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Determination of the hydrogen-bond basicity of weak and multifunctional bases: the case of lindane (γ-hexachlorocyclohexane)

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ABSTRACT: We made use of four methods for determining the hydrogen-bond (HB) basicity of lindane (γ-hexachlorocyclohexane): (i) experimental Fourier transform IR measurement of a sum of individual 1:1 equilibrium constants for the formation of 1:1 4-fluorophenol-lindane hydrogen-bonded complexes in CCl_4; (ii) calculation of the overall HB basicity from octanol–water partition coefficients; (iii) correlation of the HB basicity of chloroalkanes with the electrostatic potentials around chlorine atoms; and (iv) correlation of the HB basicity of chloroalkanes with the computed enthalpy of their complexes with hydrogen fluoride. It is consistently found that lindane remains a weak HB base because multifunctionality cannot fully compensate for the electron-withdrawing inductive effects that chlorine atoms exert over one another. Actually, only five chlorine atoms behave as HB acceptors, one axial chlorine being deactivated by inductive effects. Stereoelectronic effects lead to the formation of three-centered hydrogen bonds. Copyright © 2003 John Wiley & Sons, Ltd.

KEYWORDS: hydrogen bonding; basicity; chloroalkanes; lindane; Fourier transform infrared spectrometry; octanol–water partition coefficient; electrostatic potential

INTRODUCTION

A growing body of experimental and theoretical evidence confirms that weak hydrogen bonds (HBs) can play important roles in chemistry and biology.[1,2] Weak HBs are obviously formed between weak HB donors and weak HB acceptors, but might also occur when only one partner is weak. This second category includes the interaction between fairly strong HB donors such as phenols and weak HB acceptors such as haloalkanes.[3–5] In the present context, hydrogen-bond strength will be measured from 1:1 hydrogen-bond complexation constants[6] (and, whenever possible, HB complexation enthalpies[6]). We have recently measured[7,8] these thermodynamic properties for a number of chloroalkanes against 4-fluorophenol in tetrachloromethane solution:

$$\text{R–Cl} + \text{4-FC}_6\text{H}_4\text{OH} \quad \rightleftharpoons \quad \text{4-FC}_6\text{H}_4\text{OH}\cdots\text{Cl–R} \quad (1)$$

$$K_x = x_{\text{complex}}/(x_{\text{chloroalkane}} \cdot x_{\text{phenol}}) \quad (2)$$

$$K_c = C_{\text{complex}}/(C_{\text{chloroalkane}} \cdot C_{\text{phenol}}) \quad (3)$$

$$\Delta H^\circ = RT^2(\partial \ln K_x/\partial T)_P \quad (4)$$

The mole-fraction equilibrium constant, K_x, the correct one[9] for obtaining the standard state-infinite dilution enthalpy ΔH°, is used[10] in the calculation of the hydrogen-bonding term contributing to the octanol–water partition coefficient[11] (see below). The molar-concentration equilibrium constant, K_c, is generally used for defining the Taft's pK_{HB} scale[12] of hydrogen-bond basicity as $\log K_c$.

Because of the strong inductive electron-withdrawing effect of the chloro substituent,[13] polychloroalkanes form even weaker hydrogen bonds than monochloroalkanes, and their HB acceptor strength becomes more difficult to measure experimentally by the usual IR method.[6] Additional methods must be employed in order to assess the reliability of IR results. In this work, we shall calculate the equilibrium constants of reaction (1) for polychloroalkanes from their relationships with (i) octanol–water partition coefficients,[10] (ii) electrostatic potentials around the chlorine atoms and (iii) computed enthalpies for hydrogen-bonding complexation of hydrogen fluoride.[14]

These studies allow the issue of polyfunctionality in hydrogen bonding to be addressed. Two extreme situations, which we explain using the example of

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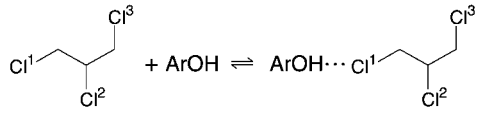
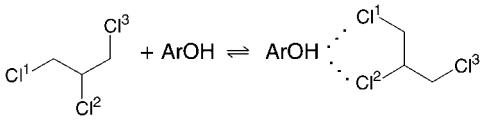
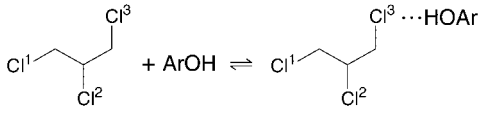
1,2,3-trichloropropane, are often encountered in solution studies. In the first one, trichloroalkane is in excess [in order to shift equilibrium (1) towards the hydrogen-bonded complex] so that neither 2:1 nor 3:1 complexes (phenol: trichloroalkane) can be significantly formed. Three different 1:1 complexes (as shown from the electrostatic potential map; see below) are mainly formed according to the following equilibria of equilibrium constants $K_{x,1}$–$K_{x,3}$:



$$K_{x,1} = x_{\text{complex 1}}/x_{\text{ArOH}} \cdot x_{\text{ClCH}_2\text{CHClCH}_2\text{Cl}} \qquad (5)$$



$$K_{x,2} = x_{\text{complex 2}}/x_{\text{ArOH}} \cdot x_{\text{ClCH}_2\text{CHClCH}_2\text{Cl}} \qquad (6)$$



$$K_{x,3} = x_{\text{complex 3}}/x_{\text{ArOH}} \cdot x_{\text{ClCH}_2\text{CHClCH}_2\text{Cl}} \qquad (7)$$

In the usual IR method,[6] one measures the equilibrium mole fraction of hydrogen-bonded 4-fluorophenol, i.e. the sum of the mole fractions of the three 1:1 complexes. Therefore, the observed (measured) equilibrium constant is the ratio $\sum_i x_{\text{complex}}/x_{\text{ArOH}} \cdot x_{\text{ClCH}_2\text{CHClCH}_2\text{Cl}}$, which is equal to the sum of the individual constants $K_{x,i}$:

$$K_x(\text{observed}) = \frac{x_{\text{complex 1}} + x_{\text{complex 2}} + x_{\text{complex 3}}}{x_{\text{ArOH}} \cdot x_{\text{ClCH}_2\text{CHClCH}_2\text{Cl}}} = K_{x,1} + K_{x,2} + K_{x,3} = \sum_i K_{x,i} \qquad (8)$$

We must point out that $\log \sum_i K_{x,i}$ $(\log \sum_i K_{c,i})$ has no thermodynamic meaning. Thus, the pK_{HB} scale,[12] and its linear transform[15] β_2^H, are ill-defined quantities for polyfunctional bases. However, in the case of *n equivalent* basic functions, the statistically corrected quantity[16] $\log(\sum_i^n K_{x,i}) - \log n$ [i.e. an $RT\ln(n)$ correction to the Gibbs energy calculated from the measured equilibrium constant] can be used for comparison with monofunctional bases. In polychloroalkanes with equivalent chlorine atoms, these statistically corrected quantities refer to the hydrogen-bond basicity per chlorine atom.

In the second situation, the 1,2,3-trichloropropane is surrounded by a large excess of HB donor molecules and takes part in multiple hydrogen bonding. If the 3:1 complex is the major species, the overall equilibrium constant[17] is the product of three individual constants corresponding to the stepwise formation of 1:1, 2:1 and 3:1 complexes.[10,17] Since $\log \Pi K_i = \Sigma \log K_i$, the summation of the logarithm of the individual constants might have some physical meaning.[18] In neat water or neat octanol, it is possible that each site of polyfunctional HB acceptor solutes will be fully utilized. We have found[10] that the hydrogen-bonding term contributing to the octanol–water partition coefficient P_{ow} of these multifunctional solutes in linear solvation energy relationships[19–24] is fairly well correlated with the sum of the $\log K_x$ values. Provided that care is taken regarding family-dependent behavior,[10] we can use the $K_{x,i}$ values [Eqns (2) and (5)–(7)] corresponding to the 1:1 association in CCl_4 of 4-fluorophenol on each site.

The aim of this work was to determine the hydrogen-bond basicity of lindane, a weak and multifunctional HB acceptor. Lindane [1a,2a,3a,4e,5e,6e-hexachlorocyclohexane or γ-hexachlorocyclohexane (γ-HCH)], is a well-known insecticide used in agriculture[25] and human therapeutics.[26] We also wanted to elucidate the structural basis of its lipophilicity (i.e. octanol–water partition coefficient) and hydrogen-bonding basicity, which are important properties of its transport to its target, its bioaccumulation and its docking to receptors.[27–29] Lastly, we wanted to revisit the recent surprising finding that hexachlorocyclohexanes are strong hydrogen-bond bases.[30]

EXPERIMENTAL

Chemicals and spectra

Tetrachloromethane, 4-fluorophenol, lindane, 1,2-dichloropropane, 1,2,3-trichloropropane, *trans*-1,2-dichlorocyclohexane, 1,4-dichlorobutane, and 2-chloropropane were commercial compounds purified as described elsewhere.[7,31] The Fourier transform (FT) IR spectrometer, the cell and the method of measuring the IR wavenumber shifts, upon hydrogen bonding, of the ν(OH) band of 4-fluorophenol were described previously.[7] The overlap of the ν(OH) bands of the free and hydrogen-bonded 4-fluorophenol was corrected using the Bruker Curve Fit software, which enables overlapping bands to be mathematically resolved into their Gauss–Lorentz components.

Determination of equilibrium constants and enthalpies

K_x (at 25 °C) and ΔH° [Eqns (2) and (4)] were measured from variations in the absorbance of the ν(OH) band of free 4-fluorophenol at 3614 cm^{-1}, with base mole fraction (K_x) and with temperature (ΔH°), as described previously.[7,8] K_x was calculated as illustrated in Table 1 for the example of lindane. The mean of four determinations gave $\Sigma K_{x,i} = 12.8 \pm 1.1$ (95%confidence level).

Table 1. Mole fraction equilibrium constants for the 1:1 complexation of 4-fluorophenol with lindane in CCl_4 at 25 °C (four determinations)[a]

	0	1	2	3	4
x_a°	4.41	4.53	4.41	4.45	4.41
x_b°	0	227.3	226.5	230.1	224.0
Absorbance A	1.066	0.854	0.813	0.838	0.830
$x_a = A/\varepsilon l$[b]		3.53	3.36	3.47	3.44
$x_c = x_a^\circ - x_a$		0.99	1.05	0.98	0.97
$x_b = x_b^\circ - x_c$		226.3	225.5	229.1	223.1
% complex[c]		21.8	23.8	22.0	22.0
$\Sigma K_{x,i}$		12.4	13.8	12.3	12.7

[a] All mole fractions are multiplied by 10^4. x_a°, x_b°; x_a, x_b and x_c are respectively the initial and equilibrium mole fractions of 4-fluorophenol (acid *a*), lindane (base *b*) and complex (*c*).
[b] $\varepsilon = 2416\,\mathrm{cm}^{-1}$, $l = 1\,\mathrm{cm}$.
[c] $x_c/x_a^\circ \cdot 100$. Percentage of hydrogen-bonded 4-fluorophenol.

Computational methods

Theoretical calculations were performed at the IDRIS (Orsay) and CINES (Montpellier) supercomputer centers using the Gaussian 98 suite of computer programs.[32]

The structures of the monomers HF and chloroalkanes and the HF–chloroalkane complexes were optimized at the B3LYP density functional theory level using the split-valence plus polarization 6–31G(d,p) basis set. Harmonic vibrational frequencies were computed at the same level of theory, to distinguish equilibrium structures from stationary point structures with imaginary vibrational frequencies and to evaluate vibrational energies. In order to obtain more accurate energies, single-point calculations were finally carried out by augmenting the basis set with diffuse functions on non-hydrogen atoms, i.e. at the B3LYP/6–31+G(d,p) level.

The enthalpies of complexation were calculated as the difference between the quantity of the complex, treated as a supermolecule, and the sum of the quantities of the monomers.[33] The enthalpy of complexation at 298.15 K, given by

$$\Delta H^\circ = \Delta E_{\mathrm{el}} + \Delta E_{\mathrm{tr}} + \Delta E_{\mathrm{rot}} + \Delta E_{\mathrm{vib}} - RT \qquad (9)$$

includes contributions arising from electronic (el), translational (tr), rotational (rot) and vibrational (vib) energies, and the $\Delta PV \approx -RT$ correction.

The binding energies of the complexes (ΔE_{el}) were calculated without correcting the basis set superposition error (BSSE), a spurious error introduced by the supermolecule approach.[33] The BSSE was assumed to be almost constant in the series of closely related HF–chloroalkane complexes.

The electrostatic potentials of chloroalkanes were calculated on the molecular surface, around each chlorine atom, with the HS95 program,[34–36] using the Gaussian archive file, and illustrated by means of the Molden program.[37] The molecular surface was defined by the 0.001 electron bohr^{-3} contour of the electronic density.[38]

RESULTS AND DISCUSSION

FTIR determination of hydrogen-bond basicity

Table 2 presents the observed K_x ($\Sigma K_{x,i}$), the enthalpies ΔH° and the entropies ΔS° for the complexation of chloroalkanes with 4-fluorophenol in CCl_4 [reaction (1)] and the IR shifts $\Delta\nu$(OH) of the 3614 cm^{-1} band of 4-fluorophenol. These new data are consistent with (and of equivalent precision to) those of chloroalkanes measured in our previous studies.[7,8] They do indeed obey the $\Delta G(\mathrm{p}K_{\mathrm{HB}})/\Delta\nu$(OH) and $\Delta H^\circ/\Delta\nu$(OH) (Badger–Bauer relationship) found previously.[7,8] Figure 1 shows that the correlation between the hydrogen-bond basicity per chlorine atom, i.e. log (K_x/n), and the IR shifts $\Delta\nu$(OH) is obeyed by mono-, di- and trichloroalkanes.

The addition of these new data to those of Ref. 8 enables the existence of a relationship:

$$\Delta H^\circ = \beta \Delta S^\circ + \mathrm{constant} \qquad (10)$$

between ΔH° and ΔS° (the compensation effect)[39] to be studied on a sample of eight mono- and dichloroalkanes. However, since ΔH° and ΔS° are obtained from the temperature dependence of log K_x, they are loaded with

Table 2. Equilibrium constants K_x, thermodynamic functions ΔH° (kJ mol^{-1}) and ΔS_x° (J K^{-1} mol^{-1}) and IR frequency shifts $\Delta\nu$(OH) (cm^{-1}) for hydrogen bonding of chloroalkanes to 4-fluorophenol in CCl_4 at 25 °C (FTIR determination)

Compound	$K_{x,\mathrm{observed}}$	$K_{x,\mathrm{observed}}/n$[a]	$-\Delta H^\circ$	$-\Delta S^\circ_{x,298}$	$\Delta\nu$(OH)
2-Chloropropane	5.15	5.15	7.57 ± 0.78	12.1 ± 2.5[c]	72
1,4-Dichlorobutane	7.26	3.63	6.25 ± 0.26	4.4 ± 0.9[c,d]	57
trans-1,2-Dichlorocyclohexane	6.52	3.26	5.75 ± 0.15[b]	3.6 ± 0.5[c,e]	50
1,2-Dichloropropane	5.00	2.50	—[f]	—[f]	41
1,2,3-Trichloropropane	5.31	1.77	—[f]	—[f]	~29
Lindane	12.8		—[f]	—[f]	~12

[a] *n* is the number of (assumed) equivalent chlorine atoms.
[b] Error limits of the slope in the regression analysis of the Van't Hoff plot.
[c] Error limits of the intercept in the regression analysis of the Van't Hoff plot.
[d] 10.2 when statistically corrected by $-R \ln 2$.
[e] 9.4 when statistically corrected by $-R \ln 2$.
[f] Too weak for a significant determination to be made.

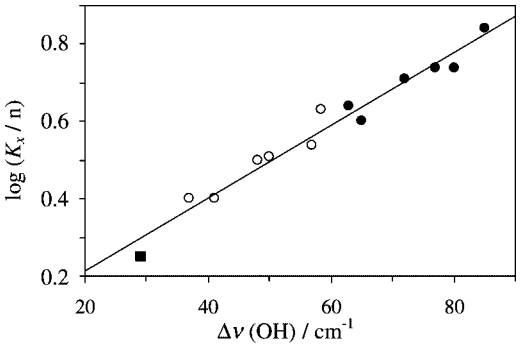


Figure 1. Relationship between the thermodynamic [log(K_x/n)] and the spectroscopic [$\Delta\nu$(OH)] hydrogen-bond basicity scales for one trichloro- (■), six dichloro- (○) and six monochloroalkanes (●) ($n = 13$, $r = 0.983$)

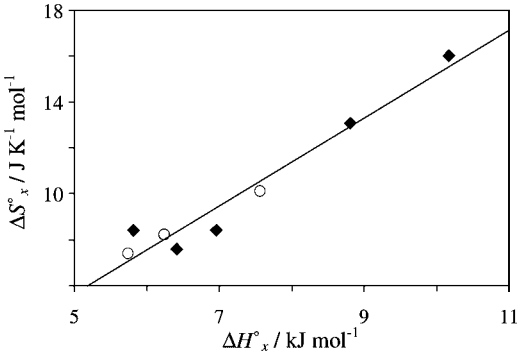


Figure 2. Compensation law for the hydrogen-bonding complexation of chloroalkanes with 4-fluorophenol in CCl_4. Data from Table 2 (○) and Ref. 8 (◆)

correlated errors, which might cause the apparently good relationship in Fig. 2 (squared correlation coefficient $r^2 = 0.947$ for eight data points). We checked, by the statistically correct method of Exner and Beranek,[40] with the program written by Ouvrard *et al.*,[41] that there is a true chemical dependence between ΔH° and ΔS°. We find for chloroalkanes an isoequilibrium temperature $\beta = 615$ K. This β value satisfactorily stands within the confidence interval (529–701 K) of the value (592 K) found previously[8] for a mixed sample of fluoro-, chloro-, bromo- and iodoalkanes. The existence of Eqn (10) indicates that the variation of ΔG (i.e. $\log K_x$) is enthalpy dependent. Hence values of $\log K_x$ might be calculated from energy-based descriptors of hydrogen-bond basicity (see below).

The K_x value of lindane seems fairly precise: $K_x = 12.8 \pm 1.1$ at the 95% confidence level. However, the low solubility of lindane in CCl_4 (ca 0.25 dm^3 mol^{-1}), and hence the low quantity of hydrogen-bonded 4-fluorophenol (Table 1), and the overlap of the free and hydrogen-bonded ν(OH) bands [$\Delta\nu$(OH) is only ca 12 cm^{-1}], make the mathematical decomposition of the two bands rather hazardous and the correctness of our result ill-defined. This requires the determination of the hydrogen-bond basicity of lindane by other approaches.

Hydrogen-bond basicity from octanol–water partition coefficients

The equilibrium constant P_{ow} for a solute partitioning between wet octanol and water is known for a large number of solutes.[42] Fundamentally, $-RT\ln P_{ow}$ measures the differential of solute–octanol and solute–water molecular interactions on the Gibbs energy scale. Attempts to unravel and quantify the various interactions encoded in the differential between wet octanol and water phases are numerous. They all conclude[19–24] that the two main terms governing the partitioning are a hydrophobic volume term and an opposing hydrophilic hydrogen-bond basicity term. They also generally agreed[22–24] that the HB acidity term cancels out in the octanol–water solvation differential. We have recently proposed[10] the simple equation

$$\log P_{ow} = 3.827V - 0.988\Sigma\lambda\log K_x + 0.046 \qquad (11)$$

for which the number of points $n = 266$, $r^2 = 0.986$ and the standard deviation from the regression $s = 0.20$. In this equation, the first term gathers contributions assumed to be roughly collinear with volume V, i.e. the endoergic solute cavity creation and the exoergic solute–solvent dispersion and induction energies.[43] The molecular volume V for any solute is calculated according to the Abraham and McGowan algorithm.[44] The second term corresponds to the effective hydrogen-bond basicity. It sums the HB basicities of the various HB acceptor sites of the solute. We have found[10] that this term can be measured by the $\log K_x$ values of reaction (1). λ is a family-dependent term, which is required for employing the simple $\log K_x$ values for 1:1 complexation in CCl_4 towards a phenol to describe the solute hydrogen bonding with bulk water and octanol, which is a much more complex phenomenon. For haloalkanes, $\lambda = 1.07$ (Ref. 10) and the hydrogen-bond basicity of chloroalkanes can be calculated from

$$\Sigma\log K_x = [-\log P_{ow} + 3.827V + 0.046]/1.057 \qquad (12)$$

Table 3 illustrates the application of Eqn (12) to a training set of 20 mono- and dihaloalkanes, for which reliable values of both P_{ow}[41] and $\Sigma\log K_x$[7] have been measured. For dihaloalkanes, we assume the equivalence of the two halogens and $\Sigma\log K_x$ can be calculated from K_x(observed) by means of the equation

$$\Sigma\log K_x = n[\log K_x(\text{observed}) - \log n] \qquad (13)$$

The differences (Table 3) between the values of $\Sigma\log K_x$ calculated from $\log P_{ow}$ and those calculated from K_x measured by FTIR spectrometry, assuming the equivalence of halogens in dihaloalkanes [Eqn (13)], range from +0.22 (relative error 34%) to −0.16 (relative error 15%), and are fairly well distributed around zero

Table 3. Comparison of the hydrogen-bond basicity of haloalkanes towards 4-fluorophenol in CCl_4 calculated from $\log P_{ow}$ and measured by FTIR spectrometry

			$\Sigma \log K_x$		
Solute	Log P_{ow}^{a}	V^{b}	From $\log P_{ow}^{c}$	From FTIR[d]	Difference
1-Fluoropentane	2.33	0.931	0.85	0.95	+0.10
2-Chloropropane	1.90	0.654	0.61	0.71	+0.10
1-Chlorobutane	2.64	0.795	0.42	0.60	+0.18
Bromocyclohexane	3.20	1.020	0.71	0.75	+0.04
2-Bromopropane	2.14	0.706	0.58	0.71	+0.13
1-Bromobutane	2.75	0.847	0.51	0.67	+0.16
1-Bromopentane	3.37	0.988	0.43	0.65	+0.22
1-Bromopropane	2.10	0.706	0.61	0.63	+0.02
Bromoethane	1.61	0.565	0.57	0.61	+0.04
Iodoethane	2.00	0.649	0.50	0.54	+0.04
Iodomethane	1.51	0.508	0.45	0.54	+0.09
1,4-Dichlorobutane	2.24	0.917	1.24	1.08	−0.16
1,3-Dichlorobutane	2.00	0.776	0.96	0.98	+0.02
1,2-Dichloropropane	2.02	0.776	0.94	0.80	−0.14
1,2-Dichloroethane	1.47	0.635	0.95	0.80	−0.15
trans-1,2-Dichlorocyclohexane	3.21	1.090	1.00	1.03	+0.03
1,3-Dibromopropane	2.37	0.881	0.99	0.96	−0.03
1,2-Dibromoethane	1.96	0.740	0.87	0.76	−0.11
1,3-Diiodopropane	3.02	1.048	0.98	0.98	0
1,2-Diiodoethane	2.71	0.907	0.76	0.72	−0.04

[a] From Ref. 42.
[b] $(cm^3\,mol^{-1})/100$.
[c] From Eqn (12).
[d] This work and Ref. 7. The pK_{HB} ($\log K_c$) in Ref. 7 are converted into K_x by the equation $\log K_x = pK_{HB} + 1.013$, since K_x and K_c are related, for dilute CCl_4 solutions, by $K_x \approx K_c \times 1000\,d/M \approx K_c \times 1000 \times 1.58439/153.82 \approx 10.3\,K_c$, where d and M are respectively the density and the molecular weight of CCl_4.

(with a mean of +0.03). These differences arise from measurement errors of P_{ow} and K_x(observed), model errors [see above for the assumptions included in Eqn (11)], and also the influence, not taken into account, of stereochemical factors on the partition coefficient.[45] Most haloalkanes of the training set can exist in several conformations[46] with different dipole moments, so the most stable conformation(s) in the apolar solvent CCl_4 may not be the same as in water and octanol, which have much higher dielectric permittivities.

Nevertheless, the results from the training set are sufficiently encouraging that we may apply Eqn (12) to lindane and other stereoisomers of known P_{ow}.[47] The results are presented in Table 4. For lindane, the comparison of $\Sigma \log K_x = 2.24$, calculated from $\log P_{ow}$, with $\Sigma K_x = 12.8$, measured by FTIR spectrometry, is not possible without making assumptions. Assuming six equivalently basic chlorines, we calculate [Eqn (13)] $\Sigma \log K_x = 1.97$. With five equivalently basic chlorines and one inert chlorine (see below), we have $\Sigma \log K_x = 2.04$. Clearly, the two different thermodynamic methods (octanol–water partition and hydrogen bonding with a phenol in CCl_4) give macroscopic values of similar magnitude for the hydrogen-bond basicity of lindane. However, a deeper view of the basicity of each chlorine of lindane is needed at the molecular level. To achieve this, we chose in the following to calculate the electrostatic potentials around each chlorine atom of lindane, its α, β and δ isomers and, for comparison, a training set of chloroalkanes.

Table 4. Calculation of the hydrogen-bond basicity of four stereoisomers of 1,2,3,4,5,6-hexachlorocyclohexane from the octanol–water partition coefficient

Isomer	Configuration	Log P_{ow}^{a}	V^{b}	$\Sigma \log K_x^{c}$
α-HCH	*a,a,e,e,e,e*	3.80	1.580	2.17
β-HCH	*e,e,e,e,e,e*	3.78	1.580	2.19
γ-HCH (lindane)	*a,a,a,e,e,e*	3.72	1.580	2.24
δ-HCH	*a,e,e,e,e,e*	4.14	1.580	1.85

[a] Ref. 47.
[b] $(cm^3\,mol^{-1})/100$.
[c] Eqn (12).

Hydrogen-bond basicity from electrostatic potentials

The electrostatic potential $V(\mathbf{r})$ created in the space around a molecule by its nuclei and electrons is defined by

$$V(\mathbf{r}) = \sum_{A} \frac{Z_A}{|\mathbf{R}_A - \mathbf{r}|} - \int \frac{\rho(\mathbf{r}')d\mathbf{r}'}{|\mathbf{r}' - \mathbf{r}|} \qquad (14)$$

where Z_A is the charge on nucleus A, located at $\mathbf{R}_A$, $\rho(\mathbf{r})$ is the electronic density function of the molecule and $\mathbf{r}'$ is a dummy integration variable. $V(\mathbf{r})$ gives the interaction energy between a proton located at $\mathbf{r}$ and the unperturbed

Table 5. Hydrogen-bond basicity, log K_x, minimum electrostatic potential on the molecular surface, $V_{s,min}$ (kJ mol^{-1}), most stable conformer, and directionality (°) of the spatial minimum of electrostatic potential, for chloroalkanes

Chloroalkane	Log K_x	$-V_{s,min}$	Directionality[c]	Conformer[d]
1-Chloroadamantane	0.84	82.47	113.1	
2-Chloro-2-methylpropane	0.74	77.28	114.4	T_{HHH}
Chlorocyclohexane	0.74	78.66	112.3	S_{CC} (axial)
2-Chloropropane	0.71	75.14	113.2	S_{HH}
1-Chloropentane	0.64	74.43	112.2	P_C
1,5-Dichloropentane	0.63[a]	67.78	110.5	$P_{H'}$ $P_{H'}$
1-Chlorobutane	0.60	73.93	111.9	P_C
1,4-Dichlorobutane	0.54[a]	62.01	111.3	$P_{H'}P_{H'}$
trans-1,2-Dichlorocyclohexane	0.51[a]	56.19	111.2	$S_{H'Cl'}S_{H'Cl'}$ (axial–axial)
1,3-Dichloropropane	0.50[a]	64.35	108.9	$P_{H'}P_{H'}$
1,2-Dichloroethane	0.40[a]	43.85	110.5	$P_{Cl}(P_{Cl})$
1,2-Dichloropropane	0.40[a]	48.20[b]	111.9	$P_{Cl'}S_{HCl}$

[a] Log $K_{x,observed}$ −log 2.
[b] Mean of two close values (see text).
[c] Defined by the Min—Cl—C angle. Min is the point of the molecular surface where V_s is minimum.
[d] Mizushima notation: type of substitution of the carbon atom is specified by P (primary), S (secondary) or T (tertiary). The subscript indicates the atom(s) in antiperiplanar position towards the chlorine atom.

charge distribution of the molecule. A (partially) positive hydrogen to be shared in a hydrogen bond will be attracted to those regions where $V(\mathbf{r})$ is negative, which are usually associated with the lone pairs of the more electronegative atoms, such as N, O, F and Cl.

The hydrogen-bond basicity has been shown[48] to be quantitatively related to the magnitudes of the most negative electrostatic potentials computed on the molecular surface, $V_{s,min}$, for a group of 33 HB acceptors of various types. Better correlations have been obtained by treating different chemical classes separately, e.g. aromatic *N*-heterocycles,[49] nitriles[50] or amines.[51] A rationale for these good family-dependent correlations between the Gibbs energy of complexation (i.e. pK_{HB} or log K_x) and electrostatic potential is (i) the family-dependent relationship between the enthalpy and entropy of association (see above), (ii) the dominant part of the energy of association is in most cases the electrostatic contribution[52] and (iii) other contributing terms may fortunately cancel out[53] or be constant or be related to the electrostatic term for a family of structurally homogeneous HB acceptors.

We calculated $V_{s,min}$ at the B3LYP/6–31 + G(d,p)// B3LYP/6–31G(d,p) level for 11 chloroalkanes that have either a single chlorine HB acceptor or two equivalent chlorine HB acceptors. We added 1,2-dichloropropane to this sample because we calculate almost equal $V_{s,min}$ values on each chlorine (− 48.33 and − 48.07 kJ mol^{-1}).). We could not add 1,2,3-trichloropropane, which shows three different $V_{s,min}$ values (− 70.16, − 48.87 and − 44.77 kJ mol^{-1}; see Table 6). It should be noted that most studied compounds are conformationally flexible. We did not fully explore the potential energy surface but, where it was deemed necessary, we optimized the geometries of various input conformations. The most stable geometries found always agree with the experimental conformations known for chloroalkanes.[46,54,55] We checked that the electrostatic potential is not generally greatly affected by changes in molecular conformation.[56] However, when a conformation brings two chlorines into spatial proximity, a significantly more negative $V_{s,min}$ is found in the region between the two atoms. We chose to report in Table 5 the electrostatic potentials calculated from the most stable (from electronic energy) conformation. This choice is somewhat arbitrary, but dictated by our ignorance of the population of various conformers in CCl_4. Also reported are (i) the log K_x for hydrogen bonding to 4-fluorophenol, statistically corrected by log 2 when two equivalent (quasi-equivalent in the case of 1,2-dichloropropane) chlorine atoms are present, and (ii) the directionality of the V_s minimum on the molecular surface. This $V_{s,min}$ directionality agrees fairly well with the directionality of the hydrogen bond to chlorine atoms found in theoretical calculations[31,33,57] or in hydrogen-bonded contacts in crystal structures.[1,31,58]

Using the data set of Table 5, we find a good linear relationship between $V_{s,min}$ and log K_x, given in Fig. 3 and

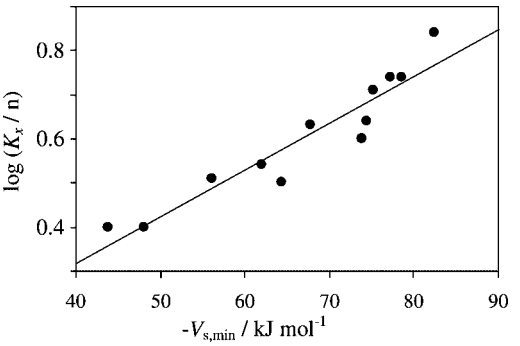


Figure 3. Correlation of the hydrogen-bond basicity scale, log(K_x/*n*), with the minimum electrostatic potential, $V_{s,min}$, on the molecular surface, located on the chlorine atoms

Table 6. Calculation of individual ($\log K_{x,i}$), and overall ($\Sigma\log K_{x,i}$) hydrogen-bond basicities of polychloroalkanes, from electrostatic potentials $V_{s,min}$ (kJ mol^{-1}); comparison with the overall hydrogen-bond basicity calculated from the octanol–water partition coefficient

Polychloroalkane	$-V_{s,min}$	N[a]	Log $K_{x,i}$	$\Sigma\log K_{x,i}$	Δ[b]
α-HCH	60.71	1	0.53		
	57.03	2	0.49		
	40.50	2	0.31	2.11	0.06
β-HCH	48.42	6	0.39	2.35	−0.17
γ-HCH (lindane)	63.30	2	0.56		
	55.60	2	0.47		
	34.50	1	0.24	2.29	−0.05
δ-HCH	54.27	2	0.46		
	50.17	2	0.41		
	41.76	2	0.32	2.37	−0.53
1,2,3-Trichloro-	70.17[c]	1	0.64		
propane	48.87[d]	1	0.41		
	44.77[e]	1	0.37	1.42	−0.27[f]

[a] Number of equivalent (relative) minima on the electrostatic potential surface.
[b] Difference between $\Sigma\log K_{x,i}$ calculated from log P_{ow} (Table 4) and from $V_{s,min}$.
[c] Absolute minimum located between Cl^1 and Cl^2 in $Cl^1CH_2CHCl^2CH_2Cl^3$.
[d] Minimum located on Cl^3 atom.
[e] Minimum located on Cl^1 atom.
[f] From a measured log P_{ow} value of 2.27 (A. J. Leo, personal communication) and the volume $V = 89.9\,cm^3\,mol^{-1}/100$, Eqn (12) yields $\Sigma\log K_{x,i} = 1.15$.

Eqn (15), where numbers in parentheses are standard deviations on the slope and intercept, respectively:

$$\log(K_x/n) = 1.06(\pm0.12)(-V_{s,min}/100) - 0.11(\pm0.08)$$
$$n = 12;\ r^2 = 0.893;\ s = 0.05 \qquad (15)$$

This correlation can be used to predict the hydrogen-bond basicity of polychloroalkanes with equivalent chlorine acceptors (e.g. β-HCH) and, most importantly, with inequivalent chlorine acceptors. In this case, $V_{s,min}$ is computed on the molecular surface around one chlorine acceptor, or between two chlorine acceptors when their spatial proximity creates a zone of high electron density (as illustrated in Plate 1). The $\log K_{x,i}$ values predicted by Eqn (15) are then summed to give a prediction for the overall hydrogen-bond basicity, $\Sigma\log K_{x,i}$. The results of these calculations for α-, β-, γ-, and δ-HCH, and 1,2,3-trichloropropane are given in Table 6. Agreement with $\Sigma\log K_{x,i}$ calculated from octanol–water partition coefficients (as illustrated in Table 4) is good, with relative differences between values predicted by the two methods ranging from 0 to 7% for all compounds except δ-HCH, for which the difference is higher (22%).

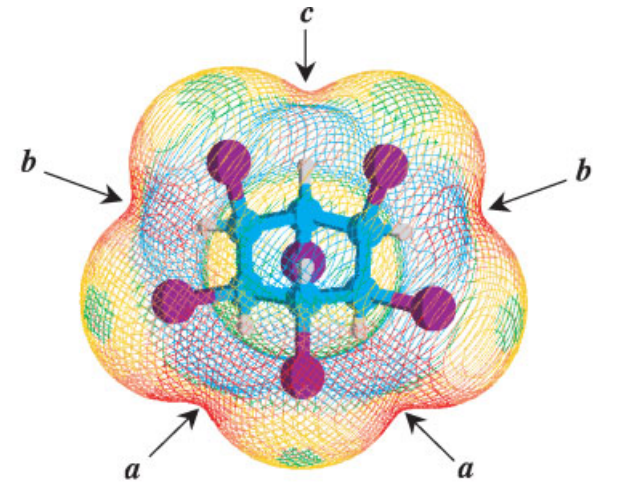
Advantages of the electrostatic potential method are the possibility of calculating *individual* complexation constants and of obtaining molecular knowledge about the electrostatic origin of hydrogen-bond basicity, through an analysis of the electrostatic potential map. For example, the map for lindane (Plate 1) shows well the subtle stereoelectronic interactions between the six negative chlorine and the six positive hydrogen atoms situated around the carbon ring. These interactions produce (i) one axial chlorine with $V_{s,min} \approx 0$, i.e. without the ability to attract the positive hydrogen of the hydroxyl of water, octanol or 4-fluorophenol, and (ii) five negative relative minima situated between the five remaining chlorines, because of the overlap of lone-pair electron densities.

Hydrogen-bond basicity from similarities between HF and 4-fluorophenol hydrogen-bonded complexes

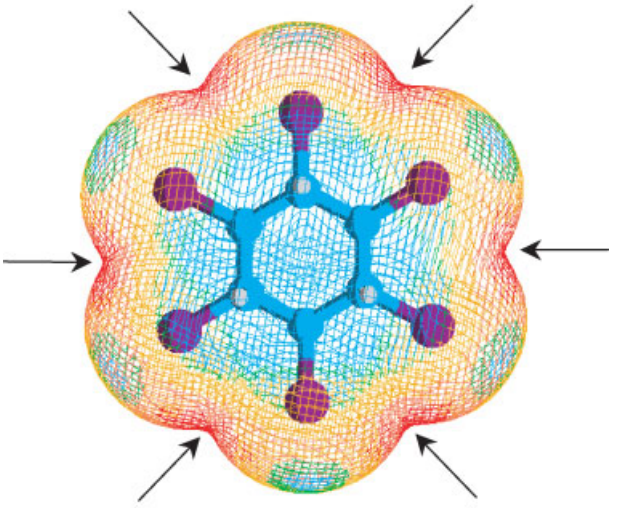
Lamarche and Platts[14] have recently shown, on a set of 40 HB acceptors including one chloroalkane, that the pK_{HB} scale (i.e. log K_x) could be correlated with the hydrogen-bond binding energy, enthalpy, and Gibbs energy (ΔE_{el}, ΔH° and ΔG°) of their hydrogen-bonded complexes with hydrogen fluoride ($r^2 = 0.906$, 0.910 and 0.927 respectively), calculated at the B3LYP/6–31+G(d,p)//B3LYP/6–31+G(d,p) level. As a last approach to the HB basicity of lindane, we also use in the following the model of HF complexes for calculating $\Sigma\log K_{x,i}$ of lindane.

For this purpose, we first established a relationship between the experimental Gibbs energies (i.e. $\log K_x$) of 4-fluorophenol complexes and the computed *enthalpies* of HF complexes for the family of chloroalkanes. As shown by Lamarche and Platts,[14] the best correlation (i) comes from computed ΔG° and (ii) seems family-independent. However, it must be taken into account that, through the entropy, ΔG°s are affected by an error of calculation. This is because, for weak hydrogen bonds, such as in chloroalkanes–HF complexes, there are a number of vibrational modes of very low frequency, hence very anharmonic.[59] Since vibrational frequencies are computed under the harmonic approximation,[60] the error affecting the vibrational entropy may be large. The error in the computed enthalpies must be smaller since, unlike the vibrational entropy, low frequencies contribute little to the zero-point vibrational energy.[33] In any case, we restricted the relative comparison between experimental ΔG° (4-fluorophenol complexes) and computed ΔH° (HF complexes) to the family of chloroalkanes and, according to the similarity principle, model and/or calculation errors are expected to be fairly small and/or constant.

Table 7 gives the results of B3LYP/6–31+G(d,p)//B3LYP/6–31G(d,p) calculations of the enthalpies of complexation of five chloroalkanes with HF. The geometry of these complexes is illustrated in Plate 2. The equilibrium complex can be described as a cyclic structure with a predominant F—H···Cl hydrogen bond distorted by secondary C—H···F hydrogen bonds (similar structures were found at the MP2/6–31+G(d,p) level for the complexes of HF with chloromethanes[57]).



γ-HCH



β-HCH

Plate 1. Molecular electrostatic potential maps of lindane (γ-HCH) and β-HCH. The isodensity surface of 0.001 e bohr^{-3} shows five relative minima [$V_{s,min} = -63.30$ (***a***), -55.60 (***b***), and -34.50 (***c***) kJ mol^{-1}] for lindane and six equivalent minima for β-HCH ($V_{s,min} = -48.42$ kJ mol^{-1}). The electrostatic potential is colour coded from red ($V_{s,min} < 0$) to blue ($V_{s,min} > 0$)

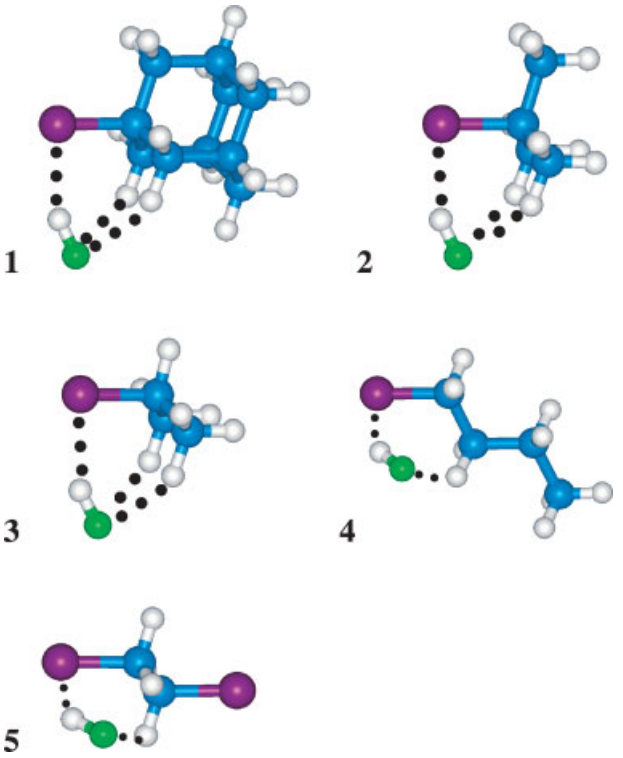


Plate 2. B3LYP/6–31G(d,p) geometries of hydrogen-bonded complexes of hydrogen fluoride with 1-chloroadamantane (**1**), 2-chloro-2-methylpropane (**2**), 2-chloropropane (**3**), 1-chlorobutane (**4**) and 1,2-dichloroethane (**5**)

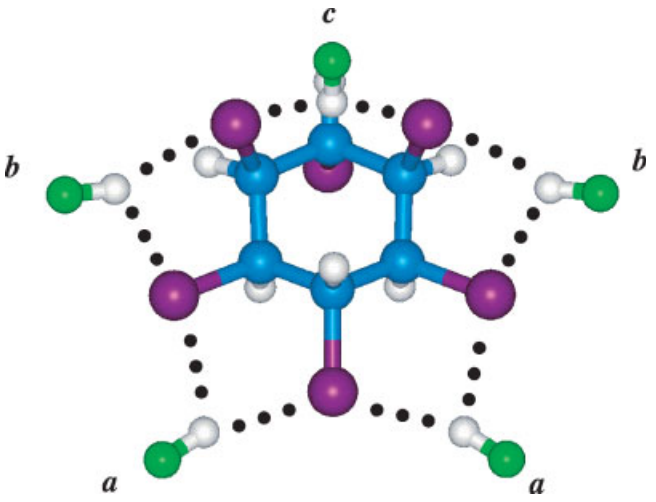


Plate 3. Superimposed B3LYP/6–31G(d,p) geometry of the five 1:1 three-centered hydrogen-bonded complexes of lindane with hydrogen fluoride. Only three 1:1 complexes (***a***, ***b***, ***c***) have different geometries (in agreement with the electrostatic potential map of Plate 1)

Table 7. Calculation of the individual (log $K_{x,i}$), and overall (Σlog $K_{x,i}$) hydrogen-bond basicity of lindane, from the B3LYP/6–31+G(d,p)//B3LYP/6–31G(d,p) computed enthalpies of 1:1 complexations with hydrogen fluoride, ΔH° (kJ mol^{-1})

Chloroalkane	$-\Delta H^\circ$	Log K_x
Training set	Comput.	Exp.
1-Chloroadamantane	13.71	0.84
2-Chloro-2-methylpropane	12.58	0.73
2-Chloropropane	11.14	0.71
1-Chlorobutane	10.14	0.60
1,2-Dichloroethane	6.43	0.39[a]
Lindane	Comput.	Est.[b]
1:1 complex *a*	5.83	0.36
1:1 complex *b*	6.48	0.40
1:1 complex *c*	0.67	0.06
	Σlog $K_{x,i}$	1.58[c]

[a] Statistically corrected by $-$log 2.
[b] Estimated from Eqn (16).
[c] Taking into account two equivalent complexes *a*, two equivalent *b* and one *c*.

These computed enthalpies correlate well with log K_x, according to the equation

$$\log K_x = -0.060(\pm 0.005)\Delta H^\circ + 0.016(\pm 0.051)$$
$$n = 5;\ r^2 = 0.982;\ s = 0.03 \qquad (16)$$

This correlation can be used to predict the HB basicity of lindane. In the optimized structures of 1:1 HF–lindane complexes, we find only five stable complexes (the axial chlorine of $V_{s,min} \approx 0$ does not give any complex, as expected), of which only three are different. These complexes are three-centered as shown in Plate 3. These observations are coherent with the electrostatic potential map of lindane, which shows five relative minima, each situated between two proximal chlorines. The log $K_{x,i}$ values predicted by Eqn (16) are then summed to give a prediction for the overall HB basicity, Σ log $K_{x,i}$. The results of these calculations are given in Table 7.

CONCLUSION

As shown in Table 8, this last method gives a lower basicity for lindane than previous ones. However, all four methods give fairly concordant results since $\Sigma K_{x,i}$ ranges from 12 to 15 and Σlog $K_{x,i}$ between 1.6 and 2.3 (see Table 8). We cannot conclude, as in a recent study,[30] that lindane 'can be regarded as a reasonably strong HB base, comparable in strength to aliphatic amines, and not far short of amides,' because the log K_x values of ethylamine, triethylamine and *N*,*N*-diethylacetamide (3.18, 2.99, and 3.48, respectively) are higher by an order of magnitude.

According to our results, lindane can be described as a weak HB acceptor. Each chlorine of lindane is individually a weaker acceptor than the chlorine of monochlorocyclohexane (comparing the values 0.24–0.56 in Table 6 or 0.06–0.40 in Table 7 with the value 0.74 of *c*-$C_6H_{11}Cl$ in Table 5), because of the electron-withdrawing inductive effect that chlorine atoms exert over one another. The overall HB basicity of lindane is raised to 1.6–2.3 by virtue of its multifunctionality (five active chlorine acceptors), but still does not attain the values of common strong monofunctional HB bases.

Table 8. Comparison of the results of four methods for the determination of the overall lindane HB basicity, Σlog $K_{x,i}$, and of the sum, $\Sigma K_{x,i}$, of individual 1:1 complexation constants of 4-fluorophenol:lindane complexes

Method	$\Sigma K_{x,i}$	Σlog $K_{x,i}$
FTIR experiment	12.8	—[a]
Experimental log P_{ow} [Eqn (12)]	—[a]	2.24
Correlation with computed $V_{s,min}$ [Eqn (15)]	14.8	2.29
Correlation with computed ΔH° (HF complexation) [Eqn (16)]	11.9	1.58

[a] Cannot be calculated since log $(\Sigma K_{x,i}) \neq \Sigma$ log $K_{x,i}$.

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