

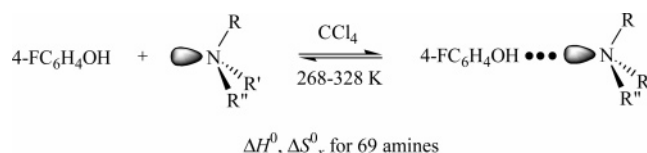
## An Enthalpic Scale of Hydrogen-Bond Basicity. 3. Ammonia, Primary, Secondary, and Tertiary Amines

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A reliable enthalpic scale of hydrogen-bond acceptor strength (basicity) is built for aliphatic amines by means of a new infrared method, from the temperature variation of hydrogen-bond equilibrium constants. Enthalpies of hydrogen bonding to a reference hydrogen-bond acceptor, 4-fluorophenol, have been determined in  $\text{CCl}_4$  and/or  $\text{C}_2\text{Cl}_4$  for ammonia and 68 primary, secondary, and tertiary amines. The scale spans from  $-23.8 \text{ kJ mol}^{-1}$  for  $i\text{-Pr}_2\text{NCH}(\text{Et})_2$  to  $-39.4 \text{ kJ mol}^{-1}$  for  $\text{Et}_3\text{N}$ . This large variation is mainly explained by the basicity-enhancing electronic effects of alkyl groups, which can be overcompensated by dramatic basicity-decreasing steric effects. Relationships between  $\Delta H^\circ$  and the change in electronic energy or the infrared shift of the OH stretching upon hydrogen bonding are studied and found useful in the prediction of the hydrogen bond enthalpies of amines with several hydrogen-bond acceptor sites. A careful statistical analysis of the enthalpy–entropy relationship shows an isoentropic tendency. The entropies of 65% of hydrogen-bonding reactions between aliphatic amines and 4-fluorophenol have a mean value of  $-55.1 \pm 4.2 \text{ J K}^{-1} \text{ mol}^{-1}$ . Amines excluded from the isoentropic set are mainly severely hindered ones. The hydrogen-bond enthalpic scale can be useful in measuring the electrostatic character of Lewis bases.

### Introduction

Despite the importance of hydrogen bonding throughout chemistry<sup>1</sup> and biochemistry,<sup>2</sup> there is a serious dearth of reliable hydrogen-bond enthalpies. It is critical to find good enthalpies of hydrogen bonding between hydrogen-bond donors and acceptors in a number of cases. For example, reliable experimental values of enthalpy are necessary for comparison with quantum-chemical calculations of the energy of the hydrogen bond.<sup>3</sup> Also there is a need of good values for testing the extrathermodynamic relationship<sup>4</sup> between enthalpy and entropy of hydrogen bond formation. In 1960, Pimentel and McClellan<sup>1</sup> proposed a monotonic relationship between  $\Delta H^\circ$  and  $\Delta S^\circ$  for hydrogen bond formation. How-

ever, in 1974, the data of Arnett et al.<sup>5</sup> indicated that “in general, a straight line correlation between  $\Delta H^\circ$  and  $\Delta S^\circ$  does not hold although a trend is clear”. Another debated correlation is the Badger–Bauer correlation<sup>6,7</sup> of the hydrogen-bond enthalpy with the infrared shift of the XH stretching frequency upon complexation. It has been supported by some workers<sup>8–18</sup> and challenged by

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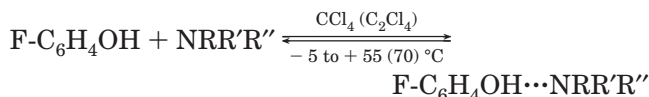
many others.<sup>5,19–27</sup> At last, opinion is divided about whether the enthalpy or the Gibbs energy is the best parameter for measuring basicity.<sup>28</sup> Gutmann,<sup>29</sup> Drago,<sup>30</sup> and Maria and Gal<sup>31</sup> chose the enthalpy for building Lewis basicity scales. However, in the field of hydrogen-bond basicity most scales are based on Gibbs energies,<sup>32–35</sup> a choice possibly dictated by the lack or inaccuracy of enthalpy data.

In parts 1 and 2 of this series we have reported an enthalpic scale of hydrogen-bond acceptor strength, i.e., hydrogen-bond basicity, for halogen (F, Cl, Br, and I)<sup>36</sup> and sulfur bases.<sup>37</sup> In this work we extend the scale to nitrogen bases, more precisely to aliphatic amines.

A number of studies<sup>5,20,38–47</sup> have been devoted to the enthalpies of hydrogen bonding between amines and hydrogen-bond donors. Unfortunately, they suffer from various shortcomings. First, they are often concerned with a restricted sample of amines. Second, they are not homogeneous, being relative to different hydrogen-bond donors (alcohols,<sup>39,45</sup> phenol,<sup>38,40,47</sup> 4-fluorophenol,<sup>5,20</sup> 4-ni-

trophenol,<sup>43</sup> and other substituted phenols<sup>44</sup>) in different solvents (*c*-C<sub>6</sub>H<sub>12</sub>,<sup>41–44</sup> CCl<sub>4</sub>,<sup>5,20,38,39</sup> C<sub>2</sub>Cl<sub>4</sub>,<sup>40</sup> and pure base<sup>5,20</sup>). At last, when obtained from the variation of the equilibrium constant with temperature, they are determined on a too-restricted range of temperature: 40,<sup>40</sup> 30,<sup>38</sup> and even only 15<sup>47</sup> or 10 °C.<sup>43</sup> Since the error in enthalpy is inversely related to the temperature range of van't Hoff plots,<sup>48</sup> the precision and/or correctness of most data might not be sufficient. In summary, literature data do not at present allow construction of an extensive, homogeneous, and reliable enthalpic scale of hydrogen-bond basicity of aliphatic amines.

We present here a set of thermodynamic data on aliphatic amines contrasting with these results. We have first selected a diversified sample of 69 amines (ammonia, 9 primary, 26 secondary, and 33 tertiary amines) including alkylamines of different chain length and chain branching, cyclic and bicyclic amines of various ring size, diamines, a tetramine, and amines substituted with various electron-withdrawing groups (F, Cl, CH=CH<sub>2</sub>, Ph, and C≡CH). Thus, we have been able to extend the hydrogen-bond enthalpic scale of aliphatic amines over 15 kJ mol<sup>-1</sup>. Second, for the purpose of homogeneity, we have used 4-fluorophenol and CCl<sub>4</sub> as standard hydrogen-bond donor and solvent, respectively. The use of C<sub>2</sub>Cl<sub>4</sub>, a solvent very close to CCl<sub>4</sub>,<sup>49</sup> has occasionally been necessary owing to the reaction of few amines with CCl<sub>4</sub>.<sup>50</sup> At last, to decrease the error in enthalpy (and entropy), the temperature dependence of equilibrium constants has been carried out over 60 °C (–5 to +55 °C) in CCl<sub>4</sub> and over 75 °C (–5 to +70 °C) in C<sub>2</sub>Cl<sub>4</sub>. Under these conditions, the reaction studied will be



With these extensive and hopefully reliable data in hand, we have analyzed a number of problems related to the thermodynamics of hydrogen bonding, namely, the prevision of enthalpies of amines bearing a second hydrogen-bond acceptor site by means of quantum-chemical calculations,<sup>3</sup> the domain of validity of the enthalpy–infrared shift relationship,<sup>6,7</sup> the existence of the enthalpy–entropy relationship,<sup>4</sup> and the usefulness of hydrogen-bond enthalpies to compare the strength of bases.<sup>28–31</sup>

## Computational Methods

**Electronic Structure Calculations.** These calculations were performed using the Gaussian 98 package<sup>51</sup> supported on a 300 MHz bi-pentium II personal computer. The hydrogen-

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bond enthalpy  $\Delta H^\circ$  in  $\text{CCl}_4$  is the sum (eq 1) of  $\Delta E_{\text{el}}$ , the change

$$\Delta H^\circ = \Delta E_{\text{el}} + \Delta E_{\text{tr}} + \Delta E_{\text{rot}} + \Delta E_{\text{vib}} + \Delta pV + \Delta H^\circ(\text{soln}) \quad (1)$$

in the electronic energy upon hydrogen bonding;  $\Delta E_{\text{tr}}$ ,  $\Delta E_{\text{rot}}$ , and  $\Delta E_{\text{vib}}$ , the changes in the translational, rotational, and vibrational energies, respectively, which can be calculated in vacuo; and of a solvation term,  $\Delta H^\circ(\text{soln})$ . In this work we have focused on the calculation of  $\Delta E_{\text{el}}$ , which is the term explaining the greatest part of the variance of  $\Delta H^\circ$ .<sup>3</sup> We have treated the amine–water complex as a supermolecule.<sup>3</sup> This method introduces a basis set superposition error (BSSE)<sup>3</sup> that was accounted for by the counterpoise procedure.<sup>52</sup> Fragment relaxation energy terms were also taken into account to estimate BSSE.<sup>53</sup> Geometries were optimized and electronic energies were calculated at the B3LYP/6-311+G(d,p) level of theory.<sup>3</sup> At a similar level, Rablen et al.<sup>54</sup> have reached a reliably accurate description of hydrogen-bonded complexes of small organic molecules with water.

**Statistics of the Enthalpy–Entropy Correlation.** The linear dependence of enthalpy and entropy within a series of related reactions (here, hydrogen bonding of 4-fluorophenol to a series of amines) must not be studied under the form of eq 2, because  $\Delta H^\circ$  and  $\Delta S^\circ$  are loaded with correlated errors when they are obtained from van't Hoff plots (eq 3).

$$\Delta H^\circ = \beta \Delta S^\circ + \text{constant} \quad (2)$$

$$\ln K_c = \frac{-\Delta H_c^\circ}{R} \frac{1}{T} + \frac{\Delta S_c^\circ}{R} \quad (3)$$

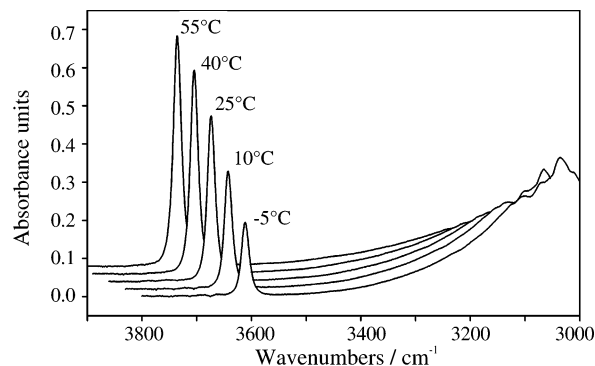
Exner<sup>55</sup> has achieved a statistically correct solution by returning to the original experimental quantities,  $\ln K_c$  and  $T$ . By substituting  $\Delta S^\circ$  from eq 2 into eq 3 one obtains eq 4.

$$\ln K_c = -\frac{\Delta H^\circ}{R}(T^{-1} - \beta^{-1}) + \text{constant} \quad (4)$$

In the coordinates  $\ln K_c$  and  $T^{-1}$ , eq 4 represents a family of straight lines with different slopes ( $-\Delta H^\circ/R$ ) intersecting at one point at  $T = \beta$  (the isoequilibrium temperature). A linear dependence in the coordinates  $\Delta H^\circ$  and  $\Delta S^\circ$  is thus mathematically, but not statistically, strictly equivalent to the constraint of a common point of intersection in the coordinates  $\ln K_c$  and  $T^{-1}$ . Thus, we have used the IKR program<sup>56</sup> written by Ouvrard et al.<sup>57</sup> in order to test several hypotheses: whether the van't Hoff lines are parallel ( $\beta^{-1} \rightarrow \infty$ , isenthalpic reactions), intersect at  $\beta^{-1} = 0$  (isoentropic reactions), intersect at any other  $\beta^{-1}$  value (isoequilibrium relationship), or do not intersect (no valid relationship between  $\Delta H^\circ$  and  $\Delta S^\circ$ ).

## Results

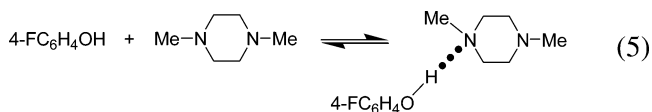
**Determination of Enthalpy and Entropy.** Accurate enthalpy and entropy measurements are done by following the absorbance of a single solution of 4-fluorophenol and amine in  $\text{CCl}_4$  and/or  $\text{C}_2\text{Cl}_4$  as a function of temperature. Our IR method has been fully described else-



**FIGURE 1.** IR determination of the enthalpy and entropy of hydrogen bonding of 4-fluorophenol ( $0.003 \text{ mol L}^{-1}$ ) to  $N,N'$ -dimethylpiperazine ( $0.01 \text{ mol L}^{-1}$ ) in  $\text{CCl}_4$ . The absorbance of the sharp OH band of free 4-fluorophenol at  $3614 \text{ cm}^{-1}$  decreases with decreasing temperature (+55 to  $-5^\circ\text{C}$ ), with a concomitant increase of the broad OH band of the complex at about  $3000 \text{ cm}^{-1}$ .

where.<sup>36,58</sup> It is adapted from the UV method first proposed by Joesten and Drago.<sup>59</sup> An important advantage of IR over UV is that the free 4-fluorophenol signal (at  $3614 \text{ cm}^{-1}$ ) is not overlapped by the hydrogen-bonded 4-fluorophenol absorption (shifted to lower frequencies) nor by the amine NH bands (also at lower frequencies). Thus the equilibrium concentration of free 4-fluorophenol is directly obtained by reading the free OH band absorbance and applying the Beer–Lambert law.

Let us recall important steps of the IR method on the example of the hydrogen bonding between 4-fluorophenol and  $N,N'$ -dimethylpiperazine in  $\text{CCl}_4$ . The formation of an 1:1 hydrogen-bonded complex can be represented by equilibrium 5. Very low concentrations (ca.  $3 \times 10^{-3} \text{ mol}$



$\text{L}^{-1}$ ) of 4-fluorophenol and a 3-fold excess of the diamine are necessary for preventing self-association of 4-fluorophenol and the significant formation of a 2(phenol):1(amine) complex, respectively. The spectra of such a single solution were recorded at five temperatures between  $-5$  and  $+55^\circ\text{C}$  and are shown in Figure 1. The method requires the preliminary determination of the absorption coefficient temperature dependence (eq 6,

$$\epsilon(t) = \epsilon(25) - 0.624(t - 25) \quad (6)$$

temperature  $t/^\circ\text{C}$ ). The absorbance and concentration data, as well as the equilibrium constants  $K_c$  calculation (relative to molar concentrations), at the various temperatures are reported in Table 1. The enthalpy and entropy relative to molar concentrations,  $\Delta H_c^\circ$  and  $\Delta S_c^\circ$ , are obtained from the slope and intercept of the  $\ln K_c$  versus  $1/T$  van't Hoff plot (eq 3) as  $\Delta H_c^\circ = -32.0 \pm 0.3 \text{ kJ mol}^{-1}$  and  $\Delta S_c^\circ = -65.6 \pm 0.8 \text{ J K}^{-1} \text{ mol}^{-1}$  (the

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**TABLE 1.** Determinations of the Enthalpy and Entropy of Hydrogen Bonding of *N,N*-dimethylpiperazine to 4-fluorophenol in CCl<sub>4</sub><sup>a</sup>

temp (°C)	-4.6	9.6	24.9	39.4	54.1
C <sub>a</sub> <sup>0</sup>	3.09	3.04	2.98	2.93	2.88
C <sub>b</sub> <sup>0</sup>	10.38	10.21	10.02	9.85	9.67
absorbance A	0.137	0.220	0.318	0.392	0.446
ε (L mol <sup>-1</sup> cm <sup>-1</sup> )	257.3	248.4	238.9	229.8	220.6
C <sub>a</sub> = A/εl	0.53	0.88	1.33	1.70	2.02
C <sub>c</sub>	2.56	2.16	1.66	1.23	0.86
C <sub>b</sub>	7.82	8.05	8.37	8.61	8.81
K <sub>c</sub> (L mol <sup>-1</sup> )	616.3	302.6	148.7	83.6	48.2
thermodynamic parameters	$\Delta H_c^\circ = -32.0 \pm 0.3 \text{ kJ mol}^{-1}$ ;		$\Delta S_c^\circ = -65.6 \pm 0.8 \text{ J K}^{-1} \text{ mol}^{-1}$		

<sup>a</sup> All concentrations in mmol L<sup>-1</sup>. C<sub>a</sub><sup>0</sup> and C<sub>b</sub><sup>0</sup> are the initial concentrations of the acid 4-fluorophenol and the base *N,N*-dimethylpiperazine, respectively. C<sub>a</sub>, C<sub>c</sub>, and C<sub>b</sub> are the equilibrium concentration of the free 4-fluorophenol, the hydrogen-bonded 4-fluorophenol (complex) and the free base, respectively. The equilibrium constant K<sub>c</sub> is given by  $K_c = C_c/C_a C_b$ . The thermodynamic parameters in the table are the mean of two determinations.

precision of the results is taken from the error limits of the slope and intercept in the regression analysis of squared correlation coefficient  $r^2 = 0.9995$  for  $n = 10$  data, 2 determinations and 5 temperatures). The Gibbs energy, relative to molar concentrations, is obtained from eq 7:

$$\Delta G_{c,298}^\circ = -298.15R \ln K_c(25^\circ\text{C}) = -12.5 \text{ kJ mol}^{-1} \quad (7)$$

It should be noted that this result can be controlled by comparison with the value calculated from  $\text{p}K_{\text{HB}}(\log K_c)$ , obtained in our previous work<sup>60</sup> as the average of five determinations in which the amine concentration was varied in order to complex various quantities of 4-fluorophenol. From  $\text{p}K_{\text{HB}} = 2.18$ <sup>60</sup> we obtain  $\Delta G_{c,298}^\circ = -298.15R \ln 10 \text{p}K_{\text{HB}} = -12.4 \text{ kJ mol}^{-1}$ . The two values match perfectly. A more systematic comparison made on a sample of 75 amines between  $\Delta G^\circ$ , obtained in our previous works<sup>60–62</sup> from “the concentration variation method”, and  $\Delta G^\circ$ , obtained in this work from the “temperature variation method”, shows a strong correlation ( $r = 0.995$ ) between the two sets. Moreover the regression coefficient and the intercept of eq 8, not significantly different from unity and zero, respectively, confirm that the two sets of Gibbs energies match very satisfactorily.

$$\Delta G_c^\circ = 0.994(\pm 0.011) \Delta G_c^{\prime\circ} + 0.18 (\pm 0.26)$$

$$n = 75, r = 0.995, s = 0.25 \text{ kJ mol}^{-1}, \text{ Fisher test} = 7403 \quad (8)$$

From concentration, absorbance, and temperature errors, the maximum relative error in K<sub>c</sub> is estimated<sup>63</sup> to be  $\pm 8\%$ , corresponding to a maximum error of  $\pm 0.25 \text{ kJ mol}^{-1}$  in  $\Delta G^\circ$ . From slope errors and the repetition of measurements we estimate<sup>63</sup> the maximum error in  $\Delta H^\circ$  to be  $\pm 0.9 \text{ kJ mol}^{-1}$ . The propagation of errors in  $\Delta H^\circ$

and  $\Delta G^\circ$  gives the entropies to  $\pm 10\%$ , i.e.,  $\pm 6 \text{ J K}^{-1} \text{ mol}^{-1}$  for the mean value ( $57 \text{ J K}^{-1} \text{ mol}^{-1}$ ) of the studied set.

Only one comparison can be made with literature results. For hydrogen bonding of 4-fluorophenol to cyclopropylamine in CCl<sub>4</sub>, a calorimetric method gives<sup>20</sup>  $\Delta H^\circ = -31.4 \pm 1.2 \text{ kJ mol}^{-1}$ . This value compares very well with our value of  $-31.9 \text{ kJ mol}^{-1}$  obtained by a van't Hoff method with an estimated error of  $\pm 0.9 \text{ kJ mol}^{-1}$ .

Table 2 presents 81 values of Gibbs energies,  $\Delta G_{x,298}^\circ$ , enthalpies,  $\Delta H^\circ$ , and entropies,  $\Delta S_{x,298}^\circ$ , for the hydrogen bonding of 4-fluorophenol to 69 amines in CCl<sub>4</sub> and/or C<sub>2</sub>Cl<sub>4</sub>. Results of measurements in C<sub>2</sub>Cl<sub>4</sub> are reported in parentheses. Data are sorted in four subseries: ammonia, primary, secondary and tertiary amines. Amines in each subseries are arranged in order of decreasing  $-\Delta H^\circ$ .

The enthalpies, entropies, and Gibbs energies of eqs 3 and 7 were first calculated on the molar concentration scale, since the K<sub>c</sub> unit is L mol<sup>-1</sup>. However Hepler<sup>64</sup> has shown that the  $\Delta H_c^\circ$  value relative to molarity is not the correct “standard-state infinite dilution”  $\Delta H^\circ$ . The thermodynamically correct value must be calculated from K<sub>x</sub> relative to mole fraction, which is related to K<sub>c</sub> by eq 9

$$K_x = K_c \bar{n} \quad (9)$$

for dilute solutions. The number of moles of solvent per liter,  $\bar{n}$ , are 10.3 for CCl<sub>4</sub> and 9.74 for C<sub>2</sub>Cl<sub>4</sub>.  $\Delta H^\circ$  is then related<sup>64</sup> to  $\Delta H_c^\circ$  by eq 10, where  $\alpha$  is the coefficient of

$$\Delta H^\circ = \Delta H_c^\circ - \alpha RT^2 \quad (10)$$

thermal expansion of the solvent. For CCl<sub>4</sub> and C<sub>2</sub>Cl<sub>4</sub> at 298 K the corrections amount to 0.9 and 0.8 kJ mol<sup>-1</sup> respectively. K<sub>x</sub> values lead to standard Gibbs energies  $\Delta G_x^\circ = -RT \ln K_x$  and entropies  $\Delta S_x^\circ = (\Delta H^\circ - \Delta G_x^\circ)/T$  that differ from  $\Delta G_c^\circ$  and  $\Delta S_c^\circ$  by  $-5.8 \text{ kJ mol}^{-1}$  and  $+16.4 \text{ J K}^{-1} \text{ mol}^{-1}$ , respectively, in CCl<sub>4</sub> at 298 K and by  $-5.6 \text{ kJ mol}^{-1}$  and  $+16.4 \text{ J K}^{-1} \text{ mol}^{-1}$ , respectively, in C<sub>2</sub>Cl<sub>4</sub> at 298 K.

If one wants to compare  $\Delta G^\circ$  and  $\Delta S^\circ$  of diamines **17**, **29**, **41**, **42**, **54**, and **56** and tetramine **68** to those of monoamines, statistical corrections  $-RT \ln n$  and  $-R \ln n$  ( $n$  being the number of equivalent nitrogen atoms) must

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**TABLE 2.** Thermodynamic Functions  $\Delta G$ ,  $\Delta H$  ( $\text{kJ mol}^{-1}$ ), and  $\Delta S$  ( $\text{J K}^{-1} \text{mol}^{-1}$ ) and IR Shifts  $\Delta\nu(\text{OH})$  ( $\text{cm}^{-1}$ ) for Hydrogen Bonding of Aliphatic Amines to 4-Fluorophenol in  $\text{CCl}_4$  and in  $\text{C}_2\text{Cl}_4$ ; Belonging to the Isoentropic Set Is Precised

		$-\Delta H^\circ$		$-\Delta S_{x,298}^\circ$		$-\Delta G_{x,298}^\circ$		$\Delta\nu(\text{OH})^a$ CCl <sub>4</sub>	isoentropic set
		CCl <sub>4</sub>	C <sub>2</sub> Cl <sub>4</sub>	CCl <sub>4</sub>	C <sub>2</sub> Cl <sub>4</sub>	CCl <sub>4</sub>	C <sub>2</sub> Cl <sub>4</sub>		
1	ammonia	31.49		53.1		15.65		276	yes
Primary Amines									
2	methylamine		35.10		56.8		18.20	356	(yes)
3	cyclohexylamine	34.26		51.1		19.03		359	yes
4	<i>t</i> -butylamine	34.20		52.7		18.49		359	yes
5	ethylamine		33.84		51.0		18.63	349	yes
6	<i>n</i> -butylamine	33.70		52.2		18.14		354	yes
7	benzylamine	32.35	31.06	54.1	49.2	16.23	16.38	324	yes (no)
8	cyclopropylamine	31.88		54.9		15.50		310	yes
9	propargylamine	28.18	30.63	45.8	53.1	14.53	14.77	284	no (yes)
10	2,2,2-trifluoroethylamine	26.88	26.10	56.9	53.9	9.92	10.00	244	yes (yes)
Secondary Amines									
11	2,2,6,6-tetramethylpiperidine	37.23		70.3		16.26		422	no
12	pyrrolidine		36.09		53.1		20.26		(yes)
13	piperidine	34.80	35.80	51.7	55.0	19.38	19.40	404	yes (yes)
14	diisopropylamine	35.97		62.9		17.21		396	no
15	diethylamine	35.74		57.7		18.53		398	yes
16	azetidine	35.67		51.0		20.48		402	yes
17	<i>N,N'</i> -dimethylethylenediamine	35.63		55.8		18.99		407	yes
18	di- <i>n</i> -butylamine	35.56		59.3		17.87		401	yes
19	<i>N</i> -methylbutylamine	35.38		56.2		18.62		395	yes
20	<i>N</i> -methylcyclohexylamine	35.21		55.7		18.60		402	yes
21	dimethylamine		35.13		56.2		18.37		(yes)
22	<i>N</i> -methyltertiobutylamine	35.09		56.1		18.36		406	yes
23	hexamethylenimine	35.08		55.0		18.69		400	yes
24	<i>N</i> -methylisopropylamine	35.01		55.6		18.43		395	yes
25	<i>N</i> -methylphenethylamine	34.92		57.4		17.82		394	yes
26	<i>N</i> -methylethylamine	34.69		53.7		18.67		394	yes
27	<i>N</i> -methylallylamine	34.07		55.9		17.41		374	yes
28	<i>N</i> -methylbenzylamine		33.54		58.4		16.12		(yes)
29	piperazine	33.32	35.03	52.0	55.9	17.82	18.38	386	yes (yes)
30	2-phenylpyrrolidine	33.27		55.2		16.82		381	yes
31	tetrahydroisoquinoline		33.10		52.2		17.54		(yes)
32	diallylamine	32.80		58.3		15.42		356	yes
33	2-(3-fluorophenyl)-pyrrolidine	31.09		53.1		15.26		361	yes
34	<i>N</i> -methylpropargylamine	31.01	29.90	53.0	49.0	15.21	15.30	336	yes (no)
35	2-(3-trifluoromethylphenyl)-pyrrolidine	30.47		56.2		13.72		348	yes
36	dichloroethylamine	30.23		59.0		12.65		330	yes
Tertiary Amines									
37	triethylamine	39.35	39.01	76.4	73.9	16.57	17.00	429	no (no)
38	tri- <i>n</i> -butylamine	38.40		80.5		14.41		430	no
39	quinuclidine	37.68	38.06	55.8	55.4	21.05	21.53	444	yes (yes)
40	tropane	35.66		55.3		19.18		446	yes
41	<i>N,N,N',N'</i> -tetramethylethylenediamine		35.49		60.6		17.43		no
42	<i>N,N,N',N'</i> -tetramethylhexane-1,6-diamine	35.15		59.0		17.57		415	yes
43	<i>N</i> -methylpyrrolidine		34.79		54.8		18.46		(yes)
44	<i>N,N</i> -dimethylcyclohexylamine	34.75		56.1		18.03		433	yes
45	<i>N,N</i> -dimethylisopropylamine	34.67		55.9		18.00		425	yes
46	<i>N</i> -butylpyrrolidine	34.53		57.3		17.43		426	yes
47	<i>N,N</i> -dimethylethylamine	34.47		54.6		18.19		418	yes
48	3-chloroquinuclidine	34.11		57.6		16.94		394	yes
49	<i>N</i> -methylpiperidine	34.04		54.4		17.81		421	yes
50	1,2,2,6,6-pentamethylpiperidine	34.03		70.8		12.91		419	no
51	<i>N,N</i> -diisopropylethylamine	33.89		74.0		11.81		414	no
52	<i>N</i> -ethylcyclohexylamine	33.60		71.4		12.31		419	no
53	trimethylamine	33.48		52.4		17.84		409	yes
54	diazabicyclooctane	33.20	35.12	47.9	52.4	18.92	19.49	417	no (yes)
55	<i>N,N</i> -dimethylbenzylamine	33.13	31.33	61.4	55.3	14.83	14.84	387	no (yes)
56	<i>N,N'</i> dimethylpiperazine	32.93		55.1		16.52		402	yes
57	3-chloromethyl-1-methylpiperidine	32.87		57.2		15.82		401	yes
58	<i>N,N</i> -dimethylallylamine	32.84		53.8		16.81		399	yes
59	<i>N</i> -methyl-2-phenylpyrrolidine	32.79		64.0		13.70		386	no
60	triallylamine	32.58		65.0		13.19		375	no
61	<i>N,N</i> -dimethylamino-propyl chloride	32.45		59.8		14.61		397	no
62	4-chloro- <i>N</i> -methylpiperidine	32.18		56.1		15.47		400	yes
63	<i>N</i> -methyl-2-(3-fluorophenyl)-pyrrolidine	31.01		63.8		12.01		372	no
64	<i>N</i> -methyl-1,2,3,4-tetrahydro-isoquinoline	30.83		49.7		16.01		383	no
65	<i>N,N</i> -dimethylpropargylamine	29.27	30.29	48.7	51.4	14.75	14.97	367	no (yes)

Table 2. (Continued)

		$-\Delta H^\circ$		$-\Delta S_{x,298}^\circ$		$-\Delta G_{x,298}^\circ$		$\Delta\nu(\text{OH})^a$ CCl <sub>4</sub>	isoentropic set
		CCl <sub>4</sub>	C <sub>2</sub> Cl <sub>4</sub>	CCl <sub>4</sub>	C <sub>2</sub> Cl <sub>4</sub>	CCl <sub>4</sub>	C <sub>2</sub> Cl <sub>4</sub>		
Tertiary Amines (Continued)									
66	<i>N</i> -methyl-2-(3-trifluoromethylphenyl)-pyrrolidine	29.26		60.6		11.18		368	no
67	<i>N,N</i> -diisopropylisobutylamine	27.15		65.8		7.51		392	no
68	hexamethylenetetramine	26.15	28.03	43.2	48.7	13.25	13.50	335	no (no)
69	<i>N,N</i> -diisopropyl-3-pentylamine	23.83		67.1		3.82			no

<sup>a</sup> IR shifts from this work for NH<sub>3</sub> and primary amines, ref 62 for secondary amines, and ref 60 for tertiary amines.

be applied to the Gibbs energy and the entropy respectively, to put these thermodynamic functions on a per nitrogen basis.

**Determination of OH Frequency Shift.** The OH stretching band of methanol at 3644 cm<sup>-1</sup> is shifted to lower wavenumbers upon hydrogen bonding to amines in CCl<sub>4</sub>. The IR shifts,  $\Delta\nu(\text{OH})$ , are given in Table 2. More reliable shifts are obtained with methanol as standard hydrogen-bond donor than with 4-fluorophenol.<sup>60</sup> Values of secondary and tertiary amines are those measured in previous works.<sup>60,62</sup> Values of NH<sub>3</sub> and primary amines have been measured for this work.

## Discussion

**Quantum-Mechanical Prediction of Hydrogen Bonding Enthalpies.** The case of amines with a second hydrogen-bond acceptor site X is very common in chemistry and biochemistry. These amines form two different 1:1 complexes with equilibrium constants  $K(\text{N})$  and  $K(\text{X})$  (insofar as an amine excess prevents the formation of a 2:1 complex). The experimental method gives the equilibrium concentration of hydrogen-bonded 4-fluorophenol, i.e., the sum of the concentration of the two 1:1 complexes. Therefore, the measured equilibrium constant is the sum of the individual constants,  $K(\text{N}) + K(\text{X})$ . As the derivative with respect to temperature,  $d\{\ln[K(\text{N}) + K(\text{X})]\}/dT$ , has no thermodynamic meaning, we cannot determine experimentally the individual enthalpies,  $\Delta H(\text{N})$  and  $\Delta H(\text{X})$ . Theoretically, a reliable absolute calculation of the hydrogen-bond enthalpy of 4-fluorophenol with a large and flexible molecule, in CCl<sub>4</sub> at 298 K, would be a very costly and time-consuming process.<sup>65</sup> We therefore sought an alternative method to predict  $\Delta H(\text{N})$  values using the techniques of quantum chemistry, with the ultimate aim of estimating  $\Delta H(\text{N})$  for any molecule purely from its structure.

In their theoretical study of hydrogen-bonded complexes of small organic molecules with water, Rablen et al.<sup>54</sup> found that their in vacuo calculated hydrogen bond energies were satisfactorily correlated with the experimental CCl<sub>4</sub> solution hydrogen-bond basicity parameter  $\beta_2^{\text{H}}$ .<sup>35</sup> This parameter is a linear transformation of the Gibbs energy of 4-fluorophenol hydrogen-bonded complexes.<sup>35</sup> We therefore investigated if a relationship might be found between (i) the experimental enthalpies of 4-fluorophenol-amine complexes in CCl<sub>4</sub> and (ii) the calculated electronic energy change (corrected for BSSE) for the hydrogen bonding of water with amines in vacuo. For doing this, we have selected 11 low-computationally

TABLE 3. Change in Electronic Energy (kJ mol<sup>-1</sup>) upon Hydrogen Bonding of Water to Amines in Vacuo: H<sub>2</sub>O + NRR'R'' = HOH...NRR'R''

no.	amine	$-\Delta E_{\text{el}}^a$
10	trifluoroethylamine	23.03
8	cyclopropylamine	26.44
9	propargylamine	26.45
53	trimethylamine	26.93
1	ammonia	27.39
21	dimethylamine	28.51
2	methylamine	28.90
40	tropine	27.64
13	piperidine	28.56
11	pyrrolidine	29.43
39	quinuclidine	29.69

<sup>a</sup> Corrected for BSSE.

demanding amines spanning a (rather) wide enthalpic range of 11 kJ mol<sup>-1</sup>. The results of our B3LYP/6-311+G(d,p)//B3LYP/6-311+G(d,p) calculations are presented in Table 3.

We find a good correlation (eq 11) between  $\Delta H_{298}^\circ$  and  $-\Delta H_{298}^\circ(4\text{-FC}_6\text{H}_4\text{OH, amines, CCl}_4) = 1.54[-\Delta E_{\text{el}}(\text{H}_2\text{O, amines, in vacuo})] - 8.97$

$$n = 11, r = 0.941, s = 1.09 \text{ kJ mol}^{-1}, F = 70 \quad (11)$$

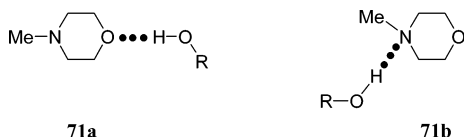
$\Delta E_{\text{el}}$  since 92% (squared  $r$ ) of the variance of  $\Delta H_{298}^\circ$  is explained by  $\Delta E_{\text{el}}$ . The greater than unity slope can be explained by the greater hydrogen-bond donor strength of 4-fluorophenol compared to that of water,<sup>35</sup> while the nonzero intercept comes from the neglect of nuclear motions and solvation.

We may wonder if the agreement would be improved by taking account of solvation effects. However, the disregard of solvation effects has already been justified since (i) PCM (polarizable continuum model) calculations

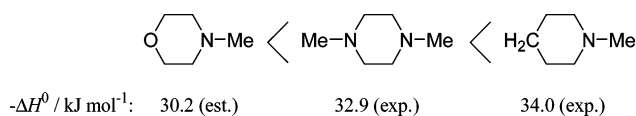
(65) We have tried an absolute calculation in vacuo of the enthalpy of the 4-fluorophenol-cyclopropylamine complex. The CPU time on Opteron 2.4 GHz or Pentium 2.2 GHz processors is the following: B3LYP/6-31+G(d,p) geometry optimization of monomers and four putative dimers, ca. 100 h; B3LYP/6-31+G(d,p) frequency calculations, ca. 12 h; MP2/6-311+G(3df,2p) electronic energy calculations of monomers and the most stable dimer, ca. 9 h; BSSE calculation, ca. 18 h. The MP2/6-311+G(3df,2p)//B3LYP/6-31+G(d,p) result is  $\Delta H^\circ = -36.32 \text{ kJ mol}^{-1}$ . This compares well with the experimental value of  $-31.88 \text{ kJ mol}^{-1}$ , if one attributes the difference of 4.44 kJ mol<sup>-1</sup> to the solvation enthalpy (for comparison the experimental CCl<sub>4</sub> solvation enthalpy of the methanol-triethylamine complex is +6.7 kJ mol<sup>-1</sup>; Hirano, E.; Kojima, K. *Bull. Chem. Soc. Jpn.* **1966**, *39*, 1216–1220). Thus, a CPU time of ca. 6 days is required to reach a chemically significant result in vacuo for a small complex (12 heavy atoms). Therefore, a reliable absolute calculation on a significant sample of larger and more flexible amines in the presence of solvent seems unlikely to be achieved today in our laboratory. Consequently, we have turned to the calculation of a simple quantum-mechanical descriptor of enthalpy (vide infra).

do not improve the agreement between the hydrogen-bond energies of 4-fluorophenol complexes in  $\text{CCl}_4$  solution and HF complexes in vacuo,<sup>66</sup> and (ii) it was observed that the relative strength of hydrogen-bond acceptors does not change on going from the gas phase to a nonpolar solution.<sup>54,67,68</sup>

The enthalpy of hydrogen bonding of 4-fluorophenol to amines in  $\text{CCl}_4$  can then be estimated, through eq 11, from the change in the electronic energy of the reaction  $\text{H}_2\text{O} + \text{NRR}'\text{R}'' \rightleftharpoons \text{HOH}\cdots\text{NRR}'\text{R}''$ , calculated in vacuo. Let us illustrate the method in the case of *N*-methylmorpholine **71**. *N*-Methylmorpholine forms simultaneously two 1:1 complexes,  $\text{OH}\cdots\text{O}$  **71a** and  $\text{OH}\cdots\text{N}$  **71b**, with

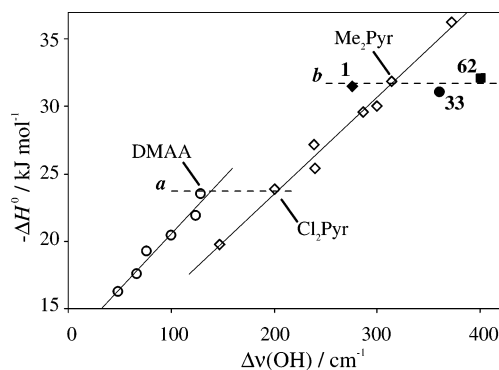


OH donors, and there is no simple experimental method for measuring the hydrogen-bond enthalpy of each site (vide supra). The calculation of  $\Delta E_{\text{el}}$  corresponding to the formation of **71b** ( $\text{R} = \text{H}$ ) makes it possible to estimate  $\Delta H^\circ$  for the formation of **71b** ( $\text{R} = \text{C}_6\text{H}_4\text{F}$ ). We find  $\Delta E_{\text{el}} = -25.14 \text{ kJ mol}^{-1}$  and, from eq 11,  $\Delta H^\circ = -30.2 \text{ kJ mol}^{-1}$ . This estimated value agrees well with the experimental values of *N,N'*-dimethylpiperazine and *N*-methylpiperidine: the basicity (minus the enthalpy) decreases when the electronegativity of the  $\gamma$  ring atom increases from carbon to nitrogen to oxygen:



**Prediction of Hydrogen Bonding Enthalpies from OH IR Shifts.** Since the Badger and Bauer observation<sup>6,7</sup> that the change in OH stretching frequency correlates with self-association energies of alcohols or energies of intramolecular hydrogen bonds, there has been a continuing controversy<sup>5,8-27</sup> concerning how well the spectral change reflects the interaction magnitude. Actually, there is a tremendous advantage to be gained if reliable spectroscopic indications of the strength of interaction can be found. Instead of the day(s) required for a van't Hoff measurement, the answer could be found in the time required to run a spectrum. Moreover many systems that do not possess the physical properties needed for a van't Hoff study could be investigated this way. Such is the very common case of hydrogen-bond acceptors with several sites (vide supra).

It seems now accepted<sup>5,11,12,36,37</sup> that the validity of the relationship between  $\Delta H^\circ$  and  $\Delta\nu(\text{OH})$  is limited to series of similar donor groups hydrogen-bonded to bases with common acceptor atoms, i.e., the Badger–Bauer relationship is family-dependent. But how must a family be exactly defined in the Badger–Bauer context?



**FIGURE 2.**  $\Delta H^\circ$  versus  $\Delta\nu(\text{OH})$  plot for the hydrogen bonding of OH donors with (○) nitriles (DMAA is *trans*-dimethylaminoacrylonitrile), (◇) pyridines ( $\text{Cl}_2\text{pyr}$  and  $\text{Me}_2\text{pyr}$  are 3,5-dichloro- and 3,5-dimethylpyridines respectively), (◆) ammonia, (●) secondary amine **33**, and (■) tertiary amine **62**. Data are from Table 2, ref 54, and unpublished works.

If one tries to define a family as a series of compounds with a common hydrogen-bond acceptor atomic site, e.g., the nitrogen atom of nitriles, pyridines, and amines, one observes in Figure 2 that nitriles and pyridines draw two different lines. In fact *trans*-dimethylaminoacrylonitrile and 3,5-dichloropyridine have nearly the same enthalpy (dashed line *a* in Figure 2), but the frequency shift is 55% higher in the pyridine. Also  $\text{NH}_3$ , 3,5-dimethylpyridine, a secondary amine **33**, and a tertiary amine **62** have very close enthalpies (dashed line *b* in Figure 2) but quite different frequency shifts.

If we limit a family to those hydrogen-bond acceptors with a common atomic site in the same hybridization state, this definition holds for nitriles (sp nitrogen) and pyridines (sp<sup>2</sup> nitrogen) as shown in Figure 2 but not for amines (sp<sup>3</sup> nitrogen). For 80 amines the correlation coefficient is only 0.745, i.e., only 55% of the variance of  $\Delta H^\circ$  is explained by  $\Delta\nu(\text{OH})$ .

A careful analysis of amines shows that primary, secondary, and tertiary amines draw three different lines in the Badger–Bauer graph as shown by eqs 12–14

$$-\Delta H^\circ(\text{NH}_2\text{R}) = 6.8(\pm 0.5)[\Delta\nu(\text{OH})/100] + 10(\pm 2)$$

$$n = 12; r = 0.970; s = 0.77 \text{ kJ mol}^{-1}; F = 158 \quad (12)$$

$$-\Delta H^\circ(\text{NHRR}') = 7.6(\pm 0.5)[\Delta\nu(\text{OH})/100] + 5(\pm 2)$$

$$n = 29; r = 0.944; s = 0.65 \text{ kJ mol}^{-1}; F = 223 \quad (13)$$

$$-\Delta H^\circ(\text{NRR}'\text{R}'') = 9.5(\pm 0.9)[\Delta\nu(\text{OH})/100] - 5(\pm 4)$$

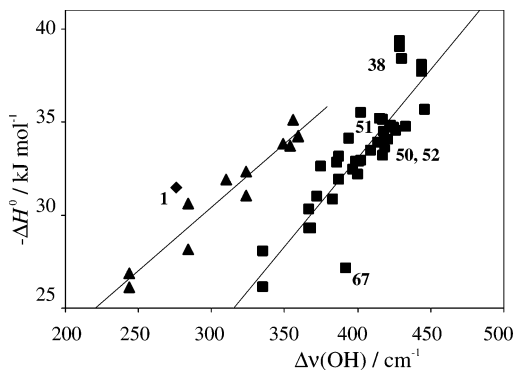
$$n = 38; r = 0.859; s = 1.6 \text{ kJ mol}^{-1}; F = 102 \quad (14)$$

and Figure 3 (for the sake of clarity secondary amines are not shown). Ammonia does not obey the eq 12 of primary amines (standing 3  $\text{kJ mol}^{-1}$  above the line) and constitutes a family per se. For primary and secondary amines the quality of correlations 12 and 13 is enough to make a good estimation of  $\Delta H^\circ$ , since the standard errors of the estimate, 0.67 and 0.64  $\text{kJ mol}^{-1}$ , are within the experimental error (0.9  $\text{kJ mol}^{-1}$ ). Such is not the case of tertiary amines for which *s* reaches almost twice the experimental error. We find the greatest deviation for the severely hindered tertiary amine *i*-BuN-*i*-Pr<sub>2</sub> **67**,

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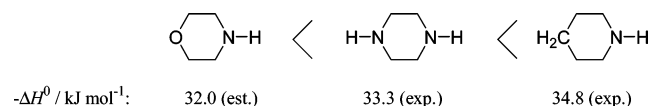


**FIGURE 3.**  $\Delta H^\circ$  versus  $\Delta\nu(\text{OH})$  plot for the hydrogen bonding of OH donors with (◆) ammonia, (▲) primary amines, and (■) tertiary amines. Hindered tertiary amines are located below (67), on (50–52) or above (38) the regression line.

which stands  $4.5 \text{ kJ mol}^{-1}$  below the line of eq 14. However, the influence of steric effects on the validity of the Badger–Bauer relationship does not appear clear-cut since, among the tertiary amines designed as hindered in our previous work,<sup>60</sup> some are found above (*n*-Bu<sub>3</sub>N **38**), on (EtN-*i*-Pr<sub>2</sub> **51**, EtN-*c*-Hex<sub>2</sub> **52** and 2,2,6,6-tetramethylpiperidine **50**), or below (*i*-BuN-*i*-Pr<sub>2</sub> **67**) the regression line. A better criterion appears to be a certain rigidity of the molecule since all bicyclic and most cyclic tertiary amines satisfactorily obey eq 14 (mean absolute deviation =  $0.7 \text{ kJ mol}^{-1}$ ).

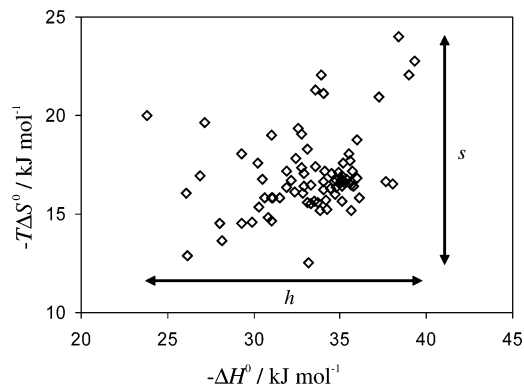
In summary, a necessary condition of validity of the Badger–Bauer relationships is the existence of a common atomic site in a common state of hybridization. This condition is not sufficient for  $sp^3$  hybridized nitrogen bases, for which ammonia and primary, secondary, and tertiary amines form four distinct families. Some rigidity of the molecular skeleton around nitrogen appears to be a last criterion in order that tertiary amines follow the Badger–Bauer relationship.

The usefulness of the Badger–Bauer relationship can be illustrated by the example of morpholine, a secondary amine for which no enthalpy can be measured owing to the presence of oxygen, a second hydrogen-bond acceptor site. From the  $\nu(\text{OH}\cdots\text{N})$  band in the IR spectrum of the complex with methanol, we get  $\Delta\nu(\text{OH}) = 360 \text{ cm}^{-1}$  and, from eq 13,  $\Delta H^\circ = -32.0 \text{ kJ mol}^{-1}$ , a value that agrees with those of piperazine and piperidine (vide supra):



**Relation between  $\Delta H^\circ$  and  $\Delta S^\circ$ .** The  $\Delta H^\circ$  and  $\Delta S^\circ$  of Table 2 have been calculated from a set of 688 equilibrium constants  $K_c$ . The statistical analysis, with the IKR program,<sup>56,57</sup> of the relationship between  $\Delta H^\circ$  and  $\Delta S^\circ$  in the  $(\ln K_c, T^{-1})$  coordinates shows, for all 688 data points, that the hydrogen bonding of 4-fluorophenol to amines in  $\text{CCl}_4$  ( $\text{C}_2\text{Cl}_4$ ) (i) is not isoenthalpic, (ii) is not isoentropic, and (iii) does not follow a compensation law (eq 2).

These statistical conclusions are trivial since they can be deduced from a direct examination of a plot of  $-\Delta H^\circ$  versus  $-T\Delta S^\circ$ . It is seen in Figure 4 that the compensation law suggested by Pimentel and McClellan (“a higher



**FIGURE 4.**  $T\Delta S^\circ$  versus  $\Delta H^\circ$  plot;  $h$  and  $s$  are the range of  $\Delta H^\circ$  and  $T\Delta S^\circ$  values, respectively.

value of  $-\Delta H$  implies stronger bonding, with a more restricted configuration in the complex, hence a greater order, leading to a larger value of  $-\Delta S^\circ$ ) is not valid. Also, the reaction is clearly neither isoenthalpic nor isoentropic since the ranges  $h$  and  $s$  of enthalpy and entropy variation (Figure 4) amount, respectively, to ca. 20 and 5 times the experimental errors in  $\Delta H^\circ$  and  $\Delta S^\circ$ . If we refer to the lead compound  $\text{NH}_3$  **1**, alkylation increases  $-\Delta H^\circ$  by  $7.9 \text{ kJ mol}^{-1}$  in the case of three ethyl substituents on nitrogen (Et<sub>3</sub>N **37**) and decreases  $-\Delta H^\circ$  by  $7.7 \text{ kJ mol}^{-1}$  in the case of two isopropyl and a 3-pentyl substituents (*i*-Pr<sub>2</sub>NCH(Et)<sub>2</sub> **69**). This double mechanism of alkyl substituents has been carefully studied in our previous work<sup>37,60,62</sup> and explained by the polarizability effect (basicity-enhancing) and the steric effect (basicity-decreasing). The balance of these effects gives to Et<sub>3</sub>N, an archetype amine, the strongest enthalpy of our set.

The enthalpy–entropy relationship is better understood if we split the sample of 69 amines into three sets. The first set is an isoentropic one. It is constructed starting from the lead compound,  $\text{NH}_3$ , which has  $\Delta S^\circ = -53.1 \text{ J K}^{-1} \text{ mol}^{-1}$ . There are 42 amines having entropies equal to that of  $\text{NH}_3$  plus or minus an arbitrary starting range of  $3 \text{ J K}^{-1} \text{ mol}^{-1}$ , i.e., between  $-50.1$  and  $-56.1 \text{ J K}^{-1} \text{ mol}^{-1}$ . With the help of the IKR program and the included statistical tests,<sup>56,57</sup> we can enlarge this isoentropic set step by step toward higher and lower entropies. At the 95% confidence level we find that 53 amines form an isoentropic set with a mean value of  $-55.1 \text{ J K}^{-1} \text{ mol}^{-1}$  and a tolerance supported by statistics of ca.  $\pm 4.2 \text{ J K}^{-1} \text{ mol}^{-1}$ , not so far from the experimental error. The belonging or not of each of 69 amines to the isoentropic set is given in Table 2. It is seen that the so-defined isoentropic set includes ammonia, 9 primary amines (75%), and 25 secondary amines (86%) but only 19 tertiary amines (50%).

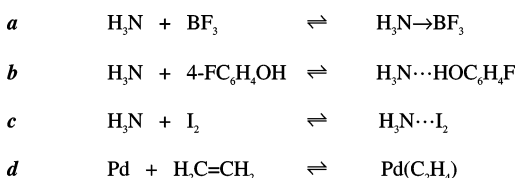
The second set contains 17 amines excluded from the isoentropic set because of a too-high entropy value. It consists mainly of tertiary amines such as *n*-Bu<sub>3</sub>N **38**, 1,2,2,6,6-pentamethylpiperidine **50**, *i*-Pr<sub>2</sub>NEt **51**, *c*-Hex<sub>2</sub>-NEt **52**, *i*-Pr<sub>2</sub>N-*i*-Bu **67**, and *i*-Pr<sub>2</sub>NCH(Et)<sub>2</sub> **69** and of a few secondary amines such as 2,2,6,6-tetramethylpiperidine **11** and *i*-Pr<sub>2</sub>NH **14**. In these amines the nitrogen is hindered by long and/or branched alkyl chains. Clearly the increase of entropy beyond the mean isoentropic value is caused by the steric effect of alkyl groups. The restricted access of the OH group to the nitrogen lone



pair leads to a greater order of the complex and to a larger value of the entropy.

The third set corresponds to nine amines having a too-low entropy value compared to the mean isoentropic value. No clear structural reasons are found to explain these weak values. We only remark that most of these amines show significant differences between  $\text{CCl}_4$  and  $\text{C}_2\text{-Cl}_4$ . Six of these nine amines have been studied in both solvents, and only one, hexamethylenetetramine **68**, keeps both entropy values too weak to join the isoentropic set.

**Hydrogen Bond Enthalpies as Lewis Basicity Parameters.** It is well-known that the electronic Lewis definition of bases as electron pair acceptors is more general than the protonic Brønsted definition.<sup>28</sup> In return it becomes more difficult to achieve the building of a quantitative scale of Lewis basicity that would be as general as the  $GB^{69}$  or  $pK_a^{70}$  scales of proton basicity. This comes from the fact that, in the Lewis definition, there is no Lewis acid that can be naturally chosen and exploited as a reference, in the same manner as the proton. In fact, there are so many kinds of chemical bonds (e.g., dative bond **a**,<sup>71</sup> hydrogen bond **b**,<sup>1</sup> halogen bond **c**,<sup>72</sup> or back-bonding **d**<sup>71</sup>) that can be formed during the



creation of a Lewis acid–base complex, that attempts to choose one reference Lewis acid, such as  $\text{SbCl}_5^{29}$  or  $\text{BF}_3^{31}$  in order to construct a quantitative scale of Lewis basicity have given scales of limited validity only. Further work has shown that at least two parameters are necessary<sup>73</sup> for measuring the strength of Lewis bases and various double parameter empirical scales have been proposed.<sup>30,73,74</sup> Valence-bond,<sup>75</sup> molecular orbital,<sup>76</sup> and density functional theories<sup>77</sup> have supported the quantification of Lewis base strength from two theoretical descriptors.<sup>75–77</sup>

Among reactions **a–d**, the interaction **b** between the hydrogen-bond acceptor  $\text{NH}_3$  and the hydrogen-bond donor 4-fluorophenol points hydrogen-bond donors  $\text{XH}$  to a particular class of Lewis acids. In a hydrogen bond there is a (small) charge transfer from the base to the antibonding  $\sigma^*(\text{XH})$  orbital,<sup>3</sup> so the formation of a hydrogen bond constitutes a Lewis acid–base reaction in

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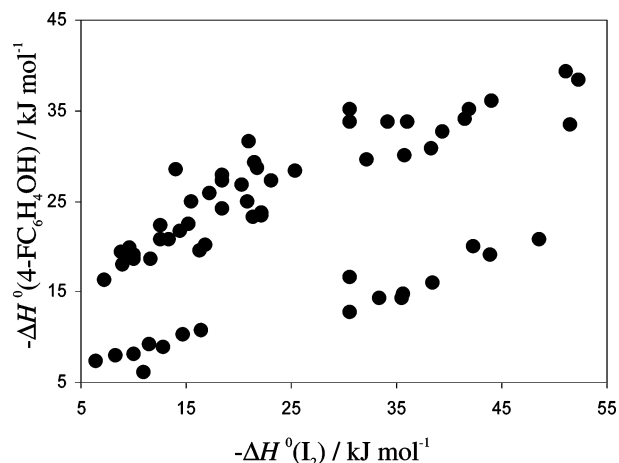
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**FIGURE 5.** Plot of the enthalpy of hydrogen bonding of 4-fluorophenol with Lewis bases,  $\Delta H^\circ(4\text{-FC}_6\text{H}_4\text{OH})$ , versus the enthalpy of complexation of diiodine,  $\Delta H^\circ(\text{I}_2)$ , to the same bases. The two enthalpic scales appear quasi-orthogonal ( $n = 62$ ,  $r^2 = 0.32$ ).

which the electron acceptor and donor are the hydrogen-bond donor and acceptor, respectively. This raises the question whether the hydrogen-bond enthalpies can be useful as a Lewis basicity parameter.

In the language of frontier molecular orbitals, we need to find a charge-controlled<sup>76</sup> and a frontier-controlled<sup>76</sup> term (or electrostatic and covalent terms in the language of other models<sup>30,73</sup>) in order to quantify the strength of intermolecular bonds. Since the hydrogen bond is mainly electrostatic in character,<sup>3</sup> the charge-controlled (electrostatic) term might be furnished by the hydrogen-bond enthalpy of the kind measured in this work. An experimental substitute for the frontier-controlled (covalent) term is more difficult to find. We have previously shown<sup>78</sup> that the enthalpy of diiodine complexation (reaction **c**) measures a kind of basicity quite different from the hydrogen-bond basicity. There is indeed a greater amount of charge transferred from the base to dihalogens than to hydrogen-bond donors.<sup>79</sup>

The two enthalpic scales,  $\Delta H^\circ(\text{I}_2 \text{ complexation})$  and  $\Delta H^\circ(4\text{-FC}_6\text{H}_4\text{OH complexation})$  are under construction in our laboratory. Here, we want only to show that the two scales encode quite different information on the strength of bases. We have selected 62 bases for which both enthalpies of complexation are available (this and previous works).<sup>37,78,80</sup> This selection covers a wide range of enthalpies both for diiodine (45.9 kJ mol<sup>-1</sup> from benzene to *n*-Bu<sub>3</sub>N) and 4-fluorophenol (33.3 kJ mol<sup>-1</sup> from thiophene to Et<sub>3</sub>N). There is also a great variety of complexation sites ( $\pi$ , O, CO, PO, SO, NO, Nsp, Nsp<sup>2</sup>, Nsp<sup>3</sup>, S, CS, PS, and PSe). We find that the correlation coefficient between  $\Delta H^\circ(\text{I}_2 \text{ complexation})$  and  $\Delta H^\circ(4\text{-FC}_6\text{H}_4\text{OH complexation})$  is only 0.569, i.e., only 32% of the variance of one scale is explained by the other (Figure 5).

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In summary, the enthalpic scale of hydrogen-bond basicity will be useful for the measurement of the electrostatic character of Lewis acid–base reactions. Further experimental work is in progress in our laboratory for extending this scale to a large variety of Lewis bases.

## Conclusions

We have constructed an extensive and reliable scale of hydrogen-bond enthalpies for ammonia, primary, secondary, and tertiary amines. This scale is useful *per se* since hydrogen bonding interactions constitute an important class of acid–base reactions and the most characteristic chemical property of amines is their ability to act as bases.<sup>81</sup>

Hydrogen-bond enthalpies are correlated to electronic interaction energies and, through family-dependent relationships, to infrared frequency shifts. These correlations are useful for extending our primary enthalpic scale to amines bearing more than one hydrogen-bond acceptor site. This situation is frequently encountered in chemistry, biochemistry, and pharmaceutical chemistry since the amine function is widely present in the structure of neurotransmitters, drugs, medicines, and alkaloids. We have recently shown<sup>58</sup> that the determination of the hydrogen bond affinity of each site of the alkaloids nicotine and nornicotine is useful for understanding their lipophilicity and molecular recognition and the thermodynamics of the nicotinic pharmacophore.

Enthalpies and Gibbs energies give the same order of hydrogen-bond basicity of amines for 65% of the reactions

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studied, because these reactions show an isoentropic tendency. Amines excluded from the isoentropic set are, mainly, severely sterically hindered ones. The separation of enthalpy and entropy is thus useful for fully understanding the hydrogen-bond acceptor strength of amines.

Hydrogen-bond enthalpies are quasi-orthogonal to diiodine complexation enthalpies. This supports the different electrostatic/covalent characters of diiodine and hydrogen-bond donors. The enthalpic scale of hydrogen-bond basicity might be useful for the measurement of the electrostatic character of Lewis acid–base reactions.

## Experimental Section

**Chemicals.** Solvents (CCl<sub>4</sub> and/or C<sub>2</sub>Cl<sub>4</sub>), amines, 4-fluorophenol, and methanol were carefully purified and dried according to procedures published elsewhere.<sup>58,60–62</sup>

**Spectra.** Infrared (IR) absorbances of the stretching OH band of 4-fluorophenol in CCl<sub>4</sub> (3614 cm<sup>-1</sup>, absorption coefficient  $\epsilon = 238 \text{ L mol}^{-1} \text{ cm}^{-1}$  at 25 °C) and/or C<sub>2</sub>Cl<sub>4</sub> (3612 cm<sup>-1</sup>,  $\epsilon = 234 \text{ L mol}^{-1} \text{ cm}^{-1}$  at 25 °C) and IR shifts of the stretching OH band of methanol (3644 cm<sup>-1</sup> in CCl<sub>4</sub>) have been measured as described elsewhere.<sup>58,60,62</sup> IR shifts  $\Delta\nu(\text{OH})$  are generally known to  $\pm 5 \text{ cm}^{-1}$ , but the accidental presence of the base elongation bands, such as the  $\nu_{as}(\text{NH}_2)$ ,  $\nu_s(\text{NH}_2)$ ,  $\nu(\text{NH})$ , or  $\nu(\equiv\text{CH})$  bands, near the maximum of the broad  $\nu(\text{OH}\cdots\text{N})$  band cause larger errors.

A Peltier thermoelectric device regulates the 1 cm path length cell temperature to  $\pm 0.2 \text{ }^\circ\text{C}$  from  $-5$  to  $+55 \text{ }^\circ\text{C}$  in CCl<sub>4</sub> ( $-5$  to  $+70 \text{ }^\circ\text{C}$  in C<sub>2</sub>Cl<sub>4</sub>). The effective temperature is measured inside the cell with a calibrated thermocouple.

**Supporting Information Available:** *Z*-matrix coordinates and B3LYP/6-311+G(d,p) electronic energies of B3LYP/6-311+G(d,p) optimized structures of 12 hydrogen-bonded complexes and their monomers. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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