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Three-centre hydrogen bonding in the complexes of *syn*-2,4-difluoroadamantane with 4-fluorophenol and hydrogen fluoride

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ABSTRACT: Hydrogen bond enthalpies for the interaction of 4-fluorophenol with *syn*-2,4-difluoroadamantane (**5**) and, for comparison, 2-fluoroadamantane (**6**) and 1,3-difluoroadamantane (**7**) have been determined by Fourier transform infrared spectrometry. Among a series of seven fluoroalkanes (**1**–**7**) it is found that *syn*-2,4-difluoroadamantane is the best hydrogen bond acceptor. This high hydrogen bond acceptor strength is explained, using electrostatic and 'atoms in molecules' properties and from density functional theory and *ab initio* calculations on hydrogen fluoride complexes, by the formation of an F···H···F three-centre hydrogen bond. In this system, the three-centre hydrogen bonding is energetically (mainly on the Gibbs energy scale) superior to the two-centre hydrogen bonding. Copyright © 2004 John Wiley & Sons, Ltd.

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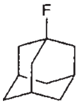
KEYWORDS: three-centre hydrogen bonding; fluoroadamantanes; *syn*-2,4-difluoroadamantane.

INTRODUCTION

Previously,[1] we have measured the hydrogen bond acceptor strength of fluoroalkanes (RF) **1**–**4** through the enthalpy of reaction (1) in which a reference

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



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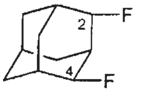
hydrogen bond donor, 4-fluorophenol, is hydrogen bonded to the fluorine atom. It was found that 1-fluoroadamantane (**1**) is the best hydrogen bond acceptor as a result of the higher polarizability effect of a bicyclic tertiary alkyl group.[2] 1,3-Difluoropropane (**4**) is the worst hydrogen bond acceptor because of the electron-withdrawing field-inductive effect that fluorines exert on each other.[2]

We report here the study of the hydrogen bond acceptor strength of fluoroadamantanes **5**–**7**.



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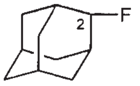

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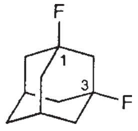

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Among these, *syn*-2,4-difluoroadamantane (**5**) deserves particular attention for two reasons. Firstly, its strong retention on a silica column suggests that it is an even better hydrogen bond acceptor than 1-fluoroadamantane (**1**). Based on the idea that the inductive effect is transmitted by successive polarization of the intervening bonds (σ-inductive effect),[3,4] this is counter-intuitive to the expected reduced HB acceptor capacity in response to the σ-electron-withdrawing influence of a fluorine substituent. On the other hand, however, the apparent enhanced hydrogen bond acceptor capacity of **5** is clearly in accord with the prediction from electrostatic field theory, namely, that a dipolar substituent effect can be modified by its geometrical orientation to be 'normal', diminished, absent or even 'reversed'.[5] Studies of proton-transfer equilibria with appropriately designed rigid model systems have revealed unequivocal examples of reversed dipolar substituent effects.[5] The relative importance of the two mechanisms of electrical transmission of polar substituent effects, described as the electrostatic field and σ-inductive effect, has been disputed over many years.[6–8] However, a general consensus seems to have been reached[5,9–16] that for remote probe groups (beyond two

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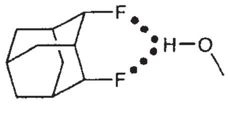
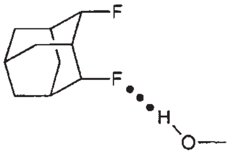
bonds) the direct field effect is clearly the dominant 'inductive' mechanism and that the σ-inductive effect is insignificant beyond the first atom of attachment.[17,18] Secondly, the unusually high fluorine–fluorine coupling constant ($^4J_{FF} = 21.01$ Hz; see supplementary material) for **5** compared with the corresponding value for the epimeric difluoride 2^{eq}, 4^{ax}-difluoroadamantane ($^4J_{FF} = 2.27$ Hz; see supplementary material) highlights the proximity of the two axial fluorines in **5**.

A possible important manifestation of this proximity might be the formation of three-centre hydrogen bonding as depicted in **5a** rather than, or in addition to, two-centre hydrogen bonding as shown in **5b**. Such three-centre hydrogen bonds are common in the solid state[19,20] and seem important in the structure of numerous biological compounds.[21] However, they have formed the subject of only a few theoretical[22,23] or spectroscopic[24] studies and, to the best of our knowledge, have not featured in any thermodynamic study. Thus the energetic superiority of three-centre hydrogen bonding relative to two-centre hydrogen bonding remains disputed.[22–24] Moreover, most of the three-centre hydrogen bonds studied have involved oxygen and nitrogen centres.[22–24] Except for the intramolecular hydrogen bond in 2-trifluoromethylphenol[25] and in 2,6-bis-(2,6-difluorophenyl)piperidine-4-ones,[26] there does not seem to be any experimental work on three-centre intermolecular hydrogen bonds involving two fluorine atoms.



5a



5b

In this work, thermodynamic functions ΔG, ΔH and ΔS for the interaction (1) of 4-fluorophenol with fluoroadamantanes **5**–**7**, as well as the infrared (IR) wavenumber shifts of the OH band caused by the hydrogen bonding, have been determined in CCl_4 solution through Fourier transform infrared (FTIR) spectrometry. These $\Delta\nu$(OH) IR shifts are often considered a spectroscopic scale of hydrogen bond acceptor strength. They are generally correlated to the hydrogen bond enthalpy in a series of related hydrogen-bonded complexes (the so-called Badger–Bauer relationship).[1,27]

We have also undertaken a theoretical study of the hydrogen bond acceptor properties of fluoroalkanes **1**–**7**. We have first calculated and located their minimum molecular electrostatic potential (MEP),[28] which defines the probable hydrogen bond acceptor site.[28] Molecular electrostatic potentials are also indicators of electron density distribution and thus should allow an estimate of the shift of charges caused by the field-inductive effect of fluorines in difluoroalkanes **4**, **5** and **7** and the electronic density in the space between the two fluorines of **5**, which is possibly increased by overlap of their lone pairs. Secondly, we calculated structures, thermodynamic parameters (ΔH, ΔG) and IR shifts of the hydrogen-bonded complexes of fluoroalkanes **1**–**7**. Instead of 4-fluorophenol we chose hydrogen fluoride as the smallest possible hydrogen bond donor in order to decrease the computational cost of the considered reaction (2). A recent theoretical study[29] has shown the existence of a linear free energy relationship between the complexes of HF and

$$\mathrm{HF} + \mathrm{RF} \rightleftharpoons \mathrm{F{-}H \cdots F{-}R} \qquad (2)$$

$4\text{-}FC_6H_4OH$ with a wide sample of hydrogen bond acceptors. The authors concluded that HF is a reasonable model for the hydrogen bond donor properties of $4\text{-}FC_6H_4OH$. Lastly, for F—H···F—R complexes we performed a topological analysis of the electron density[30,31] and a natural bond orbital (NBO)[32] analysis to characterize the bonding interactions between HF and the fluorine atoms of **1**–**7**.

EXPERIMENTAL

Chemicals

4-Fluorophenol ($4\text{-}FC_6H_4OH$) was sublimed over P_2O_5. Carbon tetrachloride (CCl_4) was distilled and then dried over 4 Å molecular sieves. Literature procedures were followed in the preparation and purification of 2-fluoroadamantane (**6**)[33] and 1,3-difluoroadamantane (**7**).[34] Their physical properties and NMR spectral details were in accord with those reported previously.[33,35,36] The synthesis of *syn*-2,4-difluoroadamantane (**5**) is reported in the supplementary material. All chemicals and their CCl_4 solutions were handled in the dry atmosphere of a glove-box.

Nuclear magnetic resonance spectra

The NMR spectra were recorded on a Gemini-300 spectrometer. The probe temperature of the instrument was 295 ± 2 K. The ^{19}F-NMR spectra were obtained under proton-decoupled conditions in dilute $CDCl_3$ solutions. The spectra were run at 282.328 MHz (64K/32K data points; spectral widths of 19569, 10279.6 and 4800.1 Hz).

Infrared spectra

Infrared spectra were recorded with a Bruker Vector 22 or a Tensor 27 FTIR spectrometer at a resolution of 1 cm^{-1}. Infrasil quartz cells of path length 1 or 0.5 cm were used for the study of the ν(OH) region. The cell temperature was regulated to within ± 0.2 °C by means of a Peltier thermoelectric device: at 25 °C for $\Delta\nu$(OH) measurements and from −5 to +55 °C for the temperature variation of equilibrium constants. The wavenumber shift of the OH band of 4-fluorophenol is defined as $\Delta\nu(\mathrm{OH}) = \nu(\text{free OH}) - \nu(\text{complex OH}) = 3614 - \nu$ (OH···F). It is measured in ternary solutions of 4-fluorophenol ($3\,\mathrm{mmol\,dm^{-3}}$), fluoroadamantane (ca. $0.1\,\mathrm{mol\,dm^{-3}}$) and CCl_4 and is known to be $\pm 2\,\mathrm{cm^{-1}}$.

Equilibrium constants and complexation enthalpies and entropies

The complexation constants K_x, Gibbs energies ΔG_x°, enthalpies ΔH° and entropies ΔS_x° of reaction (1) are defined by equations (3)–(5), where x and x^0 are the equilibrium and initial mole fractions, respectively

$$\begin{aligned} K_x &= x_{\text{complex}}/(x_{\text{fluoroadamantane}} \times x_{\text{phenol}}) \\ &= x_{\text{complex}}/[(x^0_{\text{fluoroadamantane}} - x_{\text{complex}}) \\ &\quad \times (x^0_{\text{phenol}} - x_{\text{complex}})] \end{aligned} \tag{3}$$

$$\Delta G_x^\circ = -RT \ln K_x \tag{4}$$

$$\ln K_x = -\frac{\Delta H^0}{R}\frac{1}{T} + \frac{\Delta S_x^0}{R} \tag{5}$$

The mole fraction of the complex is measured from the decrease in absorbance of the ν(OH) band of free 4-fluorophenol at $3614\,\mathrm{cm^{-1}}$ (absorption coefficient $\varepsilon = 2420\,\mathrm{cm^{-1}}$ at 25 °C CCl_4). Precise thermodynamic measurements were obtained by following the absorbance of a single solution as a function of temperature, as described previously.[1,37]

COMPUTATIONAL DETAILS

Calculations were performed using the Gaussian 98 program[38] at the Becke3LYP (geometries, frequencies, MEP, atoms in molecules) and MP2 (electronic energy variations of HF complexes) levels using a Pople style 6-31+G** basis set.[39]

Geometries

The geometries of the monomers (HF, fluoroadamantanes **1**–**7**) and their complexes were fully optimized. Four molecules (**1**, **5**, **6**, **7**) are rigid. The more stable forms of the flexible molecules—1-fluorocyclohexane (**2**), fluoropentane (**3**) and 1,3-difluoropropane (**4**)—were found to be equatorial, fully staggered and gauche–gauche, respectively, in agreement with previous studies.[40,41] The starting geometry of HF complexes was the well-known geometry of the dimer $(HF)_2$.[42] The structures of monomers and complexes were confirmed as minima through harmonic frequency calculations.

Molecular electrostatic potentials

The MEP was calculated with the Hardsurf 95 program.[43] We calculated $V_{\mathrm{S,min}}$, the minimum electrostatic potential on the molecular surface defined by the 0.001 electron $\mathrm{bohr^{-3}}$ contour of the electron density.

Thermodynamics of HF complexes

Thermodynamic properties were calculated as the difference between the quantity of the complex, treated as a supermolecule, and the sum of the quantities of the monomers. The computation of the electronic energy by the supermolecular approach introduces a spurious stabilization of the complex, commonly referred to as the basis set superposition error (BSSE).[39] We therefore applied a correction to the variation of electronic energy upon complexation by means of the full counterpoise method[44] with fragment relaxation.[45]

'Atoms in molecules' and NBO analysis

The electron densities have been computed at the critical points of the hydrogen bond interactions, within the frame of the theory of 'atoms in molecules' (AIM) proposed by Bader,[30,31] with the AIM2000 set of programs.[46] The nature of the hydrogen bonding interaction at orbital level has been studied using NBO analysis[32] on HF complexes at the B3LYP level with a 6–31+G(d,p) basis set.

RESULTS AND DISCUSSION

Hydrogen-bonded complexes with 4-fluorophenol

The spectroscopic and thermodynamic properties of the $4\text{-}FC_6H_4OH\cdots F{-}R$ complexes are given in Table 1. Results of a previous study[1] are added for comparison. The logarithm of the equilibrium constant relative to molar concentration (log K_c), the so-called pK_{HB} scale,[47] is also given in order to add the fluoroadamantanes (**5**–**7**) to the pK_{HB} database.[48] We draw attention to three important features of the results listed in Table 1:

(i) The enthalpy of complexation is more negative for *syn*-2,4-difluoroadamantane (**5**) than for 1-fluoroadamantane (**1**) and 2-fluoroadamantane (**6**) (Scheme 1). The enhanced hydrogen bond acceptor strength of **5** relative to **6** stands in stark contrast to the 'normal' electron-withdrawing polar effect of fluorine, as revealed by the reduced hydrogen bond acceptor strength of **7** (Scheme 1). Given that the two fluorines in **5** and **7** are separated by the same

Table 1. Thermodynamic functions ΔG, ΔH (kJ mol^{-1}) and ΔS (J K^{-1} mol^{-1}), IR shifts $\Delta\nu$(OH) (cm^{-1}) and pK_{HB} scale for hydrogen bonding of fluoroalkanes to 4-fluorophenol in CCl_4 (reaction 1)

No.	Fluoroalkane	pK_{HB}	$-\Delta H°$	$-\Delta S°_{x,298}$	$-\Delta G°_{x,298}$	$\Delta\nu$(OH)
5	*syn*-2,4-Difluoroadamantane[a]	0.48[b]	15.4	23.0[b]	8.5[b]	42[c]
1	1-Fluoroadamantane[d]	0.31	14.4	23.1	7.6	70
6	2-Fluoroadamantane[a]	−0.02	12.8	24.0	5.7	60
2	Fluorocyclohexane[d]	0.09	12.7	21.1	6.3	59
7	1,3-Difluoroadamantane[a]	0.30 (0.00)[e]	12.3	16.1 (21.9)[f]	7.5 (5.8)[g]	52
3	1-Fluoropentane[d]	−0.06	10.5	15.8	5.4	44
4	1,3-Difluoropropane[d]	0.03 (−0.27)[e]	9.7	12.1 (17.9)[f]	5.9 (4.2)[g]	32

[a] This work.

[b] Not statistically corrected (three-centre hydrogen bond).

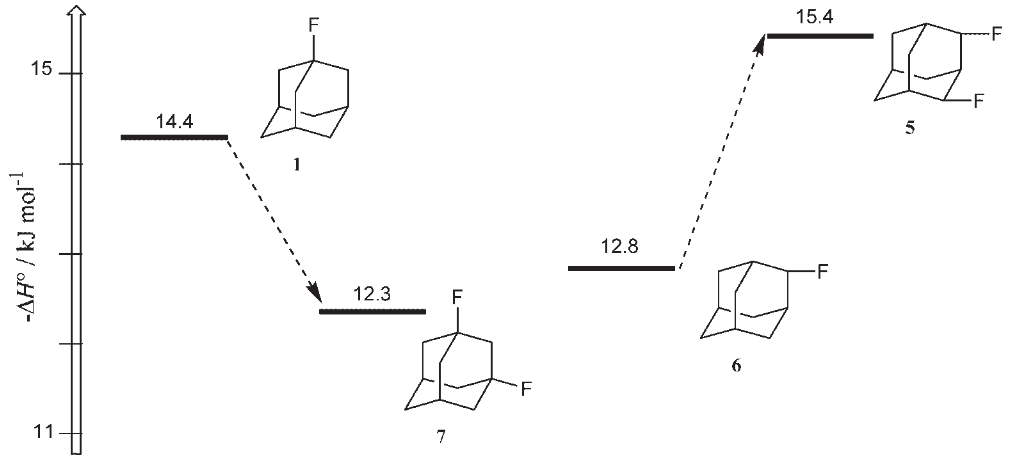
[c] Apparent shift of an unsymmetrical OH band in the complex. After separation of the two component bands, two frequency IR shifts, 44 and 66 cm^{-1}, are found (see text).

[d] Ref. 1.

[e] Statistically corrected by log 2.

[f] Statistically corrected by R ln 2 (5.8 J K^{-1} mol^{-1}).

[g] Statistically corrected by RT ln 2 (1.7 kJ mol^{-1}).



Scheme 1

number of bonds but have different spatial separations and orientations, this factor, coupled with the overlap of the fluorine lone pairs, is responsible for the hydrogen bond acceptor behaviour of **5**.[49] However, their relative importance remains to be established.

(ii) Although other complexes have a ν(OH) band that is roughly symmetrical, the ν(OH) band of the complex with *syn*-2,4-difluoroadamantane is clearly unsymmetrical. By mathematically resolving this band into two Gaussian–Lorentzian component bands, we find a main band at 3570 cm^{-1} ($\Delta\nu$(OH) = 44 cm^{-1}) and a minor band at 3548 cm^{-1} ($\Delta\nu$(OH) = 66 cm^{-1}) in a 4:1 ratio of integrated intensities (Fig. 1).

(iii) The main $\Delta\nu$(OH) IR shift of *syn*-2,4-difluoroadamantane is abnormally weak compared with the strongly negative enthalpy of complexation. Consequently, the Badger–Bauer relationship between

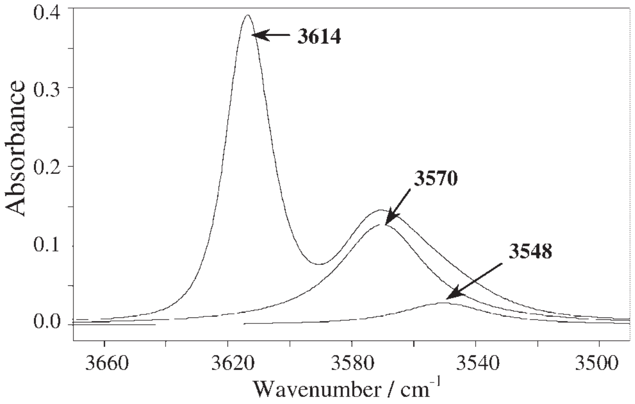


Figure 1. Infrared spectrum of a CCl_4 solution of 4-fluorophenol (4 × 10^{-3} M) and *syn*-2,4-difluoroadamantane (8 × 10^{-2} M) in the ν(OH) region, showing the sharp ν(OH) band of free 4-FC_6H_4OH at 3614 cm^{-1} and the wider unsymmetrical band of hydrogen-bonded 4-FC_6H_4OH. Decomposition of the latter gives a band at 3570 cm^{-1} that is four times more intense than that at 3548 cm^{-1}

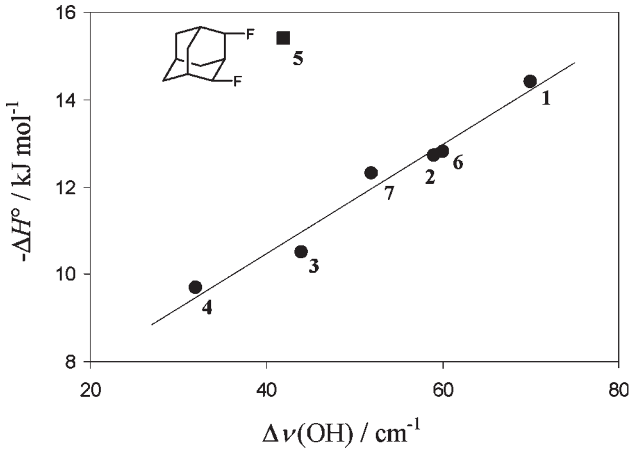


Figure 2. *syn*-2,4-Difluoroadamantane deviates strongly from the Badger–Bauer relationship ($-\Delta H^\circ = 0.1254\ \Delta\nu(\mathrm{OH}) + 5.4$, $n = 6$, $r^2 = 0.963$) in the series of fluoroalkanes

ΔH° and $\Delta\nu(\mathrm{OH})$, which is well obeyed by six fluoroalkanes (squared correlation coefficient, $r^2 = 0.963$), is not followed by *syn*-2,4-difluoroadamantane (Fig. 2).

These observations are possibly explained by the spatial proximity of the two fluorine atoms in **5** (B3LYP/6-31 + G** distance = 2.82 Å), enabling an enrichment of electron density by overlap of lone pairs and the formation of three-centre hydrogen bonding (**5a**). This peculiar structure **5a**, compared with the two-centre hydrogen bonding in the hydrogen-bonded complexes of **1**–**4**, **6** and **7**, might explain a high ΔH° value (two hydrogen bonds at a point of higher electron density), the presence of two complexes **5a** and **5b** and therefore two IR bands and a low $\Delta\nu(\mathrm{OH})$ value; these factors that optimize the energy are not necessarily optimum for a low OH force constant in the complex.

We have turned to theory in order to rationalize these experimental observations and support these hypotheses.

Table 2. Minimum electrostatic potentials on the molecular surface, $V_{\mathrm{S,min}}$ (kJ mol^{-1}), for fluoroalkanes **1**–**7** and radial, *d* (Å), and angular, θ(°), disposition of minima (B3LYP/6-31 + G** calculations)

No.	Fluoroalkane	$-V_{\mathrm{S,min}}$	d	θ
5	*syn*-2,4-Difluoroadamantane	173.8[a]	1.83	123
		~120[b]	~1.67	~140–145
1	1-Fluoroadamantane	121.5	1.67	146
6	2-Fluoroadamantane	116.1	1.67	142
2	Fluorocyclohexane (equatorial)	118.1	1.67	143
7	1,3-Difluoroadamantane	105.4	1.67	146
3	1-Fluoropentane (gauche, fully staggered)	112.2	1.67	142
4	1,3-Difluoropropane (gauche, gauche)	99.7	1.68	138

[a] Between the two fluorine atoms.

[b] Outside the region between the two fluorine atoms (see Fig. 3).

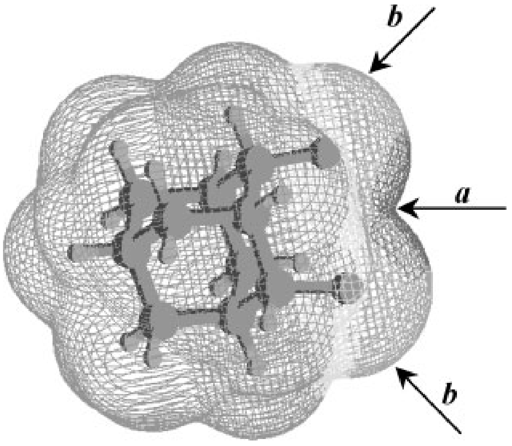


Figure 3. Molecular electrostatic potential map of *syn*-2,4-difluoroadamantane. The isodensity surface of 0.001 electron bohr^{-3} shows an absolute minimum ***a*** between the two fluorine atoms, whereas the zones ***b*** outside are less negative

Molecular electrostatic potentials of fluoroalkanes

The value and localization of MEP minima are given in Table 2. The parameters of localization are the distance *d* to the fluorine nucleus and the angle θ between the C—F and F-minimum vectors. For *syn*-2,4-difluoroadamantane it is found (Fig. 3) that point ***a*** of most negative potential (i.e. higher electron density) is situated between, and at an equal distance from, the two fluorine atoms. Points ***b***, corresponding to the minimum of other fluoroalkanes (i.e. $d \sim 1.67$ Å, $\theta \sim 140$–145 Å; see Table 2), have a potential that is less negative by ca. 47 kJ mol^{-1}. Thus the electrostatic component of the hydrogen bond energy might favour three-centre (**5a**) relative to two-centre (**5b**) hydrogen bonding. The 'normal' electron-withdrawing inductive field effect of fluorine (which operates significantly in 1,3-difluoroadamantane (**7**), where $V_{\mathrm{S,min}}$ is less negative by 16 kJ mol^{-1} than in 1-fluoroadamantane) is 'reversed' in **5** (see Introduction) and, coupled with the 2,4-proximity effect, leads to $V_{\mathrm{S,min}}$ being more negative by 58 kJ mol^{-1} than in 2-fluoroadamantane.

Thermodynamics of HF complexes

We report in Table 3 a few characteristics of the hydrogen bonding of hydrogen fluoride to fluoroalkanes **1**–**7** calculated *in vacuo*: the hydrogen bond length $\ell(\mathrm{H}\cdots\mathrm{F})$, the lengthening of the HF bond $\Delta d(\mathrm{HF})$, the frequency shift $\Delta\nu(\mathrm{HF}) = \nu$ (free HF) $- \nu$(complex HF) and the enthalpy of complexation (reaction 2). Hydrogen fluoride *in vacuo* appears to be a reasonable model of

Table 3. Hydrogen bonding of HF with fluoroalkanes: hydrogen bond length $\ell(\mathrm{H}\cdots\mathrm{F})$ (Å), HF bond lengthening Δd (HF) (Å), frequency shift $\Delta\nu$(HF) (cm^{-1}) and enthalpy of complexation ΔH°_{298} (2) ($\mathrm{kJ\,mol^{-1}}$)

No.	Fluoroalkane	$\ell(\mathrm{H}\cdots\mathrm{F})$	Δd(HF)	$\Delta\nu(\mathrm{HF})^{a}$	$-\Delta H^{\circ}_{298}\ (2)^{b}$
5	*syn*-2,4-Difluoroadamantane				
	Three-centre hydrogen bonding	2.12; 2.05	0.008	131	21.1
	Two-centre hydrogen bonding	1.70	0.014	278	20.7
1	1-Fluoroadamantane	1.69	0.015	303	22.4
6	2-Fluoroadamantane	1.69	0.014	283	20.4
2	Fluorocyclohexane (equatorial)	1.69	0.014	284	20.3
7	1,3-Difluoroadamantane	1.71	0.014	282	20.0
3	1-Fluoropentane(gauche, fully staggered)	1.71	0.013	265	19.2
4	1,3-Difluoropropane (gauche, gauche)	1.72	0.012	257	17.6

[a] Scaling factor = 0.9614.
[b] MP2/6–31+G**//B3LYP/6–31 + G** calculation, with BSSE correction and scaled (0.9804) vibrational energy.

$4\text{-}FC_6H_4OH$ in CCl_4: calculated $\Delta\nu$(HF) and ΔH°_{298} (2) gives mainly the same hydrogen bond acceptor strength order as the experimental one. The correlation between the ΔH°_{298} value of reaction (1) (Table 1) and the ΔH°_{298} value of reaction (2) (Table 3) is satisfactory for two-centre hydrogen-bonded complexes (**1–4**, **6**, **7**) ($n = 6$, $r^2 = 0.940$).

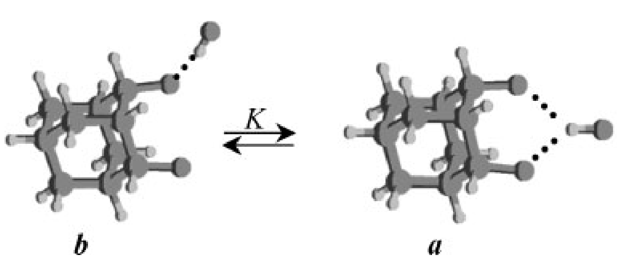
For the HF complexes of *syn*-2,4-difluoroadamantane, it appears that three-centre hydrogen bonding is slightly more favourable energetically than two-centre hydrogen bonding, whereas the two-centre hydrogen bonding gives a much larger $\Delta\nu$(HF) shift than three-centre hydrogen bonding. This latter result allows the most shifted and less intense OH component band of the $4\text{-}FC_6H_4OH$ complex (Fig. 1) to be attributed to the two-centre hydrogen-bonded complex and the less shifted and more intense component band (Fig. 1) to be attributed to the three-centre hydrogen-bonded complex. Calculations (reported in Scheme 2) of the equilibrium constant for the equilibrium between the two configurations of complexation predict $K = 1.9$ (after taking into account the statistical correction R ln 2 for the entropy of the two-centre complex), i.e. an approximate 2:1 ratio in the concentrations of the two HF complexes. This result agrees *qualitatively* with the 4:1 ratio found for $4\text{-}FC_6H_4OH$ (*vide supra*) from integrated intensities of the two component bands in the IR spectrum (Fig. 1) in so far as the intrinsic intensities of the OH stretching in the two kinds of complexes are not very different. This assumption appears reasonable in the case of HF stretching (calculated integrated intensities are 845 and 525 $\mathrm{km\,mol^{-1}}$ for the two- and three-centre hydrogen bonds, respectively).

'Atoms in molecules' and NBO investigations

Topological analysis of the electron density (ρ) is based upon critical points, i.e. where the gradient of the density vanishes. In this work we consider only bond critical points (BCPs). Properties, such as ρ, evaluated at BCPs characterize the bonding interactions present. Hydrogen bonds are generally referred to as those with $\rho_{\mathrm{BCP}} \sim 0.01$ au (van der Waals interactions having $\rho_{\mathrm{BCP}} \sim 0.001$ au). In the complexes of HF with fluoroalkanes (except *syn*-2,4-difluoroadamantane) we find *one* BCP with ρ_{BCP} varying from 0.034 to 0.036 au in the order of increasing hydrogen bond acceptor strength. A rough correlation ($n = 6$, $r^2 = 0.856$) is found between the ΔH° values of Table 1 and ρ_{BCP}.

In the three-centre complex of HF with *syn*-2,4-difluoroadamantane we find *two* separated BCPs between the hydrogen atom of hydrogen fluoride and the two fluorine atoms. The ρ_{BCP} values are 0.013 au for the longest interaction (2.12 Å) and 0.015 au for the shortest one (2.05 Å). This confirms the existence of three-centre hydrogen bonding between HF (and, by extension, $4\text{-}FC_6H_4OH$) and *syn*-2,4-difluoroadamantane.

In the two-centre complex of HF with *syn*-2,4-difluoroadamantane $\rho_{\mathrm{BCP}} = 0.035$ au. Thus the sum of the two ρ_{BCP} values (0.028 au) found in the three-centred hydrogen bond is smaller than the ρ_{BCP} value found in the corresponding two-centred hydrogen bond. We deduce that, among the various components of the hydrogen bond energy (electrostatic, exchange repulsion, polarization, charge transfer and dispersion),[50] some (possibly the charge transfer) play in favour of the two-centred



$$\Delta H^{0}_{298} = -0.40\ \mathrm{kJ\,mol^{-1}}$$
$$\Delta S^{0}_{298} = 4.0\ \mathrm{J\,K^{-1}mol^{-1}}$$
$$\Delta G^{0}_{298} = -1.58\ \mathrm{kJ\,mol^{-1}}$$
$$K_{(298)} = [\boldsymbol{a}]/[\boldsymbol{b}] = 1.9$$

Scheme 2

Table 4. Natural bond orbital analysis for HF monomer, *syn*-2,4-difluoroadamantane monomer and its two and three-centre complexes with HF

Parameter	Monomer		*syn*-2,4-Difluoroadamantane (**5**)	
	HF	**5**	Two-centre	Three-centre
q_{CT} [a]	—	—	0.028	0.012
$\bar{n}$(F) occupancy[a]	—	1.978	1.973	1.978
σ^*_{H-F} occupancy[a]	0.000	—	0.030	0.014
$\Sigma\Delta E^2$ (kJ mol^{-1})	—	—	66.7	28.2

[a] q_{CT} and occupancy values are in number of electrons.

complex. This might explain the higher $\Delta\nu$(OH) and $\Delta\nu$(HF) values in the two-centre configuration. This also explains that, in spite of a much higher electrostatic potential at point ***a*** than at point ***b*** (Fig. 3), the enthalpy of hydrogen bonding is only marginally higher (0.4 kJ mol^{-1} in Table 4) for the three-centre configuration.

Natural bond arbital analysis of the HF complexes confirms that the charge transfer interaction is larger in the two-centre hydrogen bonding. The occupancies of the orbitals $\bar{n}$(F) (mean for one lone pair) and σ^*_{H-F} that are involved in the electron donor–acceptor interaction, the charge transfer (q_{CT}) from the donor (**5**) to the acceptor (HF) and the second-order perturbation energy ($\Sigma\Delta E^2$) due to interaction of the donor and acceptor orbitals are summarized in Table 4: q_{CT} is greater, the $\bar{n}$(F) occupancy decreases more, the σ^*_{H-F} occupancy increases more and $\Sigma\Delta E^2$ is greater in the two- than in the three-centre hydrogen bonding.

CONCLUSION

syn-2,4-difluoroadamantane is the strongest hydrogen bond acceptor in the family of fluoroalkanes. It can form both three-centre and two-centre hydrogen bonds. The three-centre configuration results mainly from the high electrostatic potential in the region between the two fluorines. Enthalpy favours marginally the three-centre hydrogen bond whereas Gibbs energy seems more selective.

Supplementary material

Discussion on the NMR spectra of *syn*-2,4-difluoroadamantane (**5**) and its detailed synthesis and purification are available in Wiley Interscience.

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