJ mol^{-1}. The 4-fluorophenol affinity scale in CCl_4 is shown to be applicable to most HBDs in most media, provided a small family dependence is taken into account. The HB affinity orders are quantitatively established according to the atomic acceptor site or to its bearing functional group. A comprehensive survey of the influence of substituents on these affinity orders is then achieved, considering electronic and steric effects, as well as effects of vinylogy or iminology. Iminology is found to be more efficient than vinylogy for transmitting resonance effects. Steric effects are shown to be less important in HB affinity than in HB basicity since they mainly act on the HB entropy. The spatial proximity of two acceptor sites can favor complexation through three-center hydrogen bonds, leading to superhydrogen-bond bases on the affinity scale.

Introduction

Hydrogen-bond donors (HBDs) (e.g., water, alcohols, phenols, pyrroles, secondary amides) contain an XH group in which the hydrogen atom is bonded to an electronegative atom X and bears a partial positive charge. Therefore, the hydrogen is attracted, by means of electrostatic forces, toward regions of high electron density, mainly nonbonding or π-bonding electron pairs, of a hydrogen-bond acceptor (HBA) (e.g., amines, pyridines, ketones, sulfoxides), and a hydrogen bond (HB) is formed.[1] In addition to this electrostatic interaction, a natural bond orbital (NBO) analysis[2] of the hydrogen bond shows the existence of a small charge transfer from the nonbonding or

(1) For a comprehensive definition of the hydrogen bond, see the IUPAC web page: http://www.iupac.org/web/ins/2004-026-2-100, accessed January 2010 (IUPAC project: categorizing hydrogen bonding and other molecular interactions).

(2) Reed, A. E.; Curtiss, L. A.; Weinhold, F. *Chem. Rev.* **1988**, *88*, 899.

DOI: 10.1021/jo100461z Published on Web 05/21/2010

π-bonding electron pairs of the HBA to the antibonding orbital σ^* of the X−H bond. Therefore, in the enlarged Lewis definition of acidity and basicity,[3,4] where acids accept and bases donate *electron density*, the HBD is a Lewis acid because it accepts electron density and the HBA is a Lewis base since it donates electron density. Hydrogen bonding and hydrogen-bonded complexes can thus be considered a special class of Lewis acid−base interactions and Lewis adducts, respectively.[5,6]

The International Union of Pure and Applied Chemistry defines Lewis basicity as "the thermodynamic tendency of a substance to act as a Lewis base. Comparative measures of this property are provided by the equilibrium constants for Lewis adduct formation for a series of Lewis bases with a common reference Lewis acid."[7] Similarly, hydrogen-bond basicity can be defined as the thermodynamic tendency of a substance to act as an HBA, and a hydrogen-bond basicity scale can be constructed from the equilibrium constants K for hydrogen-bonded complex formation for a series of HBAs with a common reference HBD.

In this way, a pK_{HB} hydrogen-bond basicity scale has been constructed[8,9] from log K values measured in CCl_4 at 298 K for a series of 80 bases B against 4-fluorophenol as the reference HBD (eqs 1−3).

$$4\text{-}FC_6H_4OH + B \rightleftharpoons 4\text{-}FC_6H_4O\text{-}H\cdots B \quad (1)$$

$$K_c/\text{L mol}^{-1} = [\text{complex}]/[\text{phenol}][B] \quad (2)$$

$$pK_{HB} = \log_{10}(K_c/1\ \text{L mol}^{-1}) \quad (3)$$

This scale has further been extended to about a thousand HBAs and to polyfunctional bases and has given rise to the pK_{BHX} database[6,10] (the renaming of pK_{HB} as pK_{BHX} is justified in refs 6 and 10). The pK_{BHX} database has been explicitly targeted to explore hydrogen-bond basicity as a structure−activity relationship parameter in medicinal chemistry.[10] Because of the importance of the hydrogen bond in physical and chemical sciences, pK_{BHX} is also a promising explanatory variable of structure−property and structure−reactivity relationships in many other fields of chemistry.[6,11,12]

The pK_{BHX} values can be converted to a Gibbs energy scale through eq 4. The Gibbs energy of reaction (1) spans from about +5 kJ mol^{-1} for very weak HBAs, such as alkenes, to −35 kJ mol^{-1} for very strong HBAs, such as amine N-oxides (a shift of −5.78 kJ mol^{-1} must be applied when equilibrium constants in CCl_4 are expressed in mole fraction). As shown by eq 5, $\Delta G°$ is determined by $\Delta H°$, $\Delta S°$, and T which are, respectively, the enthalpy and the entropy of reaction (1), and the temperature of measurement. A deep understanding of the thermodynamics of hydrogen-bond basicity requires the determination of the enthalpy and the entropy of 4-fluorophenol basicity. In the following, the negative enthalpy of 4-fluorophenol basicity is also named 4-fluorophenol affinity, by analogy with the widely used terms "proton affinity" for the enthalpy of proton basicity,[13] and "metal cation affinity" for the enthalpy of metal cation basicity.[6]

$$\Delta G_c^\circ/\text{kJ mol}^{-1} = -RT\ln(10)pK_{BHX} = -5.708pK_{BHX}\ (\text{at } 298\ \text{K}) \quad (4)$$

$$\Delta G^\circ = \Delta H^\circ - T\Delta S^\circ \quad (5)$$

Although several hundred hydrogen-bond enthalpies have been determined in the past,[14] very few have been measured toward the same reference HBD in the same medium, i.e., to enable the construction of an enthalpic scale of hydrogen-bond basicity. There have been only two attempts at such a construction, the first toward 4-fluorophenol, by a "high-dilution calorimetric method" (40 HBAs) and a "pure-base method" (57 HBAs),[15,16] and the second toward pyrrole, by a "pure-solvent calorimetric method" (35 HBAs).[17]

The above scales refer to a small and insufficiently varied sample of HBAs to be of wide use in chemistry. Moreover, the scales measured in the medium of pure base are limited to liquid HBAs. Our group has therefore studied further the 4-fluorophenol affinity scale pioneered by Arnett.[15,16] The families of fluoro-, chloro-, bromo-, and iodoalkanes,[18] single-bonded sulfur bases (thiols, thioethers, and disulfides)[19] and primary, secondary, and tertiary amines[20] have already been studied, and the results are published in the three previous parts of this series. A paper devoted to the theoretical estimation of the 4-fluorophenol affinity of nitrogen bases contains about 100 experimental values.[21] A few data for new fluoroalkanes,[22] new chloroalkanes,[23] double-bonded sulfur bases,[24] and pyrrolines[25] are scattered in several papers.

This paper first reports the 4-fluorophenol affinity scale for carbon π bases (aromatics, alkenes, and alkynes), oxygen bases with many functionalities (N-oxides, phosphine oxides,

(3) Jensen, W. B. *Chem. Rev.* **1978**, *78*, 1.
(4) Drago, R. S. *J. Chem. Educ.* **1974**, *51*, 300.
(5) Pearson, R. G. *J. Am. Chem. Soc.* **1963**, *85*, 3533.
(6) Laurence, C.; Gal, J. F. *Lewis Basicity and Affinity Scales. Data and Measurement*; Wiley: Chichester, 2009.
(7) Gold, V. *Pure Appl. Chem.* **1983**, *55*, 1281.
(8) Gurka, D.; Taft, R. W. *J. Am. Chem. Soc.* **1969**, *91*, 4794.
(9) Taft, R. W.; Gurka, D.; Joris, L.; Schleyer, P. v. R.; Rakshys, J. W. *J. Am. Chem. Soc.* **1969**, *91*, 4801.
(10) Laurence, C.; Brameld, K. A.; Graton, J.; Le Questel, J.-Y.; Renault, E. *J. Med. Chem.* **2009**, *52*, 4073.
(11) Wang, X.; Salaski, E. J.; Berger, D. M.; Powell, D. *Org. Lett.* **2009**, *11*, 5662.
(12) Mehdoui, T.; Berthet, J.-C.; Thuery, P.; Ephritikhine, M. *Dalton Trans.* **2004**, 579.
(13) Gal, J.-F.; Maria, P.-C.; Raczynska, E. D. *J. Mass Spectrom.* **2001**, *36*, 699.
(14) Joesten, M. D.; Schaad, L. J. *Hydrogen Bonding*; Dekker: New York, 1974.
(15) Arnett, E. M.; Joris, L.; Mitchell, E.; Murty, T. S. S. R.; Gorrie, T. M.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1970**, *92*, 2365.
(16) Arnett, E. M.; Mitchell, E. J.; Murty, T. S. S. R. *J. Am. Chem. Soc.* **1974**, *96*, 3875.
(17) Catalan, J.; Gomez, J.; Couto, A.; Laynez, J. *J. Am. Chem. Soc.* **1990**, *112*, 1678.
(18) Ouvrard, C.; Berthelot, M.; Laurence, C. *J. Phys. Org. Chem.* **2001**, *14*, 804.
(19) Laurence, C.; Berthelot, M.; Evain, K.; Illien, B. *Can. J. Chem.* **2005**, *83*, 138.
(20) Graton, J.; Berthelot, M.; Besseau, F.; Laurence, C. *J. Org. Chem.* **2005**, *70*, 7892.
(21) Besseau, F.; Graton, J.; Berthelot, M. *Chem.—Eur. J.* **2008**, *14*, 10656.
(22) Adcock, W.; Graton, J.; Laurence, C.; Lucon, M.; Trout, N. *J. Phys. Org. Chem.* **2005**, *18*, 227.
(23) Ouvrard, C.; Lucon, M.; Graton, J.; Berthelot, M.; Laurence, C. *J. Phys. Org. Chem.* **2004**, *17*, 56.
(24) Illien, B.; Evain, K.; Berthelot, M.; Laurence, C. *J. Phys. Org. Chem.* **2003**, *16*, 608.
(25) Arnaud, V.; Berthelot, M.; Felpin, F.-X.; Lebreton, J.; Le Questel, J.-Y.; Graton, J. *Eur. J. Org. Chem.* **2009**, 4939.

sulfoxides, selenoxides, carbonyl bases, ethers, and nitro compounds), new sulfur bases (thiocarbonyl bases and phosphine sulfides), and miscellaneous first-, second-, third-, and fourth-row bases (new nitrogen bases, phosphine, selenide, telluride, arsine, and stibine). The final sample (refs 18−25 and this work) contains more than 300 bases. This gives the chemist homogeneous data for a range of HB affinities and a variety of functionalities not remotely approached before and for previously unstudied HBAs (e.g., selenoxides; vinylogous amide, urethane and nitramide; pyrrolines).

The domain of validity of the 4-fluorophenol scale is studied in the second part. Indeed, the ranking of bases may be affected if the reference HBD and/or the solvent are changed. Mainly for historical reasons, the scale has been constructed against 4-fluorophenol, but other HBDs may be chemically and biochemically relevant. It is thus important to know if CH, NH, and other OH donors rank the bases in the same order as or different from 4-fluorophenol. Unfortunately, there is a serious dearth in the literature of homogeneous, reliable, and structurally diversified hydrogen-bond enthalpies. So we have measured, for a more limited but nevertheless representative sample of bases, three new scales, namely the cyanoacetylene (a CH donor), the pyrrole (an NH donor), and the methanol (a weaker OH donor than 4-fluorophenol) affinity scales. The existence or not of linear enthalpy relationships (ΔH toward a given HBD versus ΔH toward 4-fluorophenol) enables the applicability of the 4-fluorophenol affinity scale to HBDs other than 4-fluorophenol to be tested. For technical reasons, the 4-fluorophenol affinity scale has been set up using tetrachloromethane as the solvent of reaction (1). However, it is well-known[26−28] that hydrogen-bond enthalpies are usually significantly affected by the intermolecular interactions of the HBA, the HBD, and the hydrogen-bonded complex with the solvent. Hence, it is necessary to establish whether our scale can be used in other solvents. To study the solvent effect on the 4-fluorophenol affinity, the lack of literature data obliged us to measure this property for a representative sample of bases in cyclohexane, which is less polar than CCl_4, and in dichloromethane, which is more polar. The relative permittivity of dichloromethane is close to that of octan-1-ol, often used as a membrane model. The existence or not of linear enthalpy relationships (ΔH in a given solvent versus ΔH in CCl_4) can be used to test the applicability of the 4-fluorophenol affinity scale to media other than CCl_4.

In the third part, the structural tools for tuning HB affinity are highlighted. The structure of the HBA is analyzed in order of increasing complexity as follows. First, the position in the periodic table of the *atom accepting the hydrogen bond* is considered. For example, the order O > S > Se > Te (where > means: greater HB affinity) is found for the alkyl derivatives of the elements of group 16. Second, the *functionality* of this atom is taken into account. For example, oxygen bases follow the sequence amine *N*-oxide > phosphine oxide > selenoxide > sulfoxide. Lastly, the *substituent effects* on the HB affinity of a given function are analyzed. They include various electronic (mainly field/inductive, resonance, and polarizability)[29] and steric effects and depend also on the transmitting group T. For example, the HB affinity of push−pull nitriles Me_2N-T-C≡N increases in the order 4-Me_2N-C_6H_4-C≡N < Me_2N-C≡N < Me_2N-CH=CH-C≡N < Me_2N-CH=N-C≡N.

Results and Discussion

1. Thermodynamics of Hydrogen Bonding between 4-Fluorophenol and Bases. Values of the enthalpy and entropy of 4-fluorophenol basicity measured in this work, as well as secondary values for di-*tert*-butyl ether and trimethylamine *N*-oxide, are reported in Table 1. The addition of these values to those already published provides a scale of 314 enthalpies and 310 entropies for reaction (1). The whole of the scale is presented in the Supporting Information. To our knowledge, this is the most extensive homogeneous study of the thermodynamics of hydrogen bonding that has been carried out so far. In our data, the hydrogen-bond acceptor atom belongs to four periods and four columns of the periodic table, most organic functions are studied, and varied substituents are introduced.

As a consequence of the large and varied selection of bases, the scale covers an extended enthalpic range of 40 kJ mol^{-1}. Trimethylamine *N*-oxide and 1-iodopentane have respectively the largest (44 kJ mol^{-1}) and the smallest (4 kJ mol^{-1}) affinity. A histogram of the 314 affinity values is shown in Figure 1. This distribution provides numerical criteria for a classification of O−H···B hydrogen bonds (where B is a neutral base and the OH donor is 4-fluorophenol) as "very weak", "weak", "moderate", "strong", or "very strong". Here, the strength is measured by the hydrogen-bond enthalpy at 298 K in CCl_4. The limits of these five classes can be calculated from the average (23.4 kJ mol^{-1}), the range, and the class width (8 kJ mol^{-1}). The rounded-off limits are shown in Table 2. The hydrogen-bond enthalpies measured in our work can be compared with the energy range given in the IUPAC definition of the hydrogen bond:[7] "With a few exceptions, usually involving fluorine, the [HB] energies are less than 20−25 kJ mol^{-1}." Actually, the histogram of our enthalpy results shows that many OH···O and OH···N hydrogen bonds have energies significantly greater than 25 kJ mol^{-1}, without having recourse to hydrogen fluoride as hydrogen-bond donor.

We shall discuss the effects of molecular structure on 4-fluorophenol affinities in the third section. The electronic energy change, ΔE_{el}, upon hydrogen bonding is expected to be the major descriptor of the HB enthalpy variations. The contributions of solvation and nuclear motions to these variations are small and/or quasi-constant and/or related to ΔE_{el}. In a combined experimental and theoretical study (at the MP2/aug-cc-pVTZ//B3LYP/6-31+G** level) of the hydrogen bonding of methanol with 23 HBAs, we have found[31] that 98% of the variance of the methanol affinity is explained, in vacuo, by ΔE_{el} and have estimated[31] roughly the solvation by carbon tetrachloride at 7 ± 2 kJ mol^{-1}. Similarly, ΔE_{el}, calculated[32] in vacuo for the hydrogen bonding of 4-fluorophenol with 42 varied HBAs at the MPWB1K/6-31+G** level, explains 99% of the variance of the 4-fluorophenol affinity calculated in vacuo and 84% of the variance of the 4-fluorophenol affinity measured in

(26) Drago, R. S.; Nusz, J. A.; Courtright, R. C. *J. Am. Chem. Soc.* **1974**, *96*, 2082.
(27) Christian, S. D.; Lane, E. H. In *Solutions and Solubilities*; Dack, M. R. J., Ed.; Wiley: New York, 1975; Vol. 8, p 327.
(28) Aquino, A. J. A.; Tunega, D.; Haberhauer, G.; Gerzabek, M. H.; Lischka, H. *J. Phys. Chem. A* **2002**, *106*, 1862.
(29) Topsom, R. D. *Prog. Phys. Org. Chem.* **1987**, *16*, 125.
(30) West, R.; Wilson, L. S.; Powell, D. L. *J. Organomet. Chem.* **1979**, *178*, 5.
(31) Kone, M. Ph.D. Thesis, Université de Nantes, **2005**.
(32) Graton, J. Unpublished results.

TABLE 1. Enthalpies (kJ mol^{-1}) and Entropies (J K^{-1} mol^{-1}) of Hydrogen Bonding between 4-Fluorophenol and Bases in CCl_4 (C_2Cl_4)

Lewis base	$-\Delta H°$	$-\Delta S_x°$	Lewis base	$-\Delta H°$	$-\Delta S_x°$
arenes			**ketones (continued)**		
benzene	7.3	13.4	3-methyl-5,5-dimethylcyclohexenone, isophorone	25.3	31.8
triphenylamine	(7.7)[a]	(14.8)[a]	2,6-dimethyl-γ-pyrone	28.9	29.1
methylbenzene, toluene	7.9	13.8	3-dimethylamino-5,5-dimethylcyclohexenone	32.5	33.7
1,4-dimethylbenzene, *p*-xylene	8.1	13.6	**esters, carbonate**		
1,3,5-trimethylbenzene, mesitylene	8.8	14.5	dimethyl carbonate	17.8	24.4
1,2,3,4-tetramethylbenzene, prehnitene	9.1	13.5	ethyl formate	17.9	26.4
pentamethylbenzene	10.3	16.7	methyl formate	18.0	28.8
hexamethylbenzene	10.8	16.7	methyl benzoate	19.2	27.6
pyrrole			methyl 3,3-dimethylacrylate	20.0	28.3
1-methylpyrrole	12.2	17.1	ethyl acetate	20.8	28.5
alkenes			methyl acetate	20.8	30.6
1,4-cyclohexadiene	6.2	15.2[b]	ethyl 3-dimethylaminoacrylate	27.0	30.8
1-heptene	6.8	18.2	**amides, ureas**		
cyclohexene	9.5	27.0	dimethylcarbamoyl chloride	19.6	27.6
alkynes			*N*,*N*-dimethylformamide	24.8	24.1
3-hexyne	11.1	18.6	*N*,*N*-dimethylbenzamide	26.8	27.4
2-hexyne	11.7	21.7	*N*,*N*′-dimethyl-*N*,*N*′-ethyleneurea (DMEU)	27.3	24.8
1-hexyne	11.7	22.7	1-methyl-2-pyrrolidone	27.4	25.2
amines			1-methyl-2-pyridone	28.5	28.4
1,1,1,3,3,3-hexamethyldisilazane	16.6	45.6	1,1,3,3-tetramethylurea	28.6	30.7
thiazolidine	(24.8)[a]	(40.7)[a]	*N*,*N*-dimethylacetamide	29.2	32.2
thiomorpholine	(30.4)[a]	(51.0)[a]	*N*,*N*′-dimethyl-*N*,*N*′-propyleneurea (DMPU)	30.6	30.0
tripropargylamine	(23.2)[a]	(42.0)[a]	**nitro compounds**		
six-membered *N*-heteroaromatics			1,3-dimethyl-2-nitrobenzene	10.1	14.4[b]
2-methoxypyridine	25.8	48.7	nitromethane	11.2	18.2[b]
3-iodopyridine	25.9	41.8	nitrobenzene	11.5	19.8[b]
2-phenylpyridine	27.6	46.0	4-nitroanisole	13.2	21.9[b]
amidines			1-diethylamino-2-nitroethylene	19.0	20.5[b]
1,5-diazabicyclo[4.3.0]non-5-ene (DBN)	40.8	42.3	**sulfonyl compounds**		
imines			*N*,*N*-dimethylbenzenesulfonamide	18.1	24.4[b]
N-benzylidene-*tert*-butylamine	31.1	60.1	*N*,*N*-dimethylmethanesulfonamide	18.2	22.6[b]
ethers			tetramethylene sulfone, sulfolane	18.6	21.6[b]
hexamethyldisiloxane	15.5	43.0	**sulfites, sulfoxides, selenoxides**		
1,3-dioxolane	17.6	31.4	ethylene sulfite	17.3	22.1
1,3-dioxane	19.4	33.7	dimethyl sulfite	18.2	24.1
1,4-dioxane	20.1	33.8	diethyl sulfite	19.0	24.0
cyclohexene oxide	21.3	31.2	bis(4-chlorophenyl) sulfoxide	22.9	25.4
3-methyltetrahydropyran	23.2	35.2	diphenyl sulfoxide	24.9	25.1
tetrahydropyran	23.3	34.8	methyl phenyl sulfoxide	25.8	24.3
tetrahydrofuran	23.7	35.5	bis(4-methylphenyl) sulfoxide	26.2	25.8
oxetane, trimethylene oxide	23.3	32.6	tetramethylene sulfoxide	27.2	24.8
di-*n*-butyl ether	23.8	43.4	dimethyl sulfoxide	27.9	25.6
diethyl ether	24.1	41.8	dibenzyl sulfoxide	28.1	29.2
tert-butyl methyl ether	25.9	45.2	di-*n*-butyl sulfoxide	28.8	25.4
diisopropyl ether	26.5	48.7	dimethyl selenoxide	30.7	17.8
tert-butyl ethyl ether	26.6	49.5	dibenzyl selenoxide	31.9	23.4
2,2,5,5-tetramethylhydrofuran	28.4	48.1	**amine oxide**		
cineole, eucalyptol	28.5	49.8	pyridine *N*-oxide	28.3	23.5
di-*tert*-butyl ether	29.7[c]		trimethylamine *N*-oxide	44.3[d]	
aromatic ether			**phosphoroso compounds**		
1,2-dimethoxybenzene	23.0	36.2	phosphoryl chloride	16.5	24.9
aldehydes			dichlorophenylphosphine oxide	20.9	26.2
benzaldehyde	18.6	27.3	chlorodiphenylphosphine oxide	26.3	26.7
acetaldehyde	18.9		trimethyl phosphate	27.1	24.0
ketones			triethyl phosphate	28.4	25.3
1,1,1-trifluoropropan-2-one	12.2	25.1	trimethylphosphine oxide	32.0	21.2
1,1,1-trichloropropan-2-one	12.4	21.4	hexamethylphosphoric triamide (HMPA)	33.7	24.6
1,1-dichloropropan-2-one	14.5	25.6	tri(*n*-butyl)phosphine oxide	34.6	27.1
2,2,4,4-tetramethylpentan-3-one	20.3	29.6	**thiocarbonyl compounds**		
2,4-dimethylpentan-3-one	20.5	27.7	*N*,*N*-dimethylthiocarbamoyl chloride	14.2	18.2
acetophenone	20.8	28.7	*N*,*N*-dimethylthioacetamide	20.0	24.4
nonan-5-one	21.0	28.4	**bromoalkanes**		
pentan-3-one	21.0	28.8	bromoethane	6.5	10.1
cyclohexanone	21.4	25.5	**thiophosphoroso and selenophosphoroso compounds**		
3-methylbutan-2-one	21.7	30.2	triphenylphosphine selenide	15.9	16.0
propan-2-one, acetone	22.4	32.0	triphenylphosphine sulfide	16.5	16.9

[a]To be considered with caution because of a second (weaker) hydrogen-bonding site. [b]Statistically corrected by $-R\ln(n)$, where n is the number of (quasi)-equivalent sites, in order to put these values on a per acceptor atom basis. [c]Secondary value calculated from a phenol affinity value.[30] [d]Secondary value calculated from a calorimetric measurement of -36.8 ± 1.3 kJ mol^{-1} in CH_2Cl_2. We have estimated the equation of the conversion line (HB enthalpies in CCl_4 vs HB enthalpies in CH_2Cl_2) of the *N*-oxide family from the HB enthalpies of pyridine *N*-oxide in CCl_4 and CH_2Cl_2 and the slope of the conversion line of phosphine oxides. The error on the estimation does not exceed ± 3 kJ mol^{-1}.

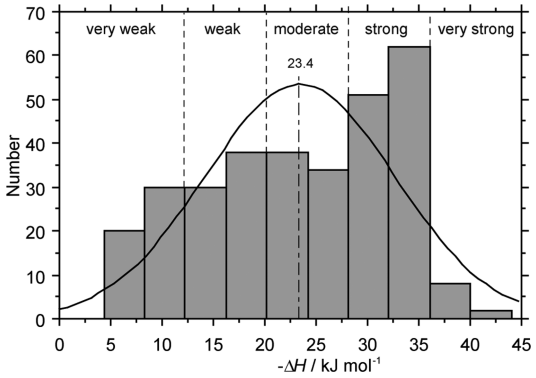


FIGURE 1. Distribution of 314 OH···B hydrogen-bond enthalpies in the 4-fluorophenol affinity scale.

TABLE 2. Classification of OH···B Hydrogen Bonds by 4-Fluorophenol Affinity (kJ mol^{-1})

hydrogen bond type	affinity range	examples	affinity
very weak	< 10	benzene	7.3
weak	10−19	tetrahydrothiophene	14.3
moderate	19−27	acetone	22.4
strong	27−35	pyridine	29.6
very strong	> 35	quinuclidine	37.7

CCl_4. This latter explained variance rises to 94, 95, and 91% when the comparison is restricted to the families of O, Nsp^2, and Nsp bases, respectively.

Hydrogen-bond entropies also span a wide range (73.5 J K^{-1} mol^{-1}, i.e., a $T\Delta S$ range of 22 kJ mol^{-1} at 298 K) from 1,3-diiodopropane (−7 J K^{-1} mol^{-1}, on the mole fraction scale) to tri-*n*-butylamine (−80.5 J K^{-1} mol^{-1}). Average entropies and their standard deviation are given for various families of bases in Table 3. The structural analysis of HB entropy variations is beyond the goal of this work, solution entropies being much more difficult to calculate and interpret than gas-phase entropies.[33] However, we notice that sterically hindered bases always show greater negative HB entropy than similar but unhindered bases. For example, $\Delta S_x^\circ = -35.5$ and −48.1 J K^{-1} mol^{-1} for tetrahydrofuran and 2,2,5,5-tetramethyltetrahydrofuran, respectively, or $\Delta S_x^\circ = -56.5$ and −70.3 J K^{-1} mol^{-1} for 1-methylpiperidine and 1,2,2,6,6-pentamethylpiperidine, respectively. Steric effects are mainly encountered in the families of secondary amines, tertiary amines, ethers, thioethers, and *N*-substituted imines, where substituents are directly attached to the HB acceptor atom and ortho-(di)substituted pyridines. In these compounds, bulky substituents may restrict the access of the OH group to the lone pair(s) of the base and lead to a reduced freedom within the complex and, consequently, to a larger (negative) value of the hydrogen-bond entropy.

We also notice that stronger hydrogen bonds often give more negative entropies. Consider, for a series of related reactions, the extrathermodynamic equation[34] (6) where ΔG°_β is the Gibbs energy change at the so-called isoequilibrium temperature β and the perturbation variable *i* is the nature of the base. Its existence has been much debated in many fields of chemistry[35] and in the case of hydrogen-bond formation.[16,36] Indeed, this apparently simple equation, sometimes called the compensation relationship, hides difficult statistical problems.[37,38] We have written a program[39] that can test whether the reactions are isoenthalpic ($\beta = 0$) or isoentropic ($\beta = \infty$) or if β is different from an error slope. We have shown that, if steric bases are excluded, the hydrogen bonding of 4-fluorophenol to bases is quasi-isoentropic for most amines[20] and roughly obeys compensation relationships with different slopes for halogenoalkanes[18] ($\beta \approx 590$ K) and for single-bonded sulfur bases[19] ($\beta \approx 780$ K). Other families are under study. Here, we are mainly interested to know how entropies will be reflected in Gibbs energies.

TABLE 3. Average Entropies (J K^{-1} mol^{-1}) of 4-Fluorophenol Basicity for Various Families of HBAs

family	$-\Delta S^\circ_x$	*n*	*s*[a]	$-\Delta S^\circ_{x(min)}$	$-\Delta S^\circ_{x(max)}$
sp^3 nitrogen bases	56	84	6.8	42.0	80.5
sp^2 nitrogen bases	45	44	5.3	34.5	60.1
ethers	40	17	6.8	31.2	49.8
carbonyls	28	37	3.2	21.4	38.3
PO, NO, SO bases	25	21	1.7	21.2	29.2
nitriles	24	18	1.9	20.7	28.2
single-bonded sulfur bases	22	26	4.2	16.1	33.9
NO_2 and SO_2 bases	20	8	3.1	14.4	24.4
fluoroalkanes	20	7	3.5	15.8	24.0
carbon π bases	17	15	4.3	10.5	27.0

[a]Standard deviation.

$$(\Delta H^\circ)_i = \beta(\Delta S^\circ)_i + \Delta G^\circ_\beta \quad (6)$$

$$(\Delta H^\circ)_i = \gamma(\Delta G^\circ_T)_i + (1-\gamma)\Delta G^\circ_\beta \quad (7)$$

Consider bases of quasi-equal affinities (in kJ mol^{-1}) such as 2,4-dimethylpyridine (31.8), cyclopropylamine (31.9), and trimethylphosphine oxide (32.0). Their entropies (in J mol^{-1} K^{-1}, on the mole fraction scale) vary from −54.9 for cyclopropylamine to −45.0 for 2,4-dimethylpyridine and to −21.2 for Me_3PO. This means that the basicities differ markedly, all due to the entropy contribution. For the same affinity, the basicities (in kJ mol^{-1}, on the mole fraction scale) are 15.5 for the amine, 18.4 for the pyridine, and 25.7 for the phosphine oxide. The comparison between affinity and basicity scales can be performed more generally through eq 7, deduced from eqs 5 and 6, where $\gamma = 1/(1 - T/\beta)$.[34] Since the harmonic mean of experimental temperatures is close to 298 K, this comparison can be safely undertaken by a simple least-squares regression.[34] Elsewhere, we have reported[6] the detailed results of this comparison and written the following conclusion: "the correlation of [4-fluorophenol] affinity and basicity scales exhibits a scatter caused by family-dependent relationships [of eq 7] and steric effects. For unhindered bases, the scatter can be analyzed into a series of crudely parallel lines for (i) amines, (ii) pyridines, (iii) [oxygen and miscellaneous] bases and (iv) π bases".

(33) Irudayam, S. J.; Henchman, R. H. *J. Phys. Chem. B* **2009**, *113*, 5871.
(34) Krug, R. R.; Hunter, W. G.; Grieger, R. A. *J. Phys. Chem.* **1976**, *80*, 2341.
(35) Liu, L.; Guo, Q. X. *Chem. Rev.* **2001**, *101*, 673.
(36) Pimentel, G. C.; McClellan, A. L. *Annu. Rev. Phys. Chem.* **1971**, *22*, 347.
(37) Krug, R. R.; Hunter, W. G.; Grieger, R. A. *J. Phys. Chem.* **1976**, *80*, 2335.
(38) Exner, O. *J. Phys. Org. Chem.* **1997**, *10*, 797.
(39) Ouvrard, C.; Berthelot, M.; Lamer, T.; Exner, O. *J. Chem. Inf. Comput. Sci.* **2001**, *41*, 1141.

2. Validity Domain of the 4-Fluorophenol Affinity Scale. 2.1. Application to Various HBDs. To investigate the applicability of the 4-fluorophenol affinity scale to other HBDs, we have constructed three new affinity scales toward (i) methanol, an OH donor weaker than 4-fluorophenol, (ii) pyrrole, an NH donor, and (iii) cyanoacetylene, a CH donor. The results are given in Table 4. The sample of bases is smaller for these new scales. However, it is representative of common HBAs since it contains Cπ, N, O, and S bases, as well as F and Cl bases for methanol and pyrrole. The existence, or not, of a common order of affinity toward the four HBDs is examined through the linear enthalpy relationship (LER) eq 8, where m and c are constants characteristic of the XH donor.

$$\text{XH affinity} = m(\text{4-fluorophenol affinity}) + c \qquad (8)$$

It is found that the methanol affinity is well correlated to the 4-fluorophenol affinity, since 96% of the variance of 41 methanol affinities is explained by the 4-fluorophenol affinity and that the standard deviation of the estimate (1.2 kJ mol^{-1}) compares well with the experimental error. Figure 2A illustrates this typical LER.

In the case of cyanoacetylene, the correlation is limited by the type of base, as shown in the plot between the cyanoacetylene and 4-fluorophenol affinities (Figure 2B). The results may be described by three roughly parallel lines, namely an upper line for Cπ bases, a middle line for oxygen bases (and also acetonitrile and tetrahydrothiophene), and a lower line for Nsp^2 and Nsp^3 bases. The line separation between the middle and lower lines amounts to about 5 kJ mol^{-1}. It appears that easily protonable bases (pyridines and amines) lose HB affinity, compared with bases that are more difficult to protonate (Nsp, S and O bases), on going from an OH to a CH donor.

The case of pyrrole is intermediate between that of methanol (family-independent LER) and cyanoacetylene (family dependent LER). The statistics (number of data n = 23, determination coefficient r^2 = 0.960, standard deviation of the estimate s = 1.2 kJ mol^{-1}) indicate a family-independent LER. However, a splitting of the data into three families, reminiscent of Figure 2B, can be detected in Figure 2C. The first family (n = 9, r^2 = 0.986, s = 0.5 kJ mol^{-1}) is constituted by oxygen bases (and also acetonitrile and tetrahydrothiophene). Cπ bases (and also fluorocyclohexane and chlorocyclohexane) deviate upward, whereas Nsp^2 and Nsp^3 bases deviate downward. The amines and pyridines lose HB affinity, compared to O bases, on going from an OH donor to pyrrole.

Results in the literature for other HB affinity scales confirm this analysis. Chloroform,[40−43] a Csp^{3}H donor, behaves similarly to cyanoacetylene, a CspH donor. The 4-fluorophenol affinity scale is applicable to all studied OH donors whether they are weaker (cyclohexanol,[44] *n*-butanol,[15] phenol,[14] and trifluoroethanol[45]) or stronger (hexafluoro-2-propanol[46] and perfluoro-2-methyl-2-propanol[47]) than 4-fluorophenol. It also applies to the NH donors HNCO[48] and HNCS[49,50] and, more importantly, to tri-*n*-butylammonium picrate,[51,52] an NH$^+$ donor. However, the 4-fluorophenol affinity scale is not related (at least

TABLE 4. Methanol, Pyrrole, and Cyanoacetylene Affinities (kJ mol^{-1}) in CCl_4 (C_2Cl_4)

	$-\Delta H°$		
HBA	methanol	pyrrole	cyanoacetylene
arenes			
benzene	~4.9	~4.3	~4.4
mesitylene	7.7	5.8	6.2
hexamethylbenzene	9.3	6.0	6.5
amines (in C_2Cl_4)			
triallylamine	20.3	16.5	9.9
dimethylamine	22.5		
tri-*n*-butylamine	23.1	21.1	
trimethylamine	23.7		
methylamine	24.4		
ethylamine	24.4		
quinuclidine	24.8	21.0	
N-methylpiperidine	25.2	20.1	12.2
diethylamine	25.5		
triethylamine	26.3	23.4	15.5
pyridines, azole			
3,5-dichloropyridine (in C_2Cl_4)	16.0	10.2	6.6
3-fluoropyridine	16.3	13.3	8.4
pyridine	19.1	15.0	9.0
4-methylpyridine	20.0		
3,5-dimethylpyridine	20.3	16.0	
1-methylimidazole	22.3		
nitrile			
acetonitrile	12.2	10.4	7.4
ethers			
1,3-dioxolane	11.9	8.5	6.1
1,4-dioxane	13.2	10.8	8.1
1,2-dimethoxybenzene	14.7		
diethyl ether	15.2		
tetrahydrofuran	16.1	12.7	10.2
carbonyl compounds			
methyl formate	9.8		
methyl acetate	14.1		
acetone	14.3	12.2	9.7
3,5,5-trimethyl-2-cyclohexen-1-one, isophorone	16.1	13.1	10.4
N,*N*-dimethylformamide	18.7		
N,*N*-dimethylacetamide	19.0		
sulfides			
dimethyl sulfide	7.8		
tetrahydrothiophene	8.0	6.8	4.1
sulfoxide, sulfone			
tetramethylenesulfone, sulfolane	13.2		
dimethyl sulfoxide	19.8	16.0	12.4
phosphoryl compounds			
trimethyl phosphate	18.5		
trimethylphosphine oxide	22.7		
hexamethylphosphoric triamide	22.8	20.7	16.5
***N*-oxide**			
pyridine *N*-oxide	20.8		
haloalkanes			
chlorocyclohexane	6.1	5.1	
fluorocyclohexane	7.2	7.5	

(40) Wiley, G. R.; Miller, S. I. *J. Am. Chem. Soc.* **1972**, *94*, 3287.
(41) Slejko, F. L.; Drago, R. S.; Brown, D. G. *J. Am. Chem. Soc.* **1972**, *94*, 9210.
(42) Wong, K. F.; Ng, S. *J. Chem. Soc., Faraday Trans. 2* **1975**, *71*, 622.
(43) Pang, T. S.; Ng, S. *J. Magn. Reson.* **1975**, *17*, 166.
(44) Rossarie, J.; Gallas, J. P.; Binet, C.; Romanet, R. *J. Chim. Phys. Phys.-Chim. Biol.* **1978**, *75*, 63.
(45) Sherry, A. D.; Purcell, K. F. *J. Phys. Chem.* **1970**, *74*, 3535.
(46) Purcell, K. F.; Stikeleather, J. A.; Brunk, S. D. *J. Am. Chem. Soc.* **1969**, *91*, 4019.
(47) Sherry, A. D.; Purcell, K. F. *J. Am. Chem. Soc.* **1972**, *94*, 1853.
(48) Nelson, J. *Spectrochim. Acta, Part A* **1970**, *26*, 109.
(49) Barakat, T. M.; Nelson, M. J.; Nelson, S. M.; Pullin, A. D. E. *Trans. Faraday Soc.* **1966**, *62*, 2674.
(50) Barakat, T. M.; Nelson, J.; Nelson, S. M.; Pullin, A. D. E. *Trans. Faraday Soc.* **1969**, *65*, 41.
(51) Flora, H. B., II; Gilkerson, W. R. *J. Am. Chem. Soc.* **1970**, *92*, 3273.
(52) Junker, M. L.; Gilkerson, W. R. *J. Am. Chem. Soc.* **1975**, *97*, 493.

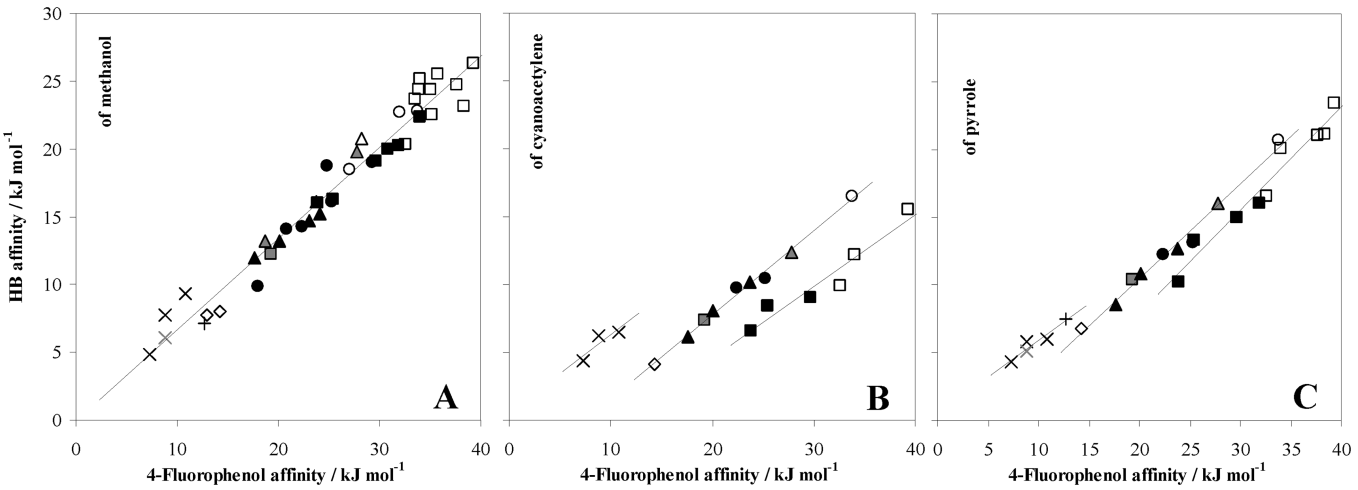


FIGURE 2. (A) Family-independent linear enthalpy relationship for hydrogen bonding of methanol and 4-fluorophenol. (B) Limited linear enthalpy relationship for hydrogen bonding of cyanoacetylene and 4-fluorophenol. The upper line represents Cπ bases, the middle line Nsp and O bases, and the lower line Nsp^2 and Nsp^3 bases (reproduced from ref 6. Copyright 2010 Wiley). (C) Slight family dependence in the linear enthalpy relationship for hydrogen bonding of pyrrole and 4-fluorophenol. The upper line represents mainly Cπ bases, the middle line mainly O bases, and the lower line Nsp^2 and Nsp^3 bases.

TABLE 5. Physicochemical Parameters (Without Units except $E_T(30)$ in kcal mol^{-1}) of Solvents Used for the Determination of 4-Fluorophenol Affinity: Comparison with the Gas Phase

medium	n^a	ε^b	π^{*c}	$E_T(30)^d$	SPP^e	SB^f	SA^g
gas phase	1	1	−1.23	~27.1	0	0	0
cyclohexane	1.426	2.02	0	30.8	0.557	0.073	0
tetrachloro methane	1.460	2.30	0.21	32.4	0.632	0.044	0
dichloro methane	1.424	9.02	0.73	40.7	0.876	0.178	0.040

[a]Refractive index at 20 °C. [b]Relative permittivity at 20 °C. [c]Solvent dipolarity/polarizability parameter from the solvatochromism of 4-nitroanisole. [d]Solvent polarity from the transition energy of a betaine numbered 30. [e]Solvent polarity parameter. [f]Solvent basicity. [g]Solvent acidity.

through a one-parameter equation) to the methylammonium cation affinity scale in the gas phase.[6] Since the HB enthalpies of tri-*n*-butylammonium picrate were obtained in polar solvents (chlorobenzene and 1,2-dichlorobenzene), it is possible that the positive charge of the NH^+ group is dispersed in the polar solvent and/or partly neutralized by the counteranion. The presence of a polar solvent and a counteranion may enable a better similarity between the conventional hydrogen bond O−H···B and the ionic hydrogen bond NH^+···B.

2.2. Application to Different Solvents. CCl_4 is the solvent of choice for the IR determination of HB enthalpies for technical and theoretical reasons. It is quite transparent to IR light in the region of interest, its solubilization power is satisfactory, and its low polarity should enable the intrinsic gas-phase affinity order to be approached. However, the applicability of the 4-fluorophenol affinity scale to other solvents needs to be tested because solution HB enthalpies depend significantly on the solvent. We have thus measured the 4-fluorophenol affinity scale in cyclohexane, a less polar solvent than tetrachloromethane, and in dichloromethane, a more polar solvent. Here, the polarity of a solvent is defined, according to Reichardt,[53] as its overall solvation ability. Table 5 presents a number of physical constants and empirical solvent parameters[53] to compare quantitatively the polarity of cyclohexane, tetrachloromethane, and dichloromethane. The 4-fluorophenol affinities in cyclohexane are given in Table 6 and those in dichloromethane in Table 7. The influence of the solvent on the ranking order of bases is studied through the LER eq 9, where a and b are constants characteristic of the solvent.

$$\text{4-FC}_6\text{H}_4\text{OH affinity (in a given solvent)} = a[\text{4-FC}_6\text{H}_4\text{OH affinity (in CCl}_4)] + b \quad (9)$$

The affinities in cyclohexane and tetrachloromethane are compared in Figure 3A. It can be seen that all the bases have greater affinities in cyclohexane than in tetrachloromethane, since they are all situated above the first bisector of the graph. However, two classes of bases can be distinguished. The first contains F, Cl, Br, I, S, Se, Nsp, and most O bases, for which the relative affinity gain in cyclohexane is roughly constant (about 23%). Consequently, these bases obey the LER (9) and their affinity order is approximately the same in cyclohexane and in tetrachloromethane. Ethers and Nsp^2 and Nsp^3 bases belong to the second class. These bases are situated to the right of the full line of eq 9. In other words, they gain affinity, compared to the first class, on going from cyclohexane to tetrachloromethane. Thus, the affinity of triethylamine in tetrachloromethane (39.4 kJ mol^{-1}) is only 2% lower than in cyclohexane (40.2 kJ mol^{-1}). Similarly, whereas in cyclohexane the affinity of 3-chloropyridine is 7.7 kJ mol^{-1} lower than the affinity of dimethyl sulfoxide, the two affinities become approximately equal in tetrachloromethane.

The comparison of the affinities in dichloromethane and tetrachloromethane (Figure 3B) yields a similar pattern: (i) all the bases are situated below the first bisector because they have lower affinities in dichloromethane, while (ii) ethers and Nsp^2 and Nsp^3 bases are nearer to the bisector, since they gain affinity, compared to the other bases, on going from CCl_4 to CH_2Cl_2. However, the data points are more scattered ($r^2 = 0.906$ for CH_2Cl_2 vs CCl_4 instead of 0.949 for c-C_6H_{12} vs CCl_4) because four classes of bases can now be distinguished.

(53) Reichardt, C. *Solvents and Solvent Effects in Organic Chemistry*; Wiley-VCH: Weinheim, 2003.

TABLE 6. Enthalpies (kJ mol^{-1}) and Entropies (J K^{-1} mol^{-1}) of Hydrogen Bonding between 4-Fluorophenol and Bases in Cyclohexane

HBA	$-\Delta H°$	$-\Delta S_x°$	HBA	$-\Delta H°$	$-\Delta S_x°$
amines			**ester**		
2,2,2-trifluoroethylamine	27.6	59.4	ethyl acetate	26.5	43.4
propargylamine	32.2	57.3	**amide**		
c-propylamine	34.3	61.0	*N,N*-dimethylacetamide	35.1	44.3
N,N-diisopropylethylamine	34.5	75.6	**sulfoxides**		
benzylamine	35.3	60.5	dimethyl sulfoxide	36.4	44.4
pyrrolidine	38.5	57.9	di-*n*-butyl sulfoxide	38.2	43.2
quinuclidine	39.9	57.7	**thioamide**		
triethylamine	40.2	75.4	*N,N*-dimethylthioacetamide	27.1	44.5
pyridines			**sulfides**		
3,5-dichloropyridine	25.9	48.9	di-*n*-butyl sulfide	17.7	31.5
3-chloropyridine	28.7	46.7	tetrahydrothiophene	18.0	30.8
pyridine	33.7	52.6	diethyl sulfide	18.2	33.1
imidazole			**haloalkanes**		
1-methylimidazole	37.5	49.2	1-iodopentane	8.2	13.3
nitriles			1-chloropentane	9.0	13.7
benzonitrile	21.3	32.4	1-bromopentane	9.0	14.3
N,N-dimethylcyanamide	28.6	39.0	1-fluoropentane	13.3	23.4
ethers			**organo derivatives of group 15 and 16 elements**		
diethyl ether	26.7	47.2	dibenzyl selenide	12.6	16.2
tetrahydrofuran	27.2	42.8	di-*n*-butyl telluride	12.7	19.7
2,2,5,5-tetramethyltetrahydrofuran	31.7	55.9	triethylstibine	≈12.8	
ketones			dimethyl selenide	16.1	30.1
acetone	26.7	42.4	triethylarsine	≈16.3	
3,5,5-trimethyl-2-cyclohexen-1-one, isophorone	31.1	43.9	triethylphosphine	21.6	36.8

TABLE 7. Enthalpies (kJ mol^{-1}) and Entropies (J K^{-1} mol^{-1}) of Hydrogen Bonding between 4-Fluorophenol and Bases in Dichloromethane

HBA	$-\Delta H°$	$-\Delta S_x°$	HBA	$-\Delta H°$	$-\Delta S_x°$
amines			**ketones**		
2,2,2-trifluoroethylamine	23.0	46.1	cyclohexanone	15.1	17.2
N,N-diallylamine	28.6	46.7	2,6-dimethyl-γ-pyrone	21.1	17.2
benzylamine	29.0	45.9	3-dimethylamino-5,5-dimethylcyclohexenone	23.9	18.9
pyrrolidine	31.4	39.8	**ester**		
triethylamine	33.1	55.6	ethyl formate	12.7	18.2
pyridines			ethyl acetate	14.5	18.5
3,5-dichloropyridine	17.8	29.0	**amide**		
3-chloropyridine	21.4	31.7	dimethylcarbamoylchloride	12.8	14.4
pyridine	24.6	33.3	*N,N*-dimethylformamide	19.1	16.6
3,5-dimethylpyridine	26.1	30.9	*N,N*-dimethylacetamide	21.2	18.2
4-*N,N*-dimethylaminopyridine	27.9	28.5	**sulfoxides**		
nitriles			dimethyl sulfoxide	19.4	12.8
benzonitrile	9.2	6.0	**amine oxide**		
acetonitrile	11.6	13.5	pyridine *N*-oxide	22.0	14.5
N,N-dimethylcyanamide	14.5	12.8	**phosphoroso compounds**		
ethers			dichlorophenylphosphine oxide	12.8	10.9
diethyl ether	17.8	27.4	triphenyl phosphate	14.2	6.2
tetrahydrofuran	18.1	23.5	trimethyl phosphate	18.1	11.1
2,2,5,5-tetramethyltetrahydrofuran	21.2	31.6	triethyl phosphate	19.0	15.7
			hexamethylphosphoric triamide (HMPA)	23.0	6.2

Indeed, Nsp^3 bases separate from Nsp^2 bases, and carbonyls split off from Nsp bases and phosphoryls.

The family dependence of the solvent effect on 4-fluorophenol affinities is established conclusively by comparing the affinities in dichloromethane and cyclohexane (Figure 3C). The extent of the affinity decrease on going from cyclohexane to dichloromethane is seen to be governed by the type of bases in the order: nitriles, sulfoxide > carbonyls > ethers > pyridines > amines

The statistics of eq 9 are summarized in Table 8. The LERs in this table should enable (i) the prediction of affinities in *c*-C_6H_{12} from the affinities in CCl_4 (or CH_2Cl_2) if one needs to approach closer gas-phase values for testing strategies of computation of hydrogen-bond energies and (ii) the prediction of affinities in CCl_4 from those in CH_2Cl_2 if bases of chemical or biological interest are not soluble in CCl_4 and if it is necessary to use the better solubilization power of CH_2Cl_2.

2.3. Is the 4-Fluorophenol Affinity Scale a General Hydrogen-Bond Affinity Scale? Summary. The 4-fluorophenol affinity scale is a reasonably general hydrogen-bond affinity scale. It applies to all OH, a number of NH, and in certain conditions, NH^+ donors. The application to CH donors, such as chloroform or alk-1-ynes, and to NH donors, such as pyrrole, suggests some family dependencies. However, conversions of the OH scale into CH and NH scales can be made through LERs. The replacement of the reference solvent, CCl_4, by an alkane does not change the affinity order of most bases, although a correction of about +2−6 kJ mol^{-1} must be applied to ethers, pyridines, and amines. Between affinities in CCl_4 and affinities in CH_2Cl_2, a common and

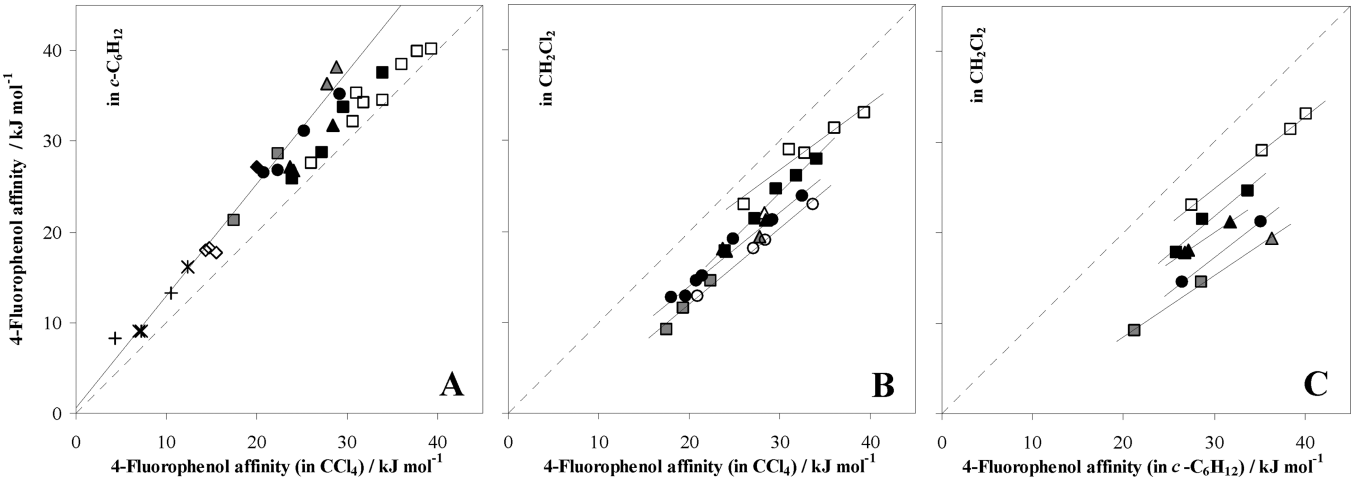


FIGURE 3. (A) Comparison of 4-fluorophenol affinities in cyclohexane and tetrachloromethane: linear enthalpy relationship (9) showing the deviation of ethers (▲), Nsp^2(■), and Nsp^3 (□) bases from the line drawn by the other bases. (B) Comparison of 4-fluorophenol affinities in dichloromethane and tetrachloromethane: limited linear enthalpy relationship showing the distinct behavior of amines (□), pyridines (■), carbonyls (●), nitriles (shaded □), and phosphoryls (○). For clarity, a number of points are not shown. (C) Family-dependent linear enthalpy relationship between the 4-fluorophenol affinities in CH_2Cl_2 and c-C_6H_{12}: nitriles and DMSO (shaded □ and shaded △), carbonyls (●), ethers (▲), pyridines (■), and amines (□). In each plot, the dashed line represents the first bisector.

TABLE 8. Relationships between 4-Fluorophenol Affinities in Cyclohexane, Tetrachloromethane, and Dichloromethane

families	slope	intercept	n	r^2	s
4-fluorophenol affinity in c-C_6H_{12} vs 4-fluorophenol affinity in CCl_4					
all bases			32	0.949	
F, Cl, Br, I, Se, S, Nsp, and O bases (except ethers)	1.23 ± 0.04	0.6 ± 0.1	17	0.983	1.3
Nsp^2 and Nsp^3 bases	0.97 ± 0.08	3.1 ± 2.5	12	0.939	1.2
4-fluorophenol affinity in CCl_4 vs 4-fluorophenol affinity in CH_2Cl_2					
all bases			30	0.906	
Nsp, PO, and SO bases	1.17 ± 0.05	4.8 ± 0.9	8	0.989	0.6
carbonyls	1.22 ± 0.07	1.8 ± 1.3	8	0.982	0.8
ethers	1.40 ± 0.18	−2.6 ± 3.7	3	0.983	0.5
Nsp^2 bases	0.99 ± 0.07	5.1 ± 1.7	5	0.986	0.5
Nsp^3 bases	1.28 ± 0.19	−5.3 ± 5.8	5	0.937	1.5
4-fluorophenol affinity in c-C_6H_{12} vs 4-fluorophenol affinity in CH_2Cl_2					
all bases			15	0.724	
Nsp and SO bases	1.48 ± 0.06	6.0 ± 1.0	3	0.998	0.4
carbonyls	1.28	6.6	2		
ethers	1.49 ± 0.06	−1.3 ± 1.1	3	0.999	0.1
Nsp^2 bases	1.14 ± 0.23	4.1 ± 5.1	3	0.962	1.1
Nsp^3 bases	1.27 ± 0.01	−2.8 ± 0.4	4	1.000	0.1

representative polar solvent, there are relationships within families, but not across families. Nevertheless, conversions can again be made through LERs.

3. Structure−Hydrogen-Bond Affinity Relationships. 3.1. Hydrogen-Bond Acceptor Atomic Site. The alkyl derivatives of elements of groups 15, 16, and 17 (R_nE) have been chosen for a discussion of the effects of the atomic site (E) of hydrogen bonding on 4-fluorophenol affinities. To minimize solvent effects, affinities were measured in cyclohexane. In spite of small length differences in the alkyl substituent(s) R, we believe that the affinities of compounds R_nE, presented in Table 6, depend essentially on the atomic structure of the element E. The order of affinities, illustrated in Figure 4, is the following:

$$R_3N >> R_2O >> R_3P >> R_2S > R_3As \approx R_2Se > RF \approx R_3Sb \approx R_2Te > RCl \approx RBr > RI$$

This sequence combines the affinity decrease in descending order in a given group and the affinity decrease in going from left to right within a given period. It cannot be explained by a simple atomic property such as electronegativity χ[54] (correlation coefficient with affinity $r = 0.025$) or hardness η[54] ($r = 0.673$). Pauling's statement[55] that "the strength of the [hydrogen] bond should increase with an increase in the electronegativity of the two bonded atoms" (X and E in $XH\cdots ER_n$) is only obeyed within a given group (Figure 5, solid lines). In contrast, within a period, there is a *decrease* in affinity with increasing electronegativity (Figure 5, dashed lines). Two simple descriptors of the base, however, give better affinity orders than electronegativity and hardness, namely the ionization energy difference ΔIE as

(54) Parr, R. G.; Pearson, R. G. *J. Am. Chem. Soc.* **1983**, *105*, 7512.
(55) Pauling, L. C. *The Nature of the Chemical Bond and the Structure of Molecules and Crystals. An Introduction to Modern Structural Chemistry*, 3rd ed.; Cornell University Press: Ithaca, NY, 1960.

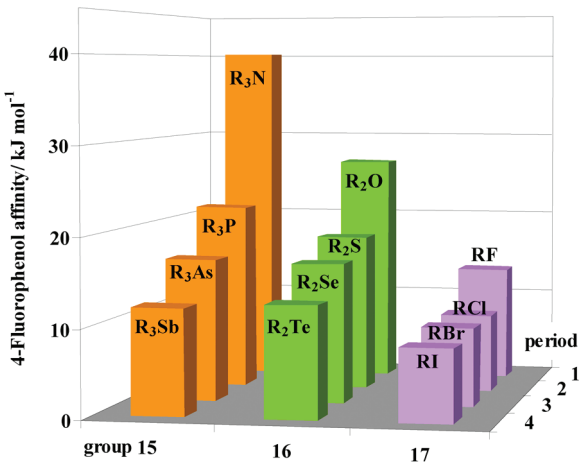


FIGURE 4. Comparison of bases R_nE (R = alkyl, E = element of group 15, 16, or 17). Variation in 4-fluorophenol affinity with position of the element E in the periodic table.

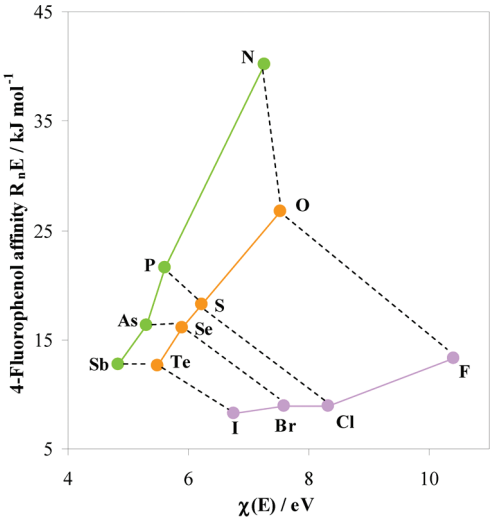


FIGURE 5. Plot of the 4-fluorophenol affinity of compounds R_nE vs the electronegativity of the hydrogen-bond acceptor atom E.

defined by Allen[56] (the difference between the energy ionizations of the base and the noble gas atom in its row) and the minimum electrostatic potential $V_{S,min}$ of the base (situated on E in the direction of a putative lone pair). The correlation with ΔIE (r = 0.911) expresses the contributions of dispersion, induction, and charge transfer to the hydrogen-bond energy, while the correlation with $V_{S,min}$ (r = 0.868) expresses the well-known importance of the electrostatic term.[57] The values of the parameters χ, η, ΔIE, and $V_{S,min}$ and figures illustrating the correlations are given in the Supporting Information.

The chalcogen order is found again in phosphine chalcogenides (Ph_3PO > Ph_3PS > Ph_3PSe), phosphates (EtO_3PO > EtO_3PS), and amides ($RCONMe_2$ > $RCSNMe_2$). In hydrogen bonding, oxygen bases always have higher affinities than the corresponding sulfur bases, according to the hard character of HBDs, the hard character of O bases (while S bases are soft), and the hard and soft acid and base principle.[5] The gain in affinity in going from sulfur to oxygen is about 40% for $RCENMe_2$, 70% for R_2E, and 100% for R_3PE.

When two potential HBA sites are kept close together, a three-center hydrogen bond can be formed. Three-center hydrogen bonds are common in solid-state structures,[58] especially in crystalline structures of biomolecules.[59] However, the thermodynamics of formation of three-center versus two-center hydrogen bonds has not received much attention. A few bases contained in our sample are likely to form three-center hydrogen bonds, such as pyridazine (1,2-diazine), nitro and sulfonyl compounds, veratrole (1,2-dimethoxybenzene), and 1,10-phenanthroline. The three-center hydrogen bond of *syn*-2,4-difluoroadamantane with HF has already been studied theoretically.[22] We shall complete this study with 4-fluorophenol as HBD. It is already known that nitro compounds[60] and veratrole-like structures[58] can form three-center hydrogen bonds in the solid state. We have performed a search in the Cambridge Structural Database[61] (CSD) on the hydrogen bonding of sulfonyl compounds and 1,10-phenanthrolines (not coordinated with a metal cation). Out of 970 crystalline structures containing both a sulfonyl group and an OH donor group, 354 structures show 449 two-center $SO_2\cdots HO$ hydrogen bonds, while only three structures clearly form three-center hydrogen bonds with the OH donor. On the contrary, in the 30 structures containing both phenanthroline and OH donor motifs, three-center hydrogen bonds are much more common. Indeed, among the 36 $N\cdots HO$ hydrogen bonds found in 21 structures, 24 are three-centered interactions and only 12 are two-centered ones.

In vacuo, DFT calculations (carried out at the MPWB1K/6-31+G** level) show, for nitromethane, and confirm, for sulfolane, that the three-center hydrogen-bonded complexes with 4-fluorophenol do not correspond to stable geometries on the potential energy surface (PES). All minima (absolute or local) on the PES correspond to two-center hydrogen-bonded complexes. Figure 6 represents the absolute minima geometries of these two-center complexes.

The experimental gas-phase structure[62] of the complex of pyridazine with water is also two-centered. The high affinity of this 1,2-diazine compared to the 1,3- and 1,4-diazines can be related to the high gas-phase basicity of a number of 1,2-diazoles and 1,2-diazines.[63] Their high proton basicity is caused by the relief, upon protonation of one nitrogen, of the repulsion between the neighboring nitrogen lone pairs.[63] A similar relief can occur upon hydrogen bonding and causes the 5.7 kJ mol^{-1} increase in affinity of pyridazine (1,2-diazine) compared to pyrimidine (1,3-diazine).

The Atoms in Molecules (AIM) topological analysis[64] of the electron density of the complex of 4-fluorophenol with veratrole shows two hydrogen-bond paths with two critical points and

(56) Allen, L. C. *J. Am. Chem. Soc.* **1975**, *97*, 6921.
(57) Buckingham, A. D. *Theoretical Treatments of Hydrogen Bonding*; Wiley: New York, 1997.
(58) Steiner, T. *Angew. Chem., Int. Ed.* **2002**, *41*, 48.
(59) Jeffrey, G. A.; Saenger, W. *Hydrogen Bonding in Biological Structures*; Springer-Verlag: Berlin, 1991.
(60) Panunto, T. W.; Urbanczyk-Lipkowska, Z.; Johnson, R.; Etter, M. C. *J. Am. Chem. Soc.* **1987**, *109*, 7786.
(61) Allen, F. H. *Acta Crystallogr. B* **2002**, *B58*, 380.
(62) Caminati, W.; Moreschini, P.; Favero, P. G. *J. Phys. Chem. A* **1998**, *102*, 8097.
(63) Taft, R. W.; Anvia, F.; Taagepera, M.; Catalan, J.; Elguero, J. *J. Am. Chem. Soc.* **1986**, *108*, 3237.
(64) Bader, R. F. W. *Atoms in Molecules: A Quantum Theory*; Clarendon: Oxford, 1994.

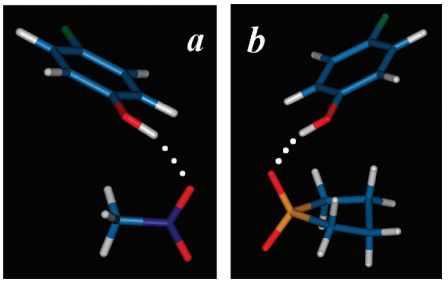


FIGURE 6. MPWB1K/6-31+G(d,p) geometries of two-center hydrogen-bonded complexes of 4-fluorophenol with (a) nitromethane, and (b) sulfolane.

electron densities at the critical points, ρ_{BCP}, of 0.018 and 0.016 au. Experimentally, this three-center hydrogen-bonded complex has a 4-fluorophenol affinity 10 kJ mol^{-1} higher than that of the two-center complex of anisole (this literature calorimetric value[15] is, however, slightly contaminated by the presence of a π complex in addition to the O complex of interest). Veratrole-like moieties appear as a substructure of numerous alkaloids active on the central nervous system and of other drugs. The high HB affinity of this substructure might constitute one of the factors which enable it to bind to receptors.

An AIM analysis of the complex of 4-fluorophenol with 1,10-phenanthroline also shows two critical points between the (O)H and the Ns with $\rho_{BCP} = 0.018$ and 0.015 au. This three-center hydrogen bond gives a 4-fluorophenol affinity to 1,10-phenanthroline which is 6.6 kJ mol^{-1} higher than that of quinoline. Thus, 1,10-phenanthroline becomes the second most basic *N*-heteroaromatic of our sample (just below a push−pull pyridine, 4-pyrrolidinopyridine).

In summary, the hydrogen-bond acceptor affinity can be significantly reinforced by putting two HBA atoms close to each other in a rigid structure. In this way, a very negative electrostatic potential can be created between the two HBA atoms. For example, $V_{S,min} = -245$ kJ mol^{-1} between the two nitrogen lone pairs of 1,10-phenanthroline while it is only −158 kJ mol^{-1} for pyridine with one lone pair. As a consequence of the increased electrostatic contribution, the hydrogen-bond energy is significantly increased, in spite of a slightly less favorable overlap of the σ^*_{OH} localized orbital with a lone pair of the HBA atom which diminishes the charge transfer contribution, as shown by an NBO analysis. For example, the occupancy of σ^*_{OH} is 0.028 electron in the complex with veratrole, while it is 0.031 electron with anisole. This testifies again to the pre-eminence of the electrostatic over the charge transfer in the hydrogen-bond energy.[57]

Figure 7 shows the structures of the three-center hydrogen-bonded complexes of 4-fluorophenol with the fluoroalkane, the ether, and the phenanthroline. The results of the electrostatic potential calculations, the AIM analysis (bond critical points), and the NBO analysis (charge transfer) are contained in the Supporting Information.

3.2. Functions and Heterocycles. The next structural effect on HB affinities after the nature of the HBA atom is the functionality of this atom. Figure 8 compares the 4-fluorophenol affinities of O, S, N, and C bases corresponding to different functions. As far as possible, similar alkyl groups were attached to the functions to obtain an intrinsic affinity order characteristic of the function alone.

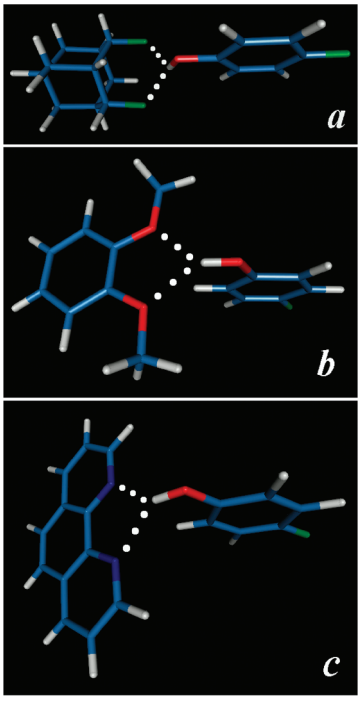


FIGURE 7. MPWB1K/6-31+G(d,p) geometries of three-center hydrogen-bonded complexes of 4-fluorophenol with (a) syn-2,4-difluoroadamantane, (b) veratrole (1,2-dimethoxybenzene), and (c) 1,10-phenanthroline.

Oxygen bases. The HB affinities of oxygen functionalities are found in the following order:

$$\text{—NO} >> \text{—PO} > \text{SeO} > \text{SO} > \text{O} > \text{C=O} > \text{SO}_2 > \text{NO}_2$$

In pnictogen oxides and chalcogen oxides, there is a significant contribution of the zwitterionic valence bond structure in which oxygen bears three lone pairs and a formal negative charge (Scheme 1). This explains why the four oxides R_3NO, R_3PO, R_2SeO, and R_2SO have the highest HB affinities of the oxygen bases. Amine oxides are singly bound with a dative bond and no back-bonding of lone pairs.[65] The presence of either two π back-bonds (negative hyperconjugation) or three π back-bonds in the phosphine oxides[66] and their absence in the amine oxides thus explains the much higher HB affinity of R_3NO. The greater HB affinity of Me_2SeO compared to Me_2SO is similarly explained[67] by a negative hyperconjugation $n_O \rightarrow \sigma^*_{S(Se)-C}$, greater in the sulfoxide than in the selenoxide.

Alkyl substituents introduce such large effects on the HB affinities of ketones and ethers that averaging is necessary to show that ethers have an HB affinity about 4 kJ mol^{-1} higher (Figure 9). A simplistic description of the lone pairs of oxygen as sp^3 hybrids in ethers and sp^2 hybrids in ketones[68] and the common dogma that a greater p character of a lone pair increases Lewis basicity explains the order ether > ketone.

(65) Schmidt, M. W.; Gordon, M. S. *Can. J. Chem.* **1985**, *63*, 1609.
(66) Gilheany, D. G. *Chem. Rev.* **1994**, *94*, 1339.
(67) Renault, E.; Le Questel, J.-Y. *J. Phys. Chem. A* **2004**, *108*, 7232.
(68) Wiberg, K. B.; Marquez, M.; Castejon, H. *J. Org. Chem.* **1994**, *59*, 6817.

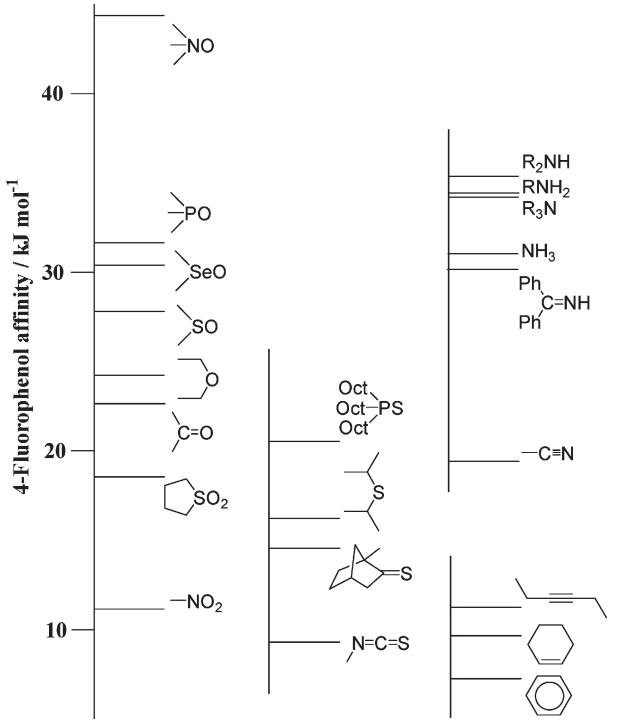
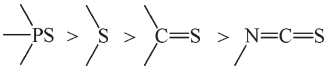


FIGURE 8. Plot of 4-fluorophenol affinity values in CCl_4 for functional groups commonly encountered in organic chemistry. The O, S, N, and C bases are grouped on different vertical axes.

SCHEME 1

Finally, the low HB affinities of sulfonyls, and even more of nitroalkanes, are not surprising if one considers the electron-attracting effect of each oxygen on the electron density of the other.

Sulfur Bases. The following HB affinity order is found for sulfur bases:



The contribution of the zwitterionic structure P^+-S^- to the PS bond[69] explains the top position of phosphine sulfides. The thioether function has a higher HB affinity than the thiocarbonyl, provided compounds with similar carbon contents are compared. The explanation for −S− > =S might not be the same as for −O− > =O. Hydrogen-bond formation to oxygen is driven by the interaction of the positive charge on hydrogen with the negative charge on oxygen, whereas with sulfur the main interaction is between the hydrogen charge and the dipole and quadrupole of sulfur.[70] In the isothiocyanate function, the electron-withdrawing effect of the N=C moiety, with its electronegative sp carbon atom,[24] might account for this function having the lowest HB affinity of the O, N, and S bases studied.

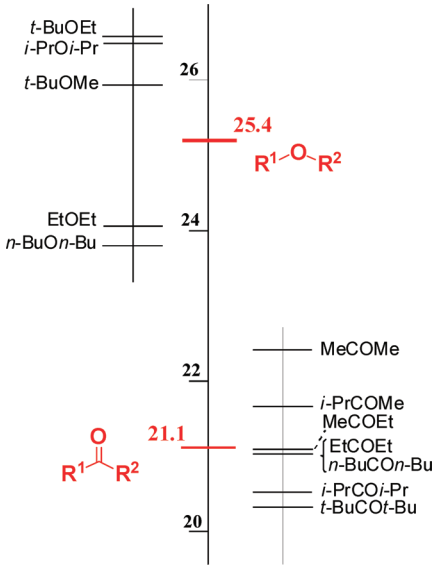
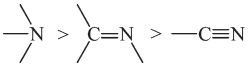


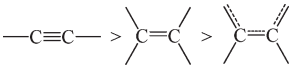
FIGURE 9. Comparison of the individual 4-fluorophenol affinities of dialkyl ethers and dialkyl ketones and of their average (red line).

Nitrogen Bases. Their affinity toward hydrogen-bond donors follows the order:



This order holds toward all Lewis acids and is most simply explained by an increased p character of the nitrogen lone pair. In the section on substituent effects, we shall comment on the 4-fluorophenol affinity order $R_2NH > RNH_2 \approx R_3N > NH_3$ which differs from that found toward the proton[71] and methanol[72] in the gas phase ($R_3N > R_2NH > RNH_2 > NH_3$).

Carbon Bases. In comparing π bases with the same carbon content (hex-3-yne, cyclohexene, and benzene), we are confident that the order



is intrinsic to the HB affinity of the alkyne, alkene, and six-membered arene functions.

Heterocycles. Heterocycles are important constituents of organic and bioactive molecules. Their 4-fluorophenol affinities are compared in Figure 10.

In saturated heterocycles, one finds the same order as that of the corresponding acyclic compounds: amines > ethers > sulfides. Thus, the most basic saturated heterocycle is quinuclidine and the least basic is 1,4-dithiane. The inversion between cineole and hexamethylenetetramine arises from the presence of four electronegative nitrogens in the latter. The low affinity of the five-membered thiazolidine, compared to its six-membered analogue thiomorpholine, remains to be explained. Figure 11 shows that the 4-fluorophenol affinity

(69) Dobado, J. A.; Martinez-Garcia, H.; Molina, J. M.; Sundberg, M. R. *J. Am. Chem. Soc.* **1998**, *120*, 8461.
(70) Platts, J. A.; Howard, S. T.; Bracke, B. R. F. *J. Am. Chem. Soc.* **1996**, *118*, 2726.
(71) Hunter, E. P. L.; Lias, S. G. *J. Phys. Chem. Ref. Data* **1998**, *27*, 413.
(72) Millen, D. J.; Mines, G. W. *J. Chem. Soc., Faraday Trans. 2* **1974**, *70*, 693.

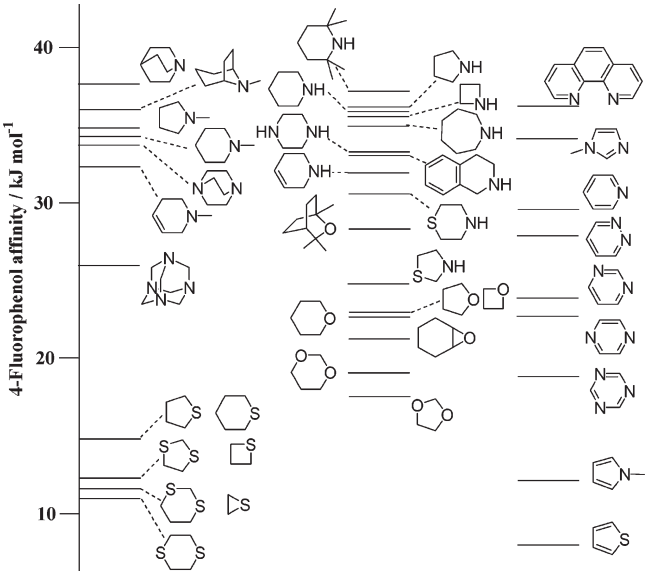


FIGURE 10. Plot of 4-fluorophenol affinity values in CCl_4 for heterocycles. Saturated and aromatic heterocycles are grouped on different vertical axes. For the sake of clarity, secondary cyclic amines and cyclic ethers are separated from tertiary cyclic amines and cyclic thioethers.

of *c*-$(CH_2)_n$NH does not vary much from $n = 3$ to $n = 6$, and similarly for *c*-$(CH_2)_n$O from $n = 3$ to $n = 5$. There is a small decrease for the most strained cyclic sulfides ($n = 2$ and 3). NBO analysis of the p character of the heteroatomic lone pair(s), reported in Table 9, shows that rehybridization of the lone pair(s) upon variation of the CN(O,S)C angle is significant only in the three-membered ring structures ($n = 2$).

In our set of *unsubstituted* heteroaromatic rings, 1,10-phenanthroline has the highest HB affinity. Next comes the imidazole ring, which can be seen as a cyclic amidine with the imino nitrogen pulling the electronic densities of the ring and of the amino nitrogen. In the six-membered azines, pyridine forms a strong OH···N hydrogen bond. However, the comparison of sp^2 nitrogen bases shows that imines are stronger HBAs than pyridine. The introduction of a second nitrogen reduces the HB affinity by different degrees in the order 1,2- > 1,3- > 1,4-diazine. The addition of a third nitrogen (1,3,5-triazine) decreases the HB affinity further. *N*-Methylpyrrole and thiophene have both nonbonding and π-bonding pairs and give n and/or π complexes.[73,74] They form weak and very weak hydrogen bonds, respectively, with 4-fluorophenol.

3.3. Substituent Effects. The HB affinity orders established above provide only benchmarks to predict HB affinity, since even relatively simple substituents introduce such large effects that these orders may become inapplicable. For example, although $Me_3PO \gg Me_2SO \gg Me_2CO$, a trisubstituted cyclohexenone (3-dimethylamino-5,5-dimethylcyclohexenone) has a higher HB affinity than the phosphine oxide and the sulfoxide. Factors that modify, singly or in any combination, 4-fluorophenol affinity values comprise electronic effects, mainly field/inductive and resonance effects and possibly polarizability effects, and steric effects. The HB affinity of a set of substituted

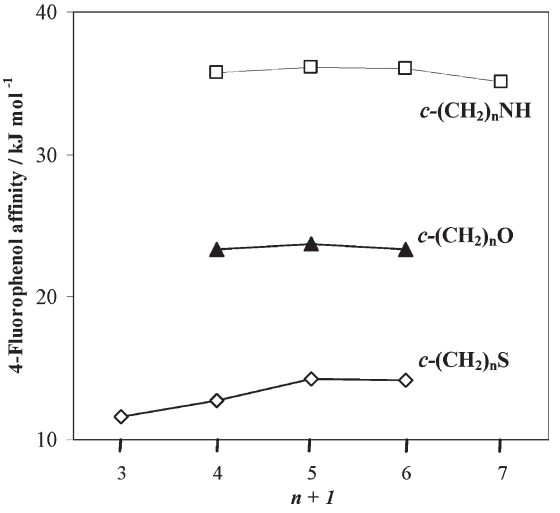


FIGURE 11. Plot of 4-fluorophenol affinity versus ring size ($n + 1$) in heterocycles *c*-$(CH_2)_n$NH, *c*-$(CH_2)_n$O, and *c*-$(CH_2)_n$S.

TABLE 9. CN(O,S)C Angles (MPWB1K/6-31+G(d,p) Level) and % p Character of the Heteroatom Lone Pair(s) of Cyclic Amines, Ethers, And Sulfides, Calculated by the NBO Procedure

heterocycle	ring size	CN(O,S)C/deg	% p
aziridine	3	61.1	65.8
azetidine	4	90.4	80.8
pyrrolidine	5	104.6	83.2
piperidine	6	112.2	84.5
azepane, hexamethyleneimine	7	116.9	86.6
oxirane	3	62.3	36.7[a]
oxetane	4	91.7	51.5[a]
tetrahydrofuran	5	110.3	59.5[a]
tetrahydropyran	6	112.0	58.9[a]
ethylene sulfide	3	48.4	19.5[a]
trimethylene sulfide	4	77.5	27.7[a]
tetrahydrothiophene	5	94.0	31.5[a]
pentamethylene sulfide	6	97.6	32.0[a]

[a]The character of the second lone pair is almost 100% p.

HBAs can be predicted by the linear structure−energy relationship[75] (10), in terms of substituent constants σ_F,[76] σ_R,[76] σ_α,[76,77] and υ[78] for field/inductive, resonance, polarizability, and steric effects, respectively, and the corresponding reaction constants ρ. The constant h is related to the unsubstituted HBA.

$$-\Delta H^\circ = \rho_F\sigma_F + \rho_R\sigma_R + \rho_\alpha\sigma_\alpha + \rho_S\upsilon + h \qquad (10)$$

Field/Inductive Effects. Most substituents are more electronegative than the hydrogen or hydrocarbon group that they replace. Consequently, they exert an electron-attracting field/inductive effect (hereafter called −I effect) decreasing the electron density around the HBA atom and thus the HB affinity. Well-known examples of such substituents are F, Cl, Br, CF_3, and CCl_3. Figure 12 shows the almost additive effect of successive chlorine substitution of the phenyl group of

(73) Legon, A. C.; Ottaviani, P. *Phys. Chem. Chem. Phys.* **2004**, *6*, 488.
(74) Munoz, M. A.; Galan, M.; Gomez, L.; Carmona, C.; Guardado, P.; Balon, M. *Chem. Phys.* **2003**, *290*, 69.
(75) Taft, R. W.; Topsom, R. D. *Prog. Phys. Org. Chem.* **1987**, *16*, 1.
(76) Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *91*, 165.
(77) Hehre, W. J.; Pau, C. F.; Headley, A. D.; Taft, R. W.; Topsom, R. D. *J. Am. Chem. Soc.* **1986**, *108*, 1711.
(78) Charton, M. *Top. Curr. Chem.* **1983**, *114*, 57.

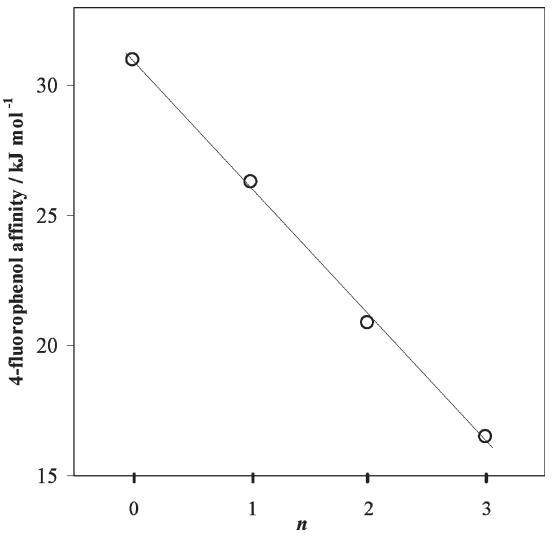


FIGURE 12. Plot of 4-fluorophenol affinities of $Cl_nPh_{3-n}PO$ vs the indicator variable *n*.

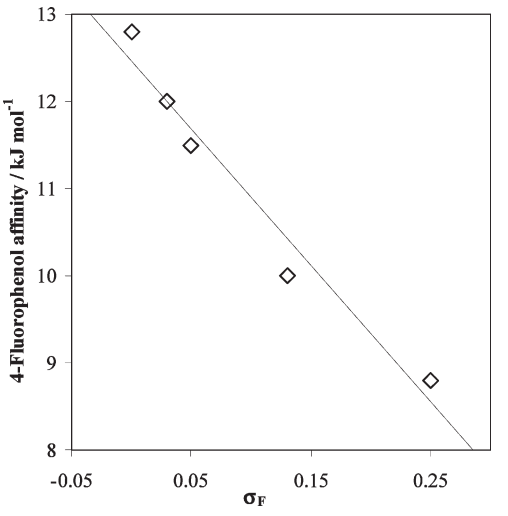


FIGURE 13. Relationship between 4-fluorophenol affinity and the field/inductive substituent constant σ_F for thioethers XSMe and the disulfide MeSSMe.

Ph_3PO on the HB affinity. Three chlorine atoms reduce this affinity so much that the hydrogen bond to Cl_3PO is among the weakest of oxygen bases. Similarly, $CF_3CH_2NH_2$, CF_3-$COCH_3$, $F(CH_2)_3F$, and $Br(CH_2)_3Br$ are the weakest HBAs of the studied primary amines, ketones, fluoroalkanes, and bromoalkanes, respectively. Substituents without heteroatoms but with electronegative sp^2 or sp carbon atoms, such as C_6H_5, $H_2C{=}CH$, or $HC{\equiv}C$, can also decrease significantly the HB affinity. For example, tripropargylamine, $(HC{\equiv}CCH_2)_3N$, has the lowest affinity of all the studied aliphatic tertiary amines.

Equation 10, reduced to its $\rho_F\sigma_F$ term, has been applied to series where the resonance effect cannot operate. Aliphatic primary amines XCH_2NH_2, secondary amines XCH_2NHMe, tertiary amines XCH_2NMe_2, as well as cyclic 2-substituted pyrrolidines and *N*-methylpyrrolidines give correlation coefficients, with σ_F alone, varying from 0.917 to 0.995, with $\rho_F \approx -20$ kJ mol^{-1}. These correlations are satisfactory, taking into account that, along a given series, steric and polarizability effects may vary, as well as the orientation of the substituent owing to conformational changes. If the reference unsubstituted amine is changed so that the series of secondary amines becomes X_2NH and that of tertiary amines becomes X_3N, disubstituted amines (for example diallylamine) and trisubstituted amines (for example tripropargylamine) can be included in the data sets, assuming the additivity of the field/inductive effect. Then ρ_F rises to -30 kJ mol^{-1} since the substituent and the function become closer. This dependence of the field/inductive effect on the distance of the HBA site from the substituent is further illustrated in the following chloroalkanes: $Cl(CH_2)_4CH_3$ (7.0), $Cl(CH_2)_5Cl$ (6.4), $Cl(CH_2)_4Cl$ (6.2), $Cl(CH_2)_3Cl$ (5.8, all values in kJ mol^{-1}). Applying eq 10 found for the X_3N series to $[CF_3(CF_2)_n]_3N$ perfluoroalkylamines yields a zero HB affinity for these amines. This explains why perfluorobutylamine was found[79] to be as inert a solvent as perfluorohexane toward trichloroacetic acid yet a strong HB donor. Equation 10 can also be applied successfully to the series XSMe ($n = 5$, $r = 0.981$) with $\rho_F = -16 \pm 2$ kJ mol^{-1}. Compared to amines X_3N, ρ_F is about twice as small, indicating a lower sensitivity of sulfur than nitrogen to field/inductive effects. The disulfide MeSSMe, included in the set of thioethers by considering disulfides as thioethers substituted by a thioalkyl group, does not deviate significantly from the regression line, as shown in Figure 13. This might indicate that the reduced HB affinity of a disulfide compared to a thioether is caused mainly by the $-$I effect of the thioalkyl substituent.

Resonance Effect. Resonance effects arise from n or π electron delocalization. Lone pair delocalization toward π systems reduces the electron density of the lone pair, and hence reduces its HB affinity. Thus, $C_6H_5NMe_2$, C_6H_5OMe, and $H_2C{=}CHSEt$ have much weaker HB affinities than their corresponding aliphatic function (Scheme 2), all the more so since the field/inductive effect operates in the same direction. The HB affinity of the nitrogen of arylamines falls so much that triphenylamine behaves mainly as a π HBA. Indeed, the infrared spectrum of its complex with 4-fluorophenol in CCl_4 shows an intense OH$\cdots\pi$ band, while a very weak OH$\cdots$N band appears only at low temperature.[80]

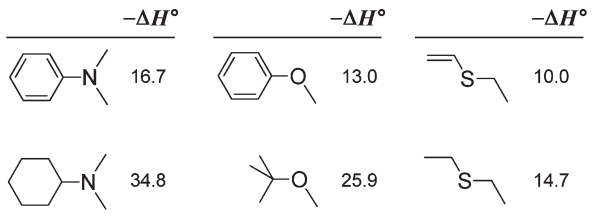
When the phenyl or vinyl substituents give π electrons to the function to which they are attached, their $-$I effect opposes their $+$R effect, and the corresponding aromatic (acrylic) HBAs generally have reduced HB affinities compared to their aliphatic counterparts (Scheme 3).

Unlike the phenyl and vinyl substituents, the $-$I effect of the NR_2 dialkylamino substituents is greatly surpassed by a strong $+$R effect. In push$-$pull systems, the nitrogen lone pair delocalization toward a resonance electron-withdrawing group (e.g., C$\equiv$N or NO_2) becomes so great that the amino nitrogen loses its HBA ability to the benefit of the pulling group. The pushing NR_2 may be attached directly to the pulling group, as in amides R_2N-COR or cyanamides R_2N-C$\equiv$N, or through a transmitter, as in vinylogous amides, R_2N-CH$=$CH-COR, or vinylogous cyanamides, R_2N-CH$=$CH-C$\equiv$N. The push$-$pull mechanism creates

(79) Nicolet, P.; Laurence, C.; Lucon, M. *J. Chem. Soc., Perkin Trans. 2* **1987**, 483.

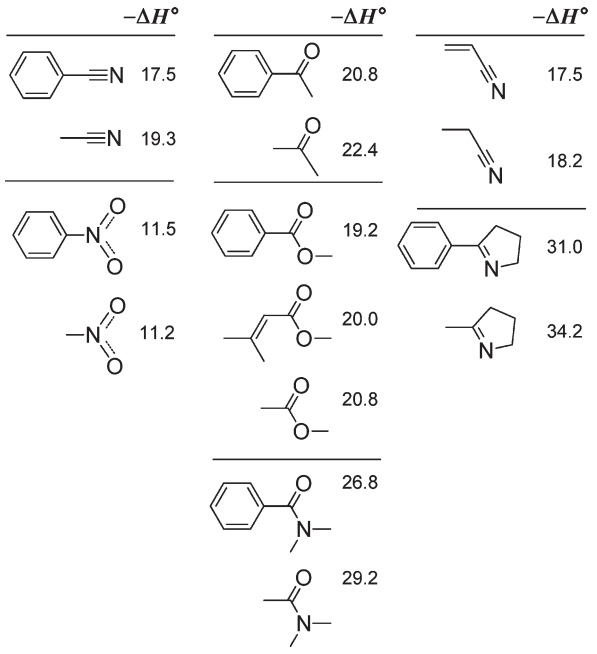
(80) Marquis, E.; Graton, J.; Berthelot, M.; Planchat, A.; Laurence, C. *Can. J. Chem.* **2004**, *82*, 1413.

SCHEME 2[a]



[a]Affinities in kJ mol^{-1}.

SCHEME 3[a]



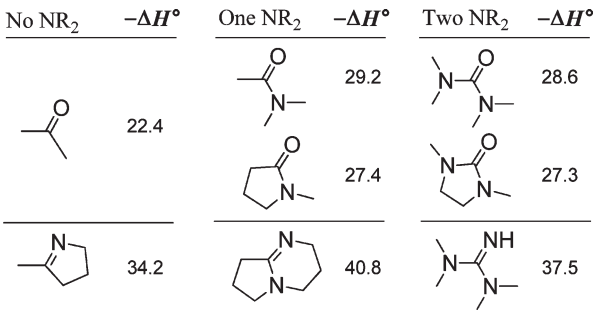
[a]Affinities in kJ mol^{-1}.

molecules that are superbasic in hydrogen bonding. For example, on the 4-fluorophenol affinity scale, 3-dimethylamino-5,5-dimethylcyclohexenone, a vinylogous amide, dominates all carbonyl bases and also sulfoxides, selenoxides, and many phosphine oxides. Other examples of the vinylogy effect are the vinylogous urethane, Me_2N-CH=CH-COOEt, and the vinylogous nitramine, Me_2N-CH=CH-NO_2, which dominate the esters and the nitro compounds respectively. Among push−pull nitriles, the iminologous cyanamide Me_2N-CH=N-C≡N exceeds the vinylogous one, Me_2N-CH=CH-C≡N. This example indicates that CH=N transmits the push−pull effect better than CH=CH. The same observation has been made in other systems.[81] It can be generalized as follows: if a basic pulling function A and a resonance electron-donating substituent D are separated by an imino group, the HB affinity of the function becomes higher than that of the parent or the vinylogous molecules, or more simply: D-A < D-CH=CH-A < D-CH=N-A.

In the same way that the resonance effect makes amides and thioamides more basic than ketones and thioketones, respectively, amidines are more basic than imines, and the

(81) Laurence, C.; Berthelot, M.; Raczynska, E.; Le Questel, J. Y.; Duguay, G.; Hudhomme, P. *J. Chem. Res., Synop.* **1990**, 250.

SCHEME 4[a]



[a]Affinities in kJ mol^{-1}.

cyclic amidine DBN has the highest 4-fluorophenol affinity (40.8 kJ mol^{-1}) of all nitrogen bases studied. Surprisingly, despite the presence of *two* NMe_2 donor groups, the tetramethylguanidine HB affinity is lower (37.5 kJ mol^{-1}). The same observation can be made when comparing ureas to amides: while the HB affinity increases strongly from ketones to amides, it does not rise further with ureas (Scheme 4).

Para-substituted aminopyridines can be described as vinylogous cyclic amidines. The effect of the pushing mechanism on HB affinity increases in the order

$$4\text{-}NH_2 < 4\text{-}NHMe < 4\text{-}NMe_2 < 4\text{-}c\text{-}(CH_2)_4N$$

so that 4-pyrrolidinopyridine has the highest 4-fluorophenol affinity (36.3 kJ mol^{-1}) of the *N*-heteroaromatics studied.

The similar HB affinities for a sulfone and sulfonamides on the one hand, and for phosphine oxides and hexamethylphosphoramide on the other hand, may be a somewhat unexpected finding given the strong +R effect of NR_2 substituents. This indicates that they do not participate in a resonance structure as is the case for carboxamides. In fact, a comparative CSD search on the structure of amides, sulfonamides, and phosphoramides showed that the two latter have pyramidal geometries, while the amide skeleton is almost planar. Indeed, the distance between the nitrogen and the plane defined by its three linked atoms is significantly different from 0.0 Å in sulfonamides and phosphoramides (89% and 45% of the structures show a distance larger than 0.1 Å). On the contrary, most of these distances (83%) are smaller than 0.1 Å in amide structures.

In all the studied aromatic systems (benzylamine, benzonitrile, pyridine, imidazole, 2-phenylpyrroline, and diphenyl sulfoxide), molecules that are ring-substituted by halogens have lower HB affinities than the unsubstituted ones. Similarly, ClC(=S)NMe_2 and ClC(=O)NMe_2 have reduced affinities compared to HC(=S)NMe_2 and HC(=O)NMe_2, respectively. Therefore, the strong −I effect of halogens prevails over their +R effect.

The respective importance of the −I and +R effects of alkoxy substituents on HB affinity is more varied. In carbonyl compounds, the HB affinity of ketones, aldehydes, esters, and carbonates follows the order MeC(=O)Me > MeC(=O)-OMe > MeC(=O)H > MeOC(=O)OMe. In aromatic systems, MeO may enhance (3-$MeOC_6H_4CH_2NH_2$ > $C_6H_5CH_2NH_2$ and 4-$MeOC_6H_4C{\equiv}N$ > $C_6H_5C{\equiv}N$) or diminish (2-MeO-C_5H_4N < C_5H_5N) the HB affinity. In the doubly vinylogous

ester, 2,6-dimethyl-γ-pyrone, the +R effect of the oxygen is predominant. It appears that the respective importance of the −I and +R effects of OR substituents depends on the distance of the OR group from the HBA site, since the −I effect always decreases while the +R effect may increase (for example, by the vinylogy effect) when this distance increases.

The respective contributions of the I and R mechanisms to the substituent effect can be analyzed by means of eq 10. Results for ring-substituted benzylamines, benzonitriles, and pyridines are reported in the Supporting Information. It is noteworthy that the field/inductive effect is the major mechanism controlling the HB affinity of ortho-substituted pyridines, since 85% of the variance of the 4-fluorophenol affinity is explained by σ_F. The +R effect only increases the HB affinity significantly in para-substituted pyridines. When the substituent is bonded directly to the function, as in $X_2C{=}O$, X_2SO, or X_3PO compounds, the substituent constants σ_F and σ_R yield generally poor correlations. A special constant, σ^{Φ}, has been defined[82] for substituents at phosphorus to correlate the dissociation constants of organophosphorus acids, as well as rate constants for their esterification or ester hydrolysis. A good correlation (eq 11, Figure 14) is obtained between the 4-fluorophenol affinities of X_1X_2-X_3PO compounds and the sum of the σ^{Φ} constants of the X substituents at phosphorus.

$$-\Delta H^{\circ}/\text{kJ mol}^{-1} = (25.3 \pm 0.5) - (2.64 \pm 0.21)\Sigma\sigma^{\Phi} \quad (11)$$

$$n = 9; r = 0.979; s = 1.3 \text{ kJ mol}^{-1}$$

The size of the substituent appears to be a significant specific effect of substituents at phosphorus. Indeed, the most negative σ^{Φ} value corresponds to the bulky *tert*-butyl group ($\sigma^{\Phi} = -1.55$ while $\sigma^{\Phi}(\text{Me}) = -0.96$ and $\sigma^{\Phi}(\text{H}) = 0$), and eq 11 predicts that $(t\text{-Bu})_3PO$ should have the highest affinity (37.6 kJ mol^{-1}) of phosphine oxides. This prediction agrees with the extremely long PO bond in $(t\text{-Bu})_3PO$ which suggests this should be regarded as a dative $P^+{-}O^-$ bond.[83] In this structure without back-bonding of the oxygen lone pairs, the oxygen atom is very basic. Calculations are needed to know if and how the opening of the CPC angles (to relax the steric strain between the three voluminous substituents at phosphorus) disfavors back-bonding.

A computational study is also necessary to explain the very low HB affinities of $Me_3SiNHSiMe_3$ and $Me_3SiOSiMe_3$ in the series of secondary amines and ethers. The +I effect of $SiMe_3$ (σ_F is negative) is affinity-enhancing. There is probably no large steric effect on the 4-fluorophenol affinities of ethers, and the steric effect is compensated by the dispersion effect in dialkyl secondary amines (see below). Therefore, the most plausible explanation for the very weak HB affinities of hexamethyldisilazane and hexamethyldisiloxane seems to be a hyperconjugative electron withdrawal from the (a) lone pair of nitrogen (oxygen) to σ^* orbitals associated with the CSiC fragments.

Steric and Polarizability Effects: The Alkyl Substituents. In organic chemistry, the effect of alkyl substituents on reactivity has been the subject of much debate. Various mechanisms, such as the inductive effect, hyperconjugation, polarizability, front strain, back strain, and/or steric hindrance to solvation have been suggested. Fortunately, gas-phase experiments and calculations have clarified the issue. For example, the increase in the gas-phase proton affinity of alkylamines upon increasing the length and branching of alkyl groups has been definitely attributed to a polarizability effect, that is a charge-induced dipole interaction between the charged nitrogen and the alkyl groups.[84] Indeed, the decomposition of the electronic protonation energies of alkylamines into electrostatic, charge transfer, and polarization terms (there are neither exchange-repulsion nor dispersion components since the proton has no electron) confirms the significant increase in the polarization term with alkylation.[85] Alkyl groups also enhance the gas-phase HB affinities of amines,[72] but here they mostly increase the dispersion energy component.[86] However, since dispersion has its origin in molecular polarization (and electron correlation), we expect a positive correlation between HB affinities and the polarizability substituent constant σ_α (in fact ρ_α is negative because the size of alkyl groups increases with *minus* σ_α), if steric effects are less important than dispersion effects, and if we choose saturated systems where the positive hyperconjugation (+R effect) cannot operate.

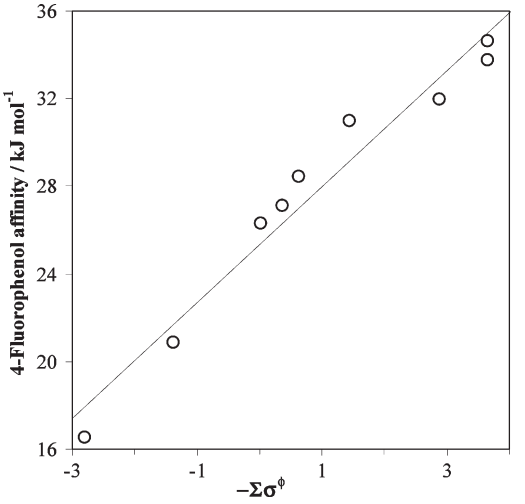


FIGURE 14. Plot of 4-fluorophenol affinity vs minus the sum of substituent constants σ^{Φ} in phosphine oxides.

Plots of $-\Delta H$ versus $-\Sigma\sigma_\alpha$ (Figure 15) can be interpreted on the basis of these hypotheses. The HB affinity of alkyl iodides, bromides, chlorides, fluorides, thioethers (and thiols), ethers, and primary amines (and ammonia) increases with the dispersion effect measured by $-\Sigma\sigma_\alpha$. Three series do not show a positive significant correlation between $-\Delta H$ and $-\Sigma\sigma_\alpha$. First, the series of alkyl secondary amines shows a slope near zero, hence a low correlation coefficient of 0.58. This can be explained by the steric effects of the two alkyl substituents, which cause $-\Delta H$ to vary in the opposite direction from dispersion effects and, hence, compensate for them. Second, the series of tertiary alkylamines are not correlated to $-\Sigma\sigma_\alpha$ ($n = 9$, $r = 0.23$). The response of $-\Delta H$

(82) Mastryukova, T. A.; Kabachnik, M. I. *J. Org. Chem.* **1971**, *36*, 1201.
(83) Rankin, D. W. H.; Robertson, H. E.; Seip, R.; Schmidbaur, H.; Blaschke, G. *J. Chem. Soc., Dalton Trans.* **1985**, 827.
(84) Aue, D. H.; Webb, H. M.; Bowers, M. T. *J. Am. Chem. Soc.* **1976**, *98*, 311.
(85) Umeyama, H.; Morokuma, K. *J. Am. Chem. Soc.* **1976**, *98*, 4400.
(86) Kone, M.; Illien, B.; Graton, J.; Laurence, C. *J. Phys. Chem. A* **2005**, *109*, 11907.

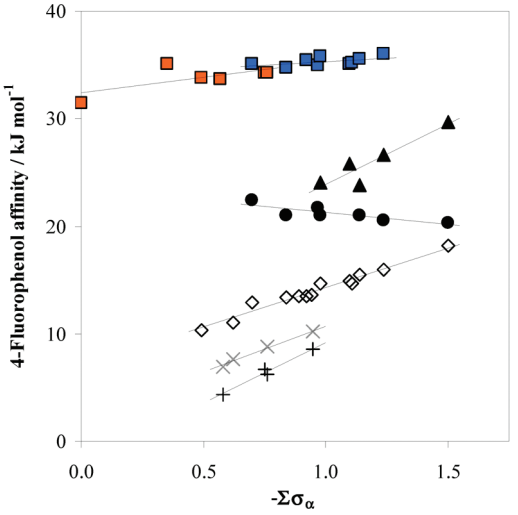


FIGURE 15. Plots of 4-fluorophenol affinity vs minus the sum of polarizability substituent constants of alkyl groups in series of alkyl-substituted HBAs. From top to bottom: secondary amines (blue box), primary amines (orange box), ethers (▲), ketones (●), thioethers (◊), chloroalkanes (×), and iodoalkanes (+). For clarity, the series RBr and RF are not shown (they behave similarly to RCl and RI).

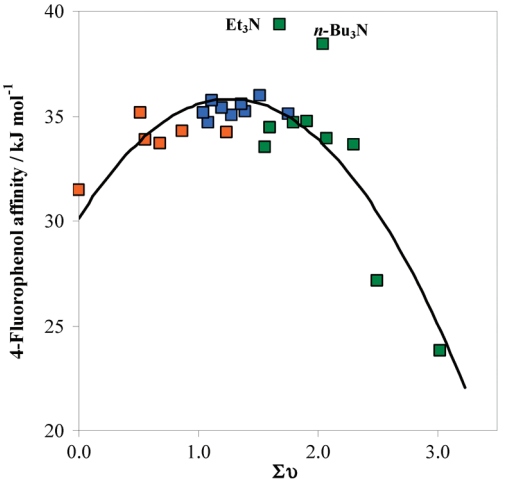


FIGURE 16. Plot of 4-fluorophenol affinity vs the sum of substituent steric constants of alkyl groups in primary (orange box), secondary (blue box) and tertiary (green box) amines.

to the combined steric and dispersion effects of three alkyl groups cannot be interpreted simply, although the low affinities of $((CH_3)_2CH)_2NCH(CH_2CH_3)_2$ and $((CH_3)_2CH)_2NCH_2CH(CH_3)_2$ are evidently caused by the steric hindrance of the nitrogen lone pair. A plot of $-\Delta H$ versus Σv (Figure 16) for 25 amines summarizes how the HB affinities depend on the size (i.e., on both the dispersion and steric effects which are mutually correlated since both depends on the size of the alkyl groups) of the substituents of nitrogen, from NH_3 ($\Sigma v = 0$) to $((CH_3)_2CH)_2NCH(CH_2CH_3)_2$ ($\Sigma v = 3.03$). For primary amines, $-\Delta H$ increases with the alkyl size (i.e., the dispersion effect predominates), for secondary amines $-\Delta H$ hardly increases (i.e., the steric effect almost compensates for the dispersion effect), while for tertiary amines $-\Delta H$ may either increase by virtue of the dispersion effect (Et_3N and n-Bu_3N) or fall dramatically because of the steric effect ($(((CH_3)_2CH)_2NCH(CH_2CH_3)_2$ and $((CH_3)_2CH)_2NCH_2CH(CH_3)_2$). Lastly, the series of alkyl ketones shows a negative correlation with $-\Sigma\sigma_\alpha$. In this unsaturated system, the dispersion effect is possibly overcompensated by steric effects and/or hyperconjugation, as far as the common concept of a more efficient C−H than C−C hyperconjugation applies here.

Both hyperconjugation and dispersion effects may also explain the regular increase in the HB affinity of polymethylbenzenes $C_6H_{6-n}Me_n$ (eq 12) with the number of methyl substituents.

$$-\Delta H°/\text{kJ mol}^{-1} = (7.2 \pm 0.2) + (0.58 \pm 0.05)n_{CH3} \quad (12)$$

$$n = 7; r = 0.983; s = 0.3 \text{ kJ mol}^{-1}$$

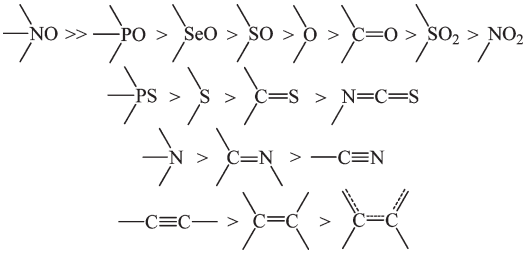
Concluding Remarks

The 4-fluorophenol affinity scale in CCl_4 is a reasonably general hydrogen-bond affinity scale of organic bases. Provided some family dependence is taken into account in linear hydrogen-bond enthalpy relationships, this scale applies to most hydrogen-bond donors and to most media.

The scale measures the intrinsic energy of the hydrogen bond satisfactorily because the contributions of gas to CCl_4 transfer enthalpies and thermal terms to the hydrogen-bond enthalpies in CCl_4 at 298 K are probably constant and/or small. This enables safe relationships to be constructed between the electronic structures of organic bases B and the energy of the O−H···B hydrogen bond. The hydrogen-bond affinity orders

$$R_3N >> R_2O >> R_3P >> R_2S > R_3As \sim R_2Se > RF \sim R_3Sb \sim R_2Te > RCl \sim RBr > RI$$

for the atomic site accepting the OH donor, and



for the function bearing this site, are now *quantitatively* established. The effects of substituents on the HB affinity of these functions are well described as additive contributions of field/inductive, resonance, and polarizability terms. When applied to *gas-phase proton* affinity, the polarizability substituent constant describes the polarization term of the energy decomposition scheme of proton affinity. However, when applied to *solution hydrogen-bond* affinity, it describes mainly the dispersion term of the hydrogen-bond energy. Although steric effects are important in the 4-fluorophenol *basicity* scale of many bases such as ethers, thioethers, secondary and tertiary amines, 2-substituted pyridines, and *N*-substituted imines, they contribute much less in the 4-fluorophenol *affinity* scale, except for a number of secondary and tertiary amines. Many computational studies will,

however, be necessary to understand in depth these affinity orders and these substituent effects from a quantum-mechanical point of view.

The similarities and dissimilarities of the 4-fluorophenol affinity scale with other Lewis affinity scales such as the $SbCl_5$, BF_3, I_2, M^+ (metal cation), or H^+ affinity scales[6] need to be studied by chemometric methods. So, the main factors determining the Lewis affinity and the many Lewis affinity-dependent chemical, physical and biological properties could be extracted from the data matrices which can now be constructed from this and other works. Preliminary correlations[20] indicate that the 4-fluorophenol affinity scale might constitute the electrostatic term (in the Drago E and C model)[6] or the hard term (in the hard and soft description of acids and bases) of a multiple parameter equation which could predict and explain a number of Lewis affinity-dependent properties.

Experimental Section

Chemicals. HBAs were generally commercially available and carefully purified by standard methods. The detailed purification methods and the synthesis of noncommercial HBAs can be found in the article or the thesis in which their pK_{BHX} value was published. The corresponding reference is in the field "reference" of the pK_{BHX} database.[10]

Spectroscopic-grade solvents were dried over 4 Å molecular sieves. The standard solvent was CCl_4. A few amines reacted with CCl_4 and were measured in C_2Cl_4 which has a very similar polarity. A number of second-, third-, and fourth-row bases (e.g., phosphines and tellurides) reacted both with CCl_4 and C_2Cl_4 and were measured in cyclohexane. Dichloromethane was also used to study the effect of a more polar solvent on HB enthalpies.

4-Fluorophenol was sublimed over P_2O_5. Spectroscopic-grade methanol was dried over 3 Å molecular sieves. Pyrrole was distilled just before use and protected from light during experiments. Cyanoacetylene was synthesized from propiolic acid as described in the literature.[87] The last step of the synthesis, the dehydration of the amide $HC{\equiv}CCONH_2$, was carried out just before the enthalpy determination owing to the poor stability of cyanoacetylene.

FTIR Spectra. The spectrometer, the cell, and the thermoregulation device have been previously described.[88]

Equilibrium Constants and Gibbs Energies. Reaction (1) represents the formation of a 1:1 complex between 4-fluorophenol and base B. If C_a, C_b, and C_c are the equilibrium concentrations, on the molar scale, of the acid 4-fluorophenol, the base B, and the complex, respectively, and if C_a° and C_b° are the initial concentrations, the equilibrium constant K_c is given by eq 13. C_a is obtained from eq 14

$$K_c/\mathrm{L\ mol^{-1}} = C_c/C_aC_b = (C_a^\circ - C_a)/[C_a(C_b^\circ - C_a^\circ + C_a)] \quad (13)$$

$$C_a = A/\varepsilon\ell \quad (14)$$

where A is the absorbance of the OH band of free 4-fluorophenol, ε is the molar absorption coefficient, and ℓ is the cell path length. C_a° (less than 5 mmol L^{-1}) and C_b° are obtained by weighing. Four to five concentrations of base are chosen so that ~20−80% of 4-fluorophenol is hydrogen-bonded. The constancy of K_c at these base concentrations indicates that the complex of 1:1 stoichiometry is almost the only species formed. A detailed laboratory experiment is given in ref 6 for the complex of 4-fluorophenol with isopropyl methyl ketone $(CH_3)_2CHCOCH_3$ in CCl_4. Here, the mean of four determinations yields K_c = 16.33 L mol^{-1} with a 95% confidence interval of ±0.16. Hence, pK_{BHX} = 1.21 and ΔG_c° = −6.91 kJ mol^{-1}. The equilibrium constant on the mole fraction scale, K_x, is related to K_c, for dilute solutions, by eq 15 where $\bar{V}_s$ is the molar volume of the solvent. Hence, $K_x \approx 168$ and $\Delta G_x^\circ \approx -12.70$ kJ mol^{-1}.

$$K_x \approx K_c/\bar{V}_s \quad (15)$$

Enthalpies. The enthalpy ΔH° is obtained from the temperature dependence of equilibrium constants K_x (eq 16) or K_c (eq 17, for dilute solutions) where α is the coefficient of thermal expansion of the

$$\Delta H^\circ = -R[\mathrm{d}\ln K_x/\mathrm{d}(1/T)] \quad (16)$$

$$\Delta H^\circ \approx -R[\mathrm{d}\ln K_c/\mathrm{d}(1/T)] - \alpha RT^2 \quad (17)$$

solvent, and at 298 K, αRT^2 = 0.91, 0.90, 0.75, and 1.03 kJ mol^{-1} for CCl_4, c-C_6H_{12}, C_2Cl_4, and CH_2Cl_2, respectively. Assuming that ΔH° is constant over the temperature range involved, a plot of ln K_x against $1/T$ should be a straight line (van't Hoff line) whose slope multiplied by $-R$ gives the enthalpy. Accurate and quick measurements are made by following the OH (NH, CH) absorbance of a *single* solution of 4-fluorophenol (methanol, pyrrole, cyanoacetylene) and base in a solvent. This method is fully described in ref [6] for the complex of 4-fluorophenol with cyclopropylamine in cyclohexane. Here, ΔH° = −34.25 ± 0.76 kJ mol^{-1}. The error limits arise from the standard deviation of the slope of the van't Hoff regression line.

There is a widespread opinion that enthalpy values obtained from the temperature dependence of equilibrium constants (hereafter called van't Hoff values) are generally less reliable than those determined by calorimetry. In ref 6, a comparison for 27 diverse bases of van't Hoff and calorimetric 4-fluorophenol affinities ranging from 17 to 35 kJ mol^{-1} yields a mean algebraic difference (−0.36 kJ mol^{-1}) close to zero and a mean absolute difference (1.18 kJ mol^{-1}) mostly within experimental error. Interestingly, our van't Hoff value for 1-methyl-2-pyrrolidone (27.4 kJ mol^{-1}) is situated between two calorimetric values (29.3[16] and 26.6[89] kJ mol^{-1}). It was concluded[6] that HB enthalpies determined by the van't Hoff method are as reliable as those measured by calorimetry, provided a sufficiently wide variation of temperature is used. In this work, we have used the widest temperature intervals permitted by the properties of the solvents, namely (in °C) −5 to +55, −5 to +80, +10 to +65, and −5 to +35 for CCl_4, C_2Cl_4, c-C_6H_{12}, and CH_2Cl_2, respectively. It is fortunate that the range of temperatures used with the standard solvent CCl_4 corresponds to a harmonic mean very close to 298 K. For example, the temperatures t = −6.1, 8.9, 24.5, 39.4, and 54.6 °C used for the system trimethyl phosphate/4-fluorophenol/CCl_4 have a harmonic mean of 296 K. This enables a safe comparison of the affinity (ΔH) and basicity (ΔG) scales without having recourse to sophisticated statistical methods[34,37] (see below).

Entropies. The entropy ΔS° can be calculated in two ways. It can first be obtained from the intercept of the van't Hoff line

(87) Murahashi, S.; Takizawa, T.; Kurioka, S.; Maekawa, S. *Nippon Kagaku Zasshi* **1956**, *77*, 1689.

(88) Graton, J.; Berthelot, M.; Gal, J.-F.; Laurence, C.; Lebreton, J.; Le Questel, J.-Y.; Maria, P.-C.; Robins, R. *J. Org. Chem.* **2003**, *68*, 8208.

(89) Abraham, M. H.; Duce, P. P.; Morris, J. J.; Taylor, P. J. *J. Chem. Soc., Faraday Trans. 1* **1987**, *83*, 2867.

(eq 18) in the single-solution experiment in which the temperature is varied. The

$$\ln K_x = (-\Delta H^\circ/RT) + (\Delta S_x^\circ/R) \quad (18)$$

$$\Delta S_x^\circ = (\Delta H^\circ - \Delta G_x^\circ)/T \quad (19)$$

entropy can also be calculated from eq 19 where ΔG_x° is calculated from the K_x value obtained from the average of the determinations in which the base concentration is varied. The two methods give results that are generally in very good agreement. However, the errors are not equivalent in the two methods. When ΔH° and ΔS° are obtained from the linear regression in eq 18, they are extracted from the same set of experimental data and the errors in the entropy estimates are highly correlated with errors in the enthalpy estimates.[37] On the contrary, in eq 19, ΔH° is determined in an experiment where the temperature is varied, while ΔG° is obtained from pK_{BHX} (eq 4) measured in an independent experiment where the base concentration is varied.

Errors. The total error is the sum of the random, the systematic, and the gross errors. Only the random error can be calculated: in K from the standard error of the mean of determinations, in ΔH° from the standard error of the regression coefficient of the least-squares van't Hoff line, and in ΔS° from the standard error of the intercept of this line. Thus, confidence limits can be given to each thermodynamic parameter. The total error can only be estimated. We did this from separate determinations by various operators on different spectrometers under varied experimental conditions. We found that the *maximum* relative error in K is about ±8%, which corresponds to ±0.04 pK units, hence, a *maximum* error of ±0.25 kJ mol^{-1} in ΔG°, and that the *maximum* errors in ΔH° and ΔS° are around ±0.8 kJ mol^{-1}and ±5 J mol^{-1} K^{-1}, respectively.

Computational Methods. Theoretical calculations were performed using the Gaussian 03 package.[90] Density-functional calculations were carried out using the MPWB1K functional, an efficient method in the field of nonbonded interactions, such as hydrogen bonding.[91−94] The geometries of hydrogen-bonded complexes of 4-fluorophenol with nitromethane, sulfolane, veratrole, 1,10-phenanthroline, and 2,4-difluoroadamantane were optimized at the MPWB1K/6-31+G(d,p) level. The harmonic frequencies were subsequently computed in order to characterize the stationary points. In the Me$_n$E series, the geometry optimizations were realized at the MPWB1K/aug-cc-pVTZ level. Since relativistic effects can no longer be neglected in molecules containing elements of the third and fourth period, the 28 core shells electron of As, Se, Br, Sb, Te, and I were described by relativistic core potentials.[95−98] The valence shells electrons of these heavy atoms and the electron shells of N, O, F, P, S, and Cl atoms were described with aug-cc-pVTZ basis sets.

For a number of systems, the following descriptors have been used in order to characterize their HB ability and/or interactions. A comparison of the charge transfer component between oxygen lone pairs and the O−H antibonding orbital is achieved through a Natural Bond Orbital analysis.[99,100] Furthermore, electron densities have been computed at the critical points of HB interactions, within the framework of Atoms in Molecules[64,101] theory (AIM) with the AIM2000 set of programs.[102] Molecular electrostatic potentials were calculated, using the Molden interface,[103] either at the MPWB1K/6-31+G(d,p) or the MPWB1K/aug-cc-pVTZ level on the molecular surface defined by the 0.001 electron bohr^{-3} contour of electron density.[104]

Supporting Information Available: Tables S1−S4. This material is available free of charge via the Internet at http://pubs.acs.org.

(90) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A.; Vreven, J. T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. *Gaussian 03*; Gaussian, Inc.: Wallingford, CT.

(91) Zhao, Y.; Truhlar, D. G. *J. Phys. Chem. A* **2004**, *108*, 6908.
(92) Zhao, Y.; Truhlar, D. G. *J. Chem. Theory Comput.* **2005**, *1*, 415.
(93) Zhao, Y.; Truhlar, D. G. *J. Phys. Chem. A* **2005**, *109*, 5656.
(94) Zhao, Y.; Truhlar, D. G. *J. Phys. Chem. A* **2005**, *109*, 6624.
(95) Stoll, H.; Metz, B.; Dolg, M. *J. Comput. Chem.* **2002**, *23*, 767.
(96) Peterson, K. A. *J. Chem. Phys.* **2003**, *119*, 11099.
(97) Peterson, K. A.; Figgen, D.; Goll, E.; Stoll, H.; Dolg, M. *J. Chem. Phys.* **2003**, *119*, 11113.
(98) Peterson, K. A.; Shepler, B. C.; Figgen, D.; Stoll, H. *J. Phys. Chem. A* **2006**, *110*, 13877.
(99) Weinhold, F.; Landis, C. R. *Valency and Bonding. A Natural Bond Orbital Donor-Acceptor Perspective*; Cambridge University Press: Cambridge, 2005.
(100) Glendening, E. D.; Reed, A. E.; Carpenter, J. E.; Weinhold, F., *Natural Bond Orbital* (*NBO*), version 3.1; Theoretical Chemistry Institute, University of Wisconsin: Madison.
(101) Bader, R. F. W. *Chem. Rev.* **1991**, *91*, 893.
(102) Biegler-Koenig, F. W.; Schonbohm, J.; Bayles, D. *J. Comput. Chem.* **2001**, *22*, 545.
(103) Schaftenaar, G.; Noordik, J. H. *J. Comput. Aided Mol. Des.* **2000**, *14*, 123.
(104) Bader, R. F. W.; Carroll, M. T.; Cheeseman, J. R.; Chang, C. *J. Am. Chem. Soc.* **1987**, *109*, 7968.