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The Nicotinic Pharmacophore: Thermodynamics of the Hydrogen-Bonding Complexation of Nicotine, Nornicotine, and Models

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The thermodynamics of the hydrogen-bonding complexation of the acetylcholine agonists nicotine and nornicotine and of model pyridines, pyrrolidines, and *N*-methylpyrrolidines has been measured in CCl_4 by FTIR spectrometry toward a reference hydrogen-bond donor, 4-fluorophenol. Various methods are devised for measuring separately the hydrogen-bond acceptor strength of each nitrogen of nicotine and nornicotine: variation of the stoichiometry of complexation; correlations with electrostatic potentials on nitrogens and with substituent constants in the series of 3-substituted pyridines, 2-substituted pyrrolidines, and 2-substituted *N*-methylpyrrolidines; and linear free energy relationships between 4-fluorophenol and hydrogen fluoride hydrogen-bonded complexes. It is consistently found that nicotine and nornicotine have two active hydrogen-bond acceptor sites, the pyridine and pyrrolidine nitrogens, and that ca. 90% (for nicotine) and 80% (for nornicotine) of the 1:1 hydrogen-bonded complexes are formed to the pyridine nitrogen, although the pyrrolidine nitrogen is the first protonation site of nicotine and nornicotine in water. The low hydrogen-bond basicity of the pyrrolidine nitrogen in nicotine is mainly explained by the inductive electron-withdrawing and steric effects of the 2-(3-pyridyl) substituent. The partition of the Gibbs energy of the isomerism of complexation ($AH\cdots Nsp^2 \rightleftharpoons AH\cdots Nsp^3$) into enthalpic and entropic contributions shows that the selectivity in favor of the pyridine nitrogen is driven by entropy. It is important to recognize the bifunctionality of nicotine in hydrogen bonding for understanding its lipophilicity and molecular recognition in non protonic media. When monoprotonated on their sp^3 nitrogen, nicotine and nornicotine keep, through their sp^2 nitrogen, a significant hydrogen-bond basicity which is greater than that of the ester group of acetylcholine.

1. Introduction

The tobacco alkaloid, nicotine (**1**) (Table 1), has a wide spectrum of biological activities,[1,2] some detrimental, some beneficial. Detrimental effects include actions on the cardiovascular and gastrointestinal systems, dependence, sleep disturbance, and, at higher doses, neuromuscular effects and seizures.[3−5] Beneficial effects have been shown on a variety of central nervous system (CNS) disorders such as Parkinson's or Alzheimer's diseases, attention deficit hyperactivity disorder, Tourette's syndrome, and schizophrenia.[6−11] These actions presumably occur as a result of nicotine's interaction with nicotinic acetylcholine receptors (nAChRs),[8] which are found on skeletal muscle at the neuromuscular junction, in the peripheral nervous system, and at numerous sites in the CNS.[8] They comprise five subunit proteins that combine at the cell surface to create a ligand-gated cation permeable pore.[12] In neuronal tissues, nAChRs possess a considerable diversity of subunit combinations.[13] In the CNS, it is generally accepted that the predominant

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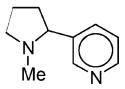
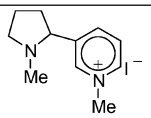
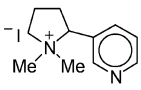
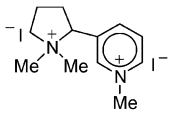
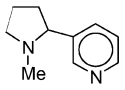
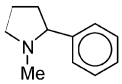
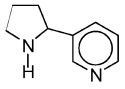
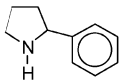
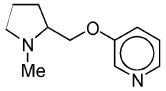
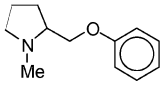
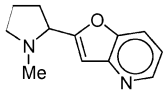
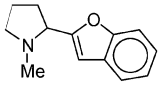
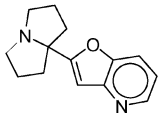
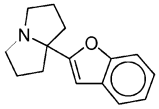
TABLE 1. Inhibition Constants K_i (nM) of Nicotinic Ligands L at *n*AChRs[a] and Gibbs Energies $\Delta G°$ (kJ mol^{-1}) for the Ligand-Exchange Reaction L_1, *n*AChR + L_2 ⇌ L_1 + L_2 , *n*AChR

No.	L_1	K_i	Ref.	No.	L_2[b]	K_i	Ref.	$\Delta G°$
1		1.15	(20)	-		no affinity	(15)	-
-		0.5	(15)	-		no affinity	(15)	-
1		1.15	(20)	-		450	(20)	14.8
2		30	(15)	-		8696	(20)	14.1
3		0.15	(21)	**4**		42	(22)	14.0
5		2.6	(23)	**7**		158	(23)	10.2
6		0.37	(23)	**8**		42	(23)	11.7

[a] The ligands were tested for *n*AChR binding in a whole rat brain preparation using [^{3}H]-(−)-cytisine. [b] L_2 is similar to L_1 but lacks the Nsp^2 lone pair, either by quaternization or changing the pyridine to a benzene ring.

nAChR which binds nicotine with high affinity is composed of α4 and β2 subunits (α4β2).[14]

Significant effort is currently being expanded to synthesize ligands exhibiting selectivity for central over peripheral nAChRs and, within the CNS, selectivity among the numerous nAChR subtypes, in order that they act via stimulation of the α4β2 receptor, as does nicotine, but possess improved side effect profiles.[14−16] In the absence of information regarding the structure of the receptor's binding site(s), the rational design of potent and selective nAChR ligands has been facilitated by the identification of a specific three-dimensional arrangement of essential chemical groups common to nAChR ligands, the so-called nicotinic pharmacophore. A nicotinic pharmacophore model was formulated in 1970 by Beers and Reich[17] and subsequently improved by Sheridan et al.[18] Other models have been recently reviewed.[19] The common feature to these models is a basic or a quaternized amino nitrogen situated a certain distance from a hydrogen-bond acceptor, the pyridine nitrogen in nicotine. These pharmacophore elements mimic, respectively, the quaternary ammonium nitrogen and the ester hydrogen-bond acceptor group of the neurotransmitter acetylcholine (ACh), $MeCOOCH_2CH_2N^+Me_3$.

Competition binding assays with radioligands in rat brain show (Table 1) that a hydrogen bond between the pyridine nitrogen and a complementary hydrogen-bond donor site on the receptor is important for high affinity binding. For example, quaternization of the pyridine nitrogen atom with a methyl group abolishes affinity.[15] In nicotine (**1**) and nornicotine (**2**), the replacement of the pyridine nitrogen atom with an sp^2 carbon atom results in an approximately 400- or 300-fold decrease in affinity, respectively.[20] Replacement of the pyridine ring of the 3-pyridyl ether (**3**) with phenyl results in a compound **4** with 280-fold reduced α4β2 affinity.[21,22] The importance of the hydrogen-bond acceptor nitrogen atom in the furo[3,2-*b*]pyridine heterocycle (**5** and **6**) is also exemplified by the benzofuran analogues (**7** and **8**) which

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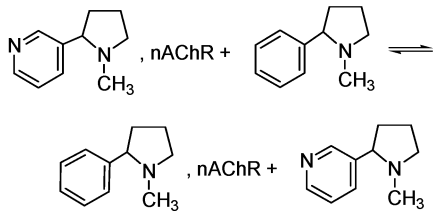
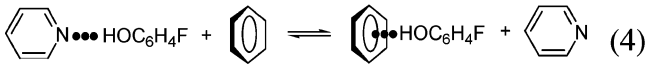
exhibit a >60-fold decrease in binding potency.[23,24] From the binding affinities K_i of Table 1, we can calculate the energetic cost of replacing a pyridine nitrogen atom −N═ with the isosteric groups −CH═. The Gibbs energies (eq 1) of the ligand-exchange reactions exemplified by reaction 2 are concordant (14.8, 14.1, 14.0, 10.2, and 11.7 kJ mol^{-1}) and are of the same order of magnitude as the Gibbs energy (eq 3) of the reaction 4 in which the hydrogen-bond donor 4-fluorophenol is exchanged between the hydrogen-bond acceptors pyridine and benzene. In eq 3, K_c(pyridine) and K_c(benzene) are the

$$\Delta G_2^0 = RT \ln [K_i (\text{-CH=}) / K_i (\text{-N=})] \quad (1)$$



(2)

$$\Delta G_4^0 = RT \ln [K_c (\text{benzene}) / K_c (\text{pyridine})] = 13.4 \text{ kJ mol}^{-1} \quad (3)$$

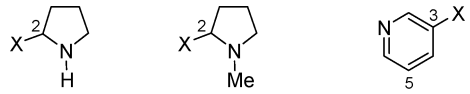


(4)

hydrogen-bonding complexation constants of pyridine[25] (nitrogen base) and benzene[26] (weak π base) with 4-fluorophenol (respectively 72 and 0.32 L mol^{-1} in CCl_4 at 298 K).

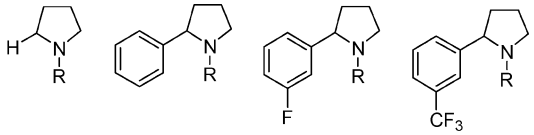
The physiological effects of nicotine and other nAChR ligands also depend on their transport to the receptor. If the skin is the point of entry into the body (because oral bioavailability is lacking in nicotine, and smoking represents a toxic and addictive form of nicotine delivery), for the nicotine to reach the CNS it must be able to penetrate the skin and, thereafter, to cross the blood−brain barrier, a membrane that surrounds the capillaries of the circulatory system in the brain. Among the physicochemical descriptors of solutes that influence their skin penetration[27] and their distribution between blood and brain,[28] an important one is hydrogen-bond basicity, i.e., hydrogen-bond acceptor strength. Thus, brain penetration and skin permeability are decreased by hydrogen-bond basicity.[29] More generally, the transport of drugs to their site of action is often modeled by their ability to partition between wet octanol, which would simulate a lipid membrane, and water.[30,31] The partition coefficient, P_{ow}, between octanol and water was proposed as a measure of lipophilicity.[30,32] The two most important molecular descriptors explaining log P_{ow} are the volume and the hydrogen-bond basicity.[33,34] Since nicotinic ligands bear two hydrogen-bond acceptor groups corresponding to the nitrogens of the pyridine and pyrrolidine rings, hydrogen-bond complexation appears in this context also to be an important property of nicotine.

Despite its importance in the docking and transport of nAChR ligands, the hydrogen-bonding complexation of these ligands does not appear to have been studied so far, except in a preliminary work on nicotine[35] which does not consider separately each nitrogen of nicotine or the monoprotonated form. This paper intends to fill this gap and give the chemist a set of thermodynamic data on the hydrogen-bonding complexation of nicotine and nornicotine, as free bases and in their monoprotonated forms, and of three series of substructures, 2-substituted pyrrolidines **a**, 2-substituted-*N*-methylpyrrolidines **b**, and 3-(or 3,5-di)substituted pyridines **c**. These substructures



a **b** **c**

will allow the structural effects influencing the hydrogen-bond basicity to be quantified, thus to calculate separately the hydrogen-bond basicity of each nitrogen of nicotine and nornicotine as free bases, and to obtain the Nsp^2 pyridine hydrogen-bond basicity of their monoprotonated forms. These latter species are difficult to study experimentally because the corresponding salts are not soluble in the apolar solvent used for the free bases and their counteranion is a competitive hydrogen-bond acceptor. In the series **a** and **b**, we have selected substituents which are isosteres of the 3-pyridyl substituent, but which have different electron-withdrawing field-inductive effects (compounds **10**−**12**, **14**−**16**). We have



R = H	**9**	**10**	**11**	**12**
R = Me	**13**	**14**	**15**	**16**

already shown[36] that the effect of the 3-pyridyl group on the proton basicity of the pyrrolidine ring is closely bracketed by 3-fluorophenyl and 3-trifluoromethylphenyl substituents. These substituents without significant hydrogen-bond acceptor sites will allow close estimates

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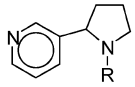
TABLE 2. Complexation Constants K_c (L mol^{-1}) and Thermodynamic Parameters ΔG, ΔH (kJ mol^{-1}), and ΔS (J K^{-1} mol^{-1}) for the Hydrogen Bonding of 4-Fluorophenol with Nicotine, Nornicotine, Pyrrolidines, and Pyridines in CCl_4 at 25 °C

Series	No.	Compound	$K_c(25)$ [a]	pK_{HB} [b]	$-\Delta H°$ [c]	$-\Delta S_x°$ [c]	$-\Delta G_x°$ [d]
	**1**	nicotine (R = Me)	126 [e]	-			
	2	nornicotine (R = H)	158 [e]	-			
	**9**	pyrrolidine	388 [f]	2.59	36.1 [g]	53.1 [g]	20.3 [g]
	10	2-phenylpyrrolidine	85	1.93	33.3	55.2	16.8
	11	2-(3-fluorophenyl)pyrrolidine	45	1.65	31.1	53.1	15.3
	12	2-(3-trifluoromethylphenyl)pyrrolidine	24	1.38	30.5	56.2	13.7
	**13**	*N*-methylpyrrolidine	156 [h]	2.19	34.8 [g]	54.8 [g]	18.5 [g]
	14	*N*-methyl-2-phenylpyrrolidine	24	1.38	32.8	64.0	13.7
	15	*N*-methyl-2-(3-fluorophenyl)pyrrolidine	12	1.09	31.0	63.8	12.0
	16	*N*-methyl-2-(3-trifluoromethylphenyl)-pyrrolidine	8	0.92	29.3	60.6	11.2
	**17**	3,5-dimethylpyridine	162 [i]	2.21	31.9	45.8	18.2
	18	3-methylpyridine	100 [i]	2.00	30.0	42.5	17.3
	19	pyridine	72 [i]	1.86	29.6	44.2	16.4
	20	3-fluoropyridine	22 [i]	1.35	25.4	40.1	13.5
	21	3-chloropyridine	20 [i]	1.31	27.2	47.0	13.2
	22	3,5-dichloropyridine	7 [i]	0.85	23.9	45.1	10.4

[a] Complexation constant measured at 25 °C by varying the base concentration (mean of four to five determinations). [b] $pK_{HB} = \log K_c(25)$. [c] From the variation of complexation constants with temperature (−5 to +55 °C). Values relative to mole fractions. [d] $\Delta G_x° = \Delta H° - 298.15\,\Delta S_x°$. [e] Summation of two 1:1 complexation constants (see text). [f] Reference 40. [g] In C_2Cl_4, because of the instability of solutions of bases in CCl_4. [h] Reference 41. [i] Reference 25.

of the enthalpies and entropies of hydrogen bonding to the pyrrolidine nitrogens of nicotine and nornicotine to be made. In the series **c** were chosen six substituents embracing a wide range of electronic effects from the 3,5-dimethylpyridine (**17**) to the 3,5-dichloropyridine (**22**) (Table 2).

We have determined the hydrogen-bond basicity of compounds **1**, **2**, and **9**−**22** by measuring their constants of complexation with a reference hydrogen-bond donor by FTIR spectrometry in CCl_4 at 298 K. For reference, we have selected 4-fluorophenol because it has proved[37,38] to be a technically good hydrogen-bond donor for the establishment of a thermodynamic hydrogen-bond basicity scale for organic and bioorganic bases B. This scale, denoted by pK_{HB}, is defined[39] as the logarithm of the constant K_c for the 1:1 complexation of B with 4-fluorophenol in CCl_4 at 298 K. We have recently constructed the pK_{HB} scale for pyridines[25] and for secondary[40] and tertiary amines.[41] Another advantage of 4-fluorophenol for this study is the similarity of Gibbs energies between the pyridine−benzene exchange (4) in the hydrogen-bonding complexation and the pyridyl−phenyl exchange (2) in the binding to nAChRs. Although probably fortuitous, this similarity might be useful for future estimations of the hydrogen-bonding contribution to the binding of ACh agonists and antagonists to nAChRs. In addition to Gibbs energies deduced from equilibrium constants K_c, the enthalpy and entropy of complexation can be obtained from the temperature variation of K_c to determine if the

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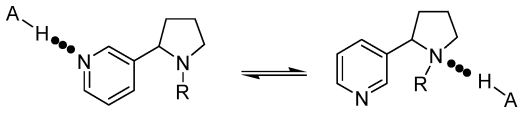
hydrogen-bond selectivity is driven by enthalpy and/or entropy.

Since nicotine and nornicotine have two potential hydrogen-bonding sites, our IR method of determining complexation constants affords only a summation of individual constants, if two 1:1 complexes are formed, or an apparent constant, if additionally 1:2 complexation occurs (1 nicotine/2 phenols). We have therefore developed methods to access each individual 1:1 complexation constant. A first method treats explicitly the formation of all species; it requires four equilibrium constants and therefore approximations are needed for solving the final equations. A second method relies on the establishment of family-dependent (series **a**−**c**) relationships between Gibbs energies of complexation and ab initio calculated electrostatic potentials around the nitrogens lone pair. A third method applies the Taft−Topsom methodology[42] to the hydrogen-bonding complexation of 3-substituted pyridines **c** and 2-substituted pyrrolidines **a** and **b**. In this method, the substituent effect on the Gibbs energy of complexation $\Delta G°$, $\delta\Delta G°$, is described by the linear structure−energy relationship (5) in terms of substituent

$$\delta\Delta G° = \rho_F \sigma_F + \rho_R \sigma_R + \rho_\alpha \sigma_\alpha \qquad (5)$$

constants, σ, and reaction constants, ρ, corresponding to three assumed additive interaction mechanisms, called field-inductive (F),[43] resonance (R),[44] and polarizability (α).[45] σ constants are calculated by ab initio methods from the variations upon substitution, in ad hoc models,[46−48] of electronic charges (σ_F, σ_R) or directional polarization potentials (σ_α). A fourth method uses the recently shown[49] similarity between hydrogen fluoride and 4-fluorophenol hydrogen-bonded complexes through the linear Gibbs energy relationship between the experimental $\Delta G°$ of 4-fluorophenol complexation in CCl_4 and the ab initio calculated $\Delta G°$ of hydrogen fluoride complexation in vacuo. Only the second and fourth methods can be applied to monoprotonated nicotine and nornicotine, since these forms cannot be easily studied experimentally through the first method (vide infra), and eq 5 is not recommended for charged substituents.[50] A last analysis considers the isomerism of complexation (6), where the hydrogen-bond donor HA is 4-fluorophenol for the experimental study or HF for theoretical calculations, to know if the selectivity of complexation is driven by enthalpy and/or entropy.



(6)

After quantification of the hydrogen-bonding strength of each site of nicotine and nornicotine, two applications of this bifunctionality are analyzed, the lipophilicity of nicotinoids, and the molecular recognition of nicotine by a diol.

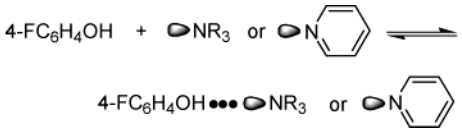
2. Experimental Section

Materials. The solvents, CCl_4 and C_2Cl_4 (used only for pyrrolidine and *N*-methylpyrrolidine which react in or are complexed with CCl_4), and the compounds pyrrolidine, *N*-methylpyrrolidine, substituted pyridines **c**, and (S)-nicotine were commercially available and carefully distilled. Their final purity was checked by gas chromatography. All were dried over activated 4 Å (1 Å = 0.1 nm) molecular sieves and/or basic aluminum oxide just before use. 4-Fluorophenol was sublimed over P_2O_5.

Nornicotine, 2-substituted pyrrolidines **a**, and 2-substituted-*N*-methylpyrrolidines **b** were synthesized using the protocol described by Jacob.[51] The compounds were obtained as racemic mixtures and their final purification (tested by FT-ICR mass spectrometry) consisted of a distillation and careful drying.

Infrared Spectrometry. FTIR spectra were recorded with a Bruker IFS48 or a Vector 22 instrument at a resolution of 1 cm^{-1}. An Infrasil quartz cell of 1 cm path length was used. The cell temperature was varied from −5 to +55 °C and controlled to ±0.2 °C by means of a Peltier thermoelectric device. With the binary solution base + CCl_4 as reference, and the ternary solution 4-fluorophenol + base + CCl_4 as sample, the obtained difference spectra correspond to a mixture of free and hydrogen-bonded 4-fluorophenol.

Equilibrium Constants K_c at 25 °C. The formation of a 1:1 complex from 4-fluorophenol and amines or pyridines can be represented by equilibrium (7). If C_c, C_a, and C_b are the



(7)

equilibrium concentrations, on the molar scale, of the complex, the acid 4-fluorophenol, and the base (amine or pyridine) respectively, and if C_a° and C_b° are the corresponding initial concentrations, then the equilibrium (complexation) constant K_c is given by (8).

$$K_c/\text{L mol}^{-1} = C_c/C_a\,C_b = (C_a^\circ - C_a)/C_a\,(C_b^\circ - C_a^\circ + C_a) \qquad (8)$$

$$C_a = A/\epsilon l \qquad (9)$$

C_a is obtained (eq 9) from the absorbance A of the free OH band of 4-fluorophenol at 3614 cm^{-1}, the absorption coefficient ϵ (238 and 234 L mol^{-1} cm^{-1}, respectively, in CCl_4 and C_2Cl_4) and the path length l (1.00 cm). C_a° and C_b° are obtained by weighing. C_a° is kept below 5 mmol L^{-1} in order to neglect the self-association of 4-fluorophenol. C_b° is adjusted so that 20−80% of 4-fluorophenol is hydrogen-bonded. The constancy of K_c calculated at different amine (pyridine) concentrations on the basis of only 1:1 complexation indicates that the 1:1 complex is almost the only species formed. For example, the complex with 2-(3-fluorophenyl)pyrrolidine gives K_c = 44.01, 44.35, 44.73, and 44.41 (mean 44.4) L mol^{-1} for C_b° ranging from 10 to 70 mmol L^{-1}. In the case of nicotine and nornicotine, we have taken into account the formation of 1:2 complexes (vide infra). From weighing, absorbance and temperature errors, the maximum relative error in K_c is estimated to be

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TABLE 3. Determination of the Complexation Enthalpy and Entropy (on the Molar Concentration Scale) for Hydrogen Bonding of 4-Fluorophenol to 2-(3-Fluorophenyl)pyrrolidine in CCl_4

T (°C)	−4.4	9.7	25.1	39.9	54.6
absorption coefficient ϵ (L mol^{-1} cm^{-1})	258.7	249.9	240.4	231.1	221.9
initial concentrations (mmol L^{-1})					
C_a°	4.1393	4.0706	3.9960	3.9239	3.8522
C_b°	29.0651	28.5828	28.0589	27.5523	27.0492
absorbance A	0.1934	0.3111	0.4466	0.5427	0.6070
equilibrium concentrations (mmol L^{-1})					
$C_a = A/\epsilon l$	0.7475	1.2447	1.8580	2.3482	2.7352
$C_c = C_a^\circ - C_a$	3.3919	2.8259	2.1380	1.5756	1.1170
$C_b = C_b^\circ - C_c$	25.6732	25.7569	25.9208	25.9766	25.9321
equilibrium constants K_c (L mol^{-1})	176.76	88.14	44.39	25.83	15.75
thermodynamic parameters	$-\Delta H_c^\circ = 30.1$ kJ mol^{-1}		$-\Delta S_c^\circ = 69.0$ J K^{-1} mol^{-1}		

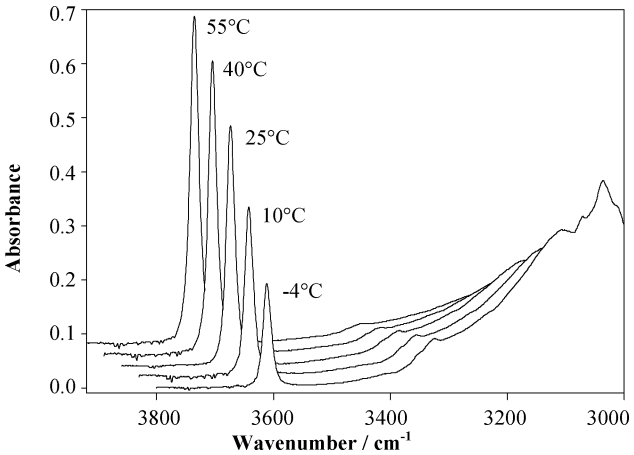

FIGURE 1. IR determination of the enthalpy and entropy for hydrogen bonding of 2-(3-fluorophenyl)pyrrolidine to 4-fluorophenol in CCl_4. The absorbance of the sharp OH band of free 4-fluorophenol at 3614 cm^{-1} decreases with decreasing temperature (+55 to −4 °C) with a concomitant increase in the broad OH band of the complex.

±8%, corresponding to maximum errors of ±0.04 and ±0.25 kJ mol^{-1} in log K_c (pK_{HB}) and $\Delta G°$, respectively.

Determination of Enthalpy and Entropy. Precise enthalpy measurements are done by following the absorbance of *a single solution* as a function of temperature. In a typical measurement, the spectra of a solution containing ca. 4 mmol L^{-1} of 4-fluorophenol and a base concentration adjusted as described above are recorded at five temperatures between −5 and +55 °C. The method requires the preliminary determination of the temperature dependence of the absorption coefficient (eq 10, temperature t/°C). Figure 1 shows the IR

$$\epsilon(t) = \epsilon(25) - 0.624(t - 25) \qquad (10)$$

spectra recorded for the complex of 4-fluorophenol with 2-(3-fluorophenyl)pyrrolidine. The absorbance and concentration data and the calculation of complexation constants at the various temperatures from one such experiment are reported in Table 3. The enthalpy and entropy relative to molar concentrations, ΔH_c° and ΔS_c°, are obtained from the slope and intercept of a ln K_c versus 1/T van't Hoff plot (eq 11) as $-\Delta H_c^\circ$

$$\ln K_c = -\frac{\Delta H_c^\circ}{R}\frac{1}{T} + \frac{\Delta S_c^\circ}{R} \qquad (11)$$

$= 30.1 \pm 0.4$ kJ mol^{-1} and $-\Delta S_c^\circ = 69.0 \pm 1.4$ J K^{-1} mol^{-1} (the precision of the results is taken from the error limits of the slope and intercept in the regression analysis of squared correlation coefficient $r^2 = 0.9994$ for $n = 5$ temperatures). A second experiment yields $-\Delta H_c^\circ = 30.4 \pm 0.6$ kJ mol^{-1} and $-\Delta S_c^\circ = 70.2 \pm 1.9$ J K^{-1} mol^{-1} ($r^2 = 0.9990$ for $n = 5$). The means from these two measurements are 30.2 kJ mol^{-1} and 69.6 J K^{-1} mol^{-1}.

The entropy can also be obtained (eq 12) from the enthalpy of the single solution experiment and the Gibbs energy, calculated (eq 13) from K_c (25 °C) which is obtained from the average of the determinations in which the base concentration

$$\Delta S_{c,298}^\circ = (\Delta H_{c,298}^\circ - \Delta G_{c,298}^\circ)/298.15 \qquad (12)$$

$$\Delta G_{c,298}^\circ = -298.15R \ln K_c\,(25\ °C) \qquad (13)$$

is varied. The two methods give results that are in excellent agreement. For the complex of 2-(3-fluorophenyl)-pyrrolidine, K_c (25 °C) = 44.4 L mol^{-1} (vide supra), $\Delta G_{c,298}^\circ = -9.40$ kJ mol^{-1} (eq 13), and $-\Delta S_{c,298}^\circ = 69.7$ J K^{-1} mol^{-1} (eq 12), a value not significantly different from that (69.6) determined from eq 11.

The enthalpies, entropies, and Gibbs energies of eqs 11−13 are calculated on the molar concentration scale, since the K_c unit is L mol^{-1}. Hepler has shown[52] that the ΔH_c° value relative to molar concentration is not the correct "standard-state infinite dilution" $\Delta H°$, which must be calculated from K_x relative to mole fraction, and is related to ΔH_c° by eq 14, where α is the coefficient of thermal expansion of the solvent.

$$\Delta H° = \Delta H_c^\circ - \alpha RT^2 \qquad (14)$$

For CCl_4 at 298 K, the correction term amounts to 0.9 kJ mol^{-1}. K_x values lead to standard Gibbs energies $\Delta G_x^\circ = -RT \ln K_x$ and entropies ΔS_x° that differ from ΔG_c° and ΔS_c° by −5.8 kJ mol^{-1} and +16.3 J K^{-1} mol^{-1}, respectively (in CCl_4 at 298 K).

From slope errors and the repetition of measurements, we estimate the maximum error in ΔH as ±0.8 kJ mol^{-1}. The propagation of errors in ΔH and ΔG gives the entropies to ±5%.

3. Computational Methods

Theoretical calculations have been performed using the Gaussian 94 or 98[53] packages supported on the IDRIS and CINES supercomputers.

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3.1. Geometries of Hydrogen-Bond Acceptors and HF. Starting from experimental structures found in the Mogadoc database,[54] the geometries of pyrrolidine, *N*-methylpyrrolidine, pyridine, substituted pyridines **c**, and hydrogen fluoride were optimized at the B3LYP/6-31G(d,p) level. The geometries of nicotine and nornicotine and substituted pyrrolidines **a** and **b** have been satisfactorily calculated at the same level in a previous work.[36] Nicotine and nornicotine protonated on the pyrrolidine nitrogen were optimized as chloride salts, starting from X-ray structures of corresponding salts.[55,56]

3.2. Electrostatic Potentials. Electrostatic potentials on the molecular surface, around each nitrogen lone pair (V_S < 0) and around the hydrogens of the pyridine ring (V_S > 0), are calculated at the B3LYP/6-31+G(d,p) level. Diffuse functions are included here in order better to take the lone pair properties into account. The molecular surface was defined[57] by the 0.001 electron/bohr^3 contour of the electronic density.

3.3. Hydrogen-Bonded Complexes of Hydrogen Fluoride on the Pyridine Nitrogen. The experimental geometry of the pyridine−HF complex[58] served as an initial estimate for optimizing the geometries of FH···Nsp^2 complexes at the B3LYP/6-31G(d,p) level. Frequency calculations were performed on these geometries to check that the computed structures were true minima. Thermodynamic parameters of complexation were calculated at the B3LYP/6-31+G(d,p) level. The basis set superposition error (BSSE) was not accounted for because it is expected to be quasi-constant in this series of closely related complexes.

3.4. Isomerism of Complexation (eq 6). The enthalpies and entropies of the isodesmic reaction 6 were calculated for nicotine (R = Me) and nornicotine (R = H) at the B3LYP/6-31+G(d,p)//B3LYP/6-31G(d,p) level. The starting geometries of the FH···Nsp^3 complexes were taken from the experimental structures of the HF complexes with amines.[59] That the BSSE may not be the same for each site was taken into account by using the counterpoise procedure.[60,61]

4. Results and Discussion

Table 2 summarizes the complexation constants and the thermodynamic parameters for the hydrogen-bonding complexation of 4-fluorophenol with nicotine, nornicotine, pyrrolidines **a** and **b**, and pyridines **c**, in CCl_4 (or C_2Cl_4 for **3** and **7**) at 25 °C. For pyridine and 3,5-dichloropyridine, our van't Hoff complexation enthalpies, of −29.6 and −23.9 kJ mol^{-1}, respectively, compare well with literature calorimetric results[62] of −29.7 and −22.6 kJ mol^{-1}.

4.1. Total Complexation Constants of Nicotine and Nornicotine. Nicotine (nornicotine) YZ, composed of two hydrogen-bond acceptor rings Y and Z, can exist in very dilute CCl_4 solution of 4-fluorophenol (AH) either as the free base (concentration C_b), the 1:1 complexes on sites Y (C_{1Y}) and Z (C_{1Z}), or the 1:2 complex (C_2). The simultaneous equilibria and their equilibrium constant expressions are as follows:

$$\mathrm{YZ} + \mathrm{AH} \rightleftharpoons \mathrm{AH}\cdots\mathrm{YZ} \quad K_{1Y} = C_{1Y}/C_aC_b \tag{15}$$

$$\mathrm{YZ} + \mathrm{AH} \rightleftharpoons \mathrm{YZ}\cdots\mathrm{HA} \quad K_{1Z} = C_{1Z}/C_aC_b \tag{16}$$

$$\mathrm{AH}\cdots\mathrm{YZ} + \mathrm{AH} \rightleftharpoons \mathrm{AH}\cdots\mathrm{YZ}\cdots\mathrm{HA} \quad K_{2Z} = C_2/C_aC_{1Y} \tag{17}$$

$$\mathrm{YZ}\cdots\mathrm{HA} + \mathrm{AH} \rightleftharpoons \mathrm{AH}\cdots\mathrm{YZ}\cdots\mathrm{HA} \quad K_{2Y} = C_2/C_aC_{1Z} \tag{18}$$

The ratio (19), calculated from the only experimentally accessible concentrations C_a°, C_b°, and C_a (see the Experimental Section), is only an apparent equilibrium constant, which can be rewritten as (20) from the conservation of nicotine ($C_b^\circ = C_b + C_{1Y} + C_{1Z} + C_2$) and of 4-fluorophenol ($C_a^\circ = C_a + C_{1Y} + C_{1Z} + 2C_2$):

$$K_{app} = (C_a^\circ - C_a)/C_a\,(C_b^\circ - C^\circ{}_a + C_a) \tag{19}$$

$$K_{app} = (C_{1Y} + C_{1Z} + 2C_2)/C_a\,(C_b - 2C_2) \tag{20}$$

In the absence of 1:2 complex, (i.e., $C_2 = 0$), K_{app} becomes a true constant, called K_1, which is the sum of the two 1:1 constants that we are looking for:

$$K_1 = (C_{1Y} + C_{1Z})/C_a\,C_b = K_{1Y} + K_{1Z} \tag{21}$$

Following the method of Clotman et al.,[63] it is practical to define a constant K_2 (eq 22), because K_{app} can be simply

$$\frac{1}{K_2} = \frac{1}{K_{2Y}} + \frac{1}{K_{2Z}} \tag{22}$$

expressed as a function of constants K_1 and K_2 and of the experimentally accessible concentration C_a (eq 23). Dividing each term of eq 23 by K_1 ($2C_a + K_{app}C_a^2$) gives eq 24. Equation 24 is that of a straight line whose intercept is $-K_2$ and whose slope is $1/K_1$. Good values of K_1 and K_2 are dependent upon a large variation of

$$K_{app} = K_1 + K_1K_2(2C_a + K_{app}C_a^2) \tag{23}$$

$$\frac{1}{2C_a + K_{app}C_a^2} = \left(\frac{1}{K_1}\right)\frac{K_{app}}{2C_a + K_{app}C_a^2} - K_2 \tag{24}$$

coordinates, which is obtained by varying widely the ratio C_b°/C_a° (from 0.1 to 15). The least-squares method gives K_1 values of 127 ± 1 and 156 ± 1 L mol^{-1} and K_2 values of 16 ± 1 and 28 ± 5 L mol^{-1} for nicotine and nornicotine, respectively.

These K_1 values correspond to the total complexation constants (i.e., the sum of the 1:1 complexation constants of each site) for the pyridine and pyrrolidine nitrogens. To calculate each 1:1 complexation constant requires an approximation. We can assume $K_{1Y} = K_{2Y}$ and $K_{1Z} = K_{2Z}$ if we make the reasonable assumption that the sites of complexation are sufficiently independent (they are four bonds away in different nonconjugated rings) that the complexation of one site does not change significantly the

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TABLE 4. Minimum Electrostatic Potentials on the Molecular Surface, $V_{S,min}$ (kJ mol^{-1}), around the Nitrogens of Nicotine, Nsp^3-Monoprotonated Nicotine, Nornicotine, Nsp^3-Monoprotonated Nornicotine, Pyrrolidines, and Pyridines, Calculated at the B3LYP/6-31+G(d,p)//B3LYP/6-31G(d,p) Level

no.	compd	site	$-V_{S,min}$
1	nicotine	Nsp^3	81.04
1	nicotine	Nsp^2	163.34
1$^+$	Nsp^3-protonated nicotine, Cl$^-$	Nsp^2	134.18
2	nornicotine	Nsp^3	93.89
2	nornicotine	Nsp^2	164.22
2$^+$	Nsp^3-protonated nornicotine, Cl$^-$	Nsp^2	133.76
9	pyrrolidine	Nsp^3	150.92
10	2-phenylpyrrolidine	Nsp^3	112.05
11	2-(3-fluorophenyl)pyrrolidine	Nsp^3	100.12
12	2-(3-trifluoromethylphenyl)pyrrolidine	Nsp^3	88.41
13	*N*-methylpyrrolidine	Nsp^3	133.13
14	*N*-methyl-2-phenylpyrrolidine	Nsp^3	99.08
15	*N*-methyl-2-(3-fluorophenyl)pyrrolidine	Nsp^3	86.82
16	*N*-methyl-2-(3-trifluoromethylphenyl)-pyrrolidine	Nsp^3	76.86
17	3,5-dimethylpyridine	Nsp^2	166.57
18	3-methylpyridine	Nsp^2	161.92
19	pyridine	Nsp^2	157.03
20	3-fluoropyridine	Nsp^2	140.04
21	3-chloropyridine	Nsp^2	136.90
22	3,5-dichloropyridine	Nsp^2	118.45

hydrogen-bond basicity of the other. Equation 22 becomes

$$K_2 = (K_{1Y}\,K_{1Z})/(K_{1Y} + K_{1Z}) \qquad (25)$$

The solutions of the quadratic equation constructed from the sum (eq 21) and the product (contained in eq 25) of our two unknowns are

$K_{1Y} = 107 \pm 3$ and $K_{1Z} = 19 \pm 2$ L mol^{-1} for nicotine

and

$K_{1Y} = 128 \pm 8$ and $K_{1Z} =$ 30 ± 8 L mol^{-1} for nornicotine

Clearly, the K_{1Y} values correspond to that of 3-methylpyridine in Table 2; thus, we can attribute K_{1Y} to the pyridine nitrogen complexation. Consequently, K_{1Z} corresponds to the pyrrolidine nitrogen complexation.

Although based on an approximation, this partition of the total complexation constant has the virtue of showing experimentally (i) the existence of two active hydrogen-bond acceptor sites in nicotine and nornicotine and (ii) that the predominant site is the pyridine nitrogen. This last result clearly distinguishes between the pK_{HB} scale of hydrogen-bond acceptor strength and the pK_a scale of proton basicity, on which the pyrrolidine nitrogen of nicotine or nornicotine is the preferred protonation site in water.[64,65]

4.2. Calculation of 1:1 Complexation Constants from Electrostatic Potentials. Following the pioneering work of Politzer et al.,[66−68] several authors have shown the existence of family-dependent relationships between the hydrogen-bond basicity and the minimum electrostatic potential around the nitrogen lone pair of aromatic N-heterocycles,[69] nitriles,[70] and amines.[40,41] It seems possible therefore to calculate the basicity of each nitrogen of nicotine and nornicotine from their nitrogen minimum electrostatic potential, $V_{S,min}$, if we can establish good relationships between pK_{HB} and the nitrogen electrostatic potentials of 3-substituted pyridines **c** or 2-substituted pyrrolidines **a** and **b**. So we have calculated V_S, at the B3LYP/6-31+G(d,p)//B3LYP/6-31G(d,p) level, for each nitrogen of nicotine and nornicotine and for the pyridines **c** and pyrrolidines **a** and **b**. The results are presented in Table 4. For nicotine and nornicotine the most negative V_S is on the pyridine nitrogen (Figure 2), showing that the electrostatic contribution to the hydrogen-bond energy favors the pyridine nitrogen.

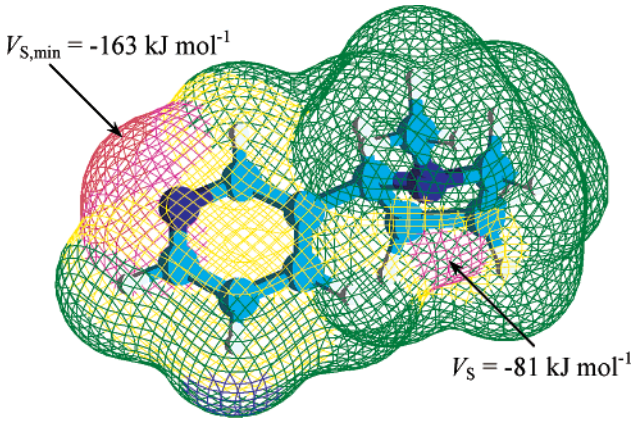

FIGURE 2. Electrostatic potential, calculated at the B3LYP/6-31+G(d,p) level, on the molecular surface of nicotine. The most negative V_S are on the nitrogens (red regions), and the minimum is on the pyridine nitrogen.

Good family-dependent relationships are obtained between pK_{HB} and $V_{S,min}$ for pyridines (eq 26), pyrrolidines (eq 27), and *N*-methylpyrrolidines (eq 28), as shown by the squared correlation coefficient r^2 and the

$$\text{p}K_{HB}\ (\text{pyridines}) = 2.82\ (\pm 0.13)\ (-V_{S,min}/100) - 2.54\ (\pm 0.19) \qquad (26)$$

$$n = 6 \quad r^2 = 0.992 \quad s = 0.05$$

$$\text{p}K_{HB}\ (\text{pyrrolidines}) = 1.91\ (\pm 0.11)\ (-V_{S,min}/100) - 0.27\ (\pm 0.13) \qquad (27)$$

$$n = 4 \quad r^2 = 0.993 \quad s = 0.05$$

$$\text{p}K_{HB} = (N\text{-methylpyrrolidnes}) = 2.29(\pm\ 0.07)\ (-V_{S,min}/100) - 0.87\ (\pm 0.08) \qquad (28)$$

$$n = 4 \quad r^2 = 0.998 \quad s = 0.03$$

standard deviation of the estimate, *s*. From the electrostatic potentials of nicotine and nornicotine (Table 4), these equations allow the prediction of pK_{HB}, and therefore, complexation constants, for each nitrogen of neutral nicotine and nornicotine. These values are given in Table

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TABLE 5. Nicotine and Nornicotine Complexes with 4-Fluorophenol in CCl_4 at 298 K: Partition of the Total Complexation Constant K_1 (L mol^{-1}) into Separate Constants of Complexation (L mol^{-1}) to the Pyridine and Pyrrolidine Nitrogens

method	K(Nsp^2)[a]	K(Nsp^3)[b]	K_1(calcd)[c]	%(Nsp^2)[d]
Nicotine: K_1(expt) = 126				
experimental	107[e]	19[e]		85
electrostatic potentials	116	10	126	92
substituent constants	103	11	114	90
hydrogen fluoride complexes	107	*f*		
mean result	**108**	**13**		
Nornicotine: K_1(expt) = 158				
experimental	128[e]	30[e]		81
electrostatic potentials	123	34	157	78
substituent constants	114	34	148	77
hydrogen fluoride complexes	122	f		
mean result	**122**	**33**		

[a] Equilibrium constant for complexation of the pyridine nitrogen. [b] Equilibrium constant for complexation of the pyrrolidine nitrogen. [c] K_1(calcd) = K(Nsp^2) + K(Nsp^3). [d] Percentage of complexation of the pyridine nitrogen = 100. K(Nsp^2)/[K(Nsp^2) + K(Nsp^3)]. [e] See text for the assumptions of this method. [f] Not studied (see text).

TABLE 6. Values of Field-Inductive (σ_F), Resonance (σ_R), and Polarizability (σ_α) Substituent Constants, Calculated by ab Initio Methods, from Graton et al.[36]

substituent	series	σ_F	σ_R	σ_α[a]
H	**a**, **b**, **c**	0	0	0
phenyl	**a**, **b**	+0.061	*b*	−0.91
3-fluorophenyl	**a**, **b**	+0.126	*b*	−0.90
3-pyridyl	**a**, **b**	+0.143	*b*	−0.88
3-trifluoromethylphenyl	**a**, **b**	+0.166	*b*	−0.92
pyrrolidin-2-yl	**c**	−0.034	−0.061	−0.68
N-methylpyrrolidin-2-yl	**c**	−0.015	−0.037	−0.82

[a] Also used as steric parameter (see text). [b] Not relevant to this study.

5. They confirm that hydrogen-bonding occurs predominantly, but not exclusively, on the pyridine nitrogen. The Nsp^2 electrostatic potentials of protonated nicotine and nornicotine (Table 4) will give as well an estimation of complexation constants (vide infra).

4.3. Calculation of 1:1 Complexation Constants from Substituent Constants. We have previously[25] applied the Taft−Topsom eq 5 to the complexation of 3-substituted pyridines with 4-fluorophenol and have obtained[25] eq 29. From the σ_α, σ_F, and σ_R values of the 3-

$$pK_{HB}\text{ (pyridines)} = 1.86(\pm0.02) - 0.10(\pm0.03)\sigma_\alpha - 1.79(\pm0.04)\sigma_F - 1.14(\pm0.05)\,\sigma_R \quad (29)$$

$$n = 10 \quad r^2 = 0.998 \quad s = 0.02$$

(pyrrolidin-2-yl) and 3-(*N*-methylpyrrolidin-2-yl) substituents, ab initio calculated in a previous work[36] and reported in Table 6, we can calculate the complexation constants K(Nsp^2) for nicotine and nornicotine. They are reported in Table 5.

The prediction of K(Nsp^3) requires the establishment of the Taft−Topsom eq 5 for the complexation of 4-fluorophenol with pyrrolidines **a** and **b**. In these series, there is no resonance effect, because the pyrrolidine ring is saturated, but a steric effect must operate, because the 2-substituent must hinder the attachment of 4-fluorophenol to the nitrogen lone pair. Therefore, the Taft−Topsom equation is rewritten as eq 30, in which pK°_{HB} refers to the unsubstituted pyrrolidine and σ_S is a steric parameter. The small data number requires the simplification of this equation into (31), which is justified by the correlation between steric and polarizability parameters (both depend on the electronic cloud size[71]). A multiple

$$pK_{HB}(\text{pyrrolidines}) = pK^\circ_{HB} + \rho_\alpha\sigma_\alpha + \rho_F\,\sigma_F + \rho_S\sigma_S \quad (30)$$

$$pK_{HB}(\text{pyrrolidines}) = pK^\circ_{HB} + \rho_F\,\sigma_F + (\rho_\alpha + \rho'_s)\,\sigma_\alpha \quad (31)$$

linear regression of pK_{HB} (Table 2) into σ_F and σ_α (Table 6) gives eqs 32 for pyrrolidines **a** and 33 for *N*-methylpyrrolidines **b**. The $-\sigma_\alpha$ values being larger for more polarizable substituents which stabilize ($\rho_\alpha < 0$), and for

$$pK_{HB}\text{ (pyrrolidines)} = 2.59(\pm0.05) - 5.09(\pm0.62)\sigma_F + 0.37(\pm0.10)\sigma_\alpha \quad (32)$$

$$n = 4 \quad r^2 = 0.997 \quad s = 0.05$$

$$pK_{HB}\text{ (}N\text{-methylpyrrolidines)} = 2.19(\pm0.01) - 4.34(\pm0.13)\sigma_F + 0.60(\pm0.02)\sigma_\alpha \quad (33)$$

$$n = 4 \quad r^2 = 0.9998 \quad s = 0.01$$

bulkier groups which destabilize ($\rho_S > 0$), the hydrogen-bonded complexes, the positive sign of the σ_α regression coefficient indicates the predominance of steric over polarizability effects, particularly in the 2-substituted-*N*-methylpyrrolidines. From the σ_F and σ_α values of the 2-(3-pyridyl) substituent (Table 6), we calculate K(Nsp^3) for nicotine and nornicotine (Table 5).

This method, which gives results in close agreement with the two previous ones (see Table 5), has the advantage of explaining why the predominant site of hydrogen-bonding in nicotine and nornicotine is the pyridine nitrogen, despite the lower hydrogen-bond basicity of pyridine (pK_{HB} = 1.86) than pyrrolidine (pK_{HB} = 2.59) and *N*-methylpyrrolidine (pK_{HB} = 2.19). This inversion comes from steric and electronic interactions between the two rings. The pyrrolidine ring increases slightly, by synergetic electronic effects, the Nsp^2 hydrogen-bond basicity of nornicotine (similar effects operate in nicotine) compared to pyridine: the addition of polarizability ($\rho_\alpha\sigma_\alpha$ = +0.07), field-inductive ($\rho_F\sigma_F$ = +0.06), and resonance ($\rho_R\sigma_R$ = +0.07) effects amounts to +0.20 pK unit (1.14 kJ mol^{-1} on the Gibbs energy scale). In contrast, the pyridine ring decreases strongly the Nsp^3 hydrogen-bond basicity of nornicotine compared to pyrrolidine (−1.06 pK unit, 6.1 kJ mol^{-1}) and of nicotine compared to *N*-methylpyrrolidine (−1.15 pK unit, 6.6 kJ mol^{-1}), by the addition of a field-inductive electron-withdrawing effect ($\rho_F\sigma_F$ = −0.73 in nornicotine, −0.62 in nicotine) and the steric effect of the pyridyl group in the ortho position. This effect can be estimated as −0.53 pK unit (i.e., $\rho'_S\sigma_S$, assuming ρ_α small compared to ρ'_S) in nicotine and −0.33 pK in nornicotine. The greater steric effect in nicotine was expected, since tertiary amines are

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TABLE 7. Hydrogen Bonding of Hydrogen Fluoride to the sp² Nitrogen of Pyridines, Nicotine, Nornicotine, and Their Nsp³-Protonated Forms[a]

no.	compd	$-\Delta E_{el}$	$-\Delta H^\circ_{298}$	$-\Delta S^\circ_{298}$	$-\Delta G^\circ_{298}$
1	nicotine	53.73	46.79	121	10.65
1$^+$	Nsp³-protonated nicotine, Cl^-	50.42	43.72	120	7.91
2	nornicotine	54.07	47.22	121	11.21
2$^+$	Nsp³-protonated nornicotine, Cl^-	50.19	43.28	122	6.89
17	3,5-dimethylpyridine	54.19	47.37	119	11.85
18	3-methylpyridine	52.97	46.15	118	10.94
19	pyridine	51.27	44.54	120	8.80
20	3-fluoropyridine	46.36	39.63	120	3.87
21	3-chloropyridine	45.49	38.87	120	3.11
22	3,5-dichloropyridine	40.76	34.26	120	−1.39

[a] Electronic energies, enthalpies (kJ mol^{-1}), entropies (J K^{-1} mol^{-1}), and Gibbs energies (kJ mol^{-1}) of complexation, calculated at the B3LYP/6-31+G(d,p)//B3LYP/6-31G(d,p) level.

well-known to be more sensitive than secondary ones to steric crowding around the nitrogen in hydrogen-bonding complexation.[40,41]

4.4. Calculation of 1:1 Complexation Constants from Hydrogen Fluoride Hydrogen-Bonded Complexes. Today a reliable absolute calculation of the Gibbs energy of complexation of 4-fluorophenol with each site of nicotine and nornicotine, in CCl_4 at 298 K, seems unlikely to be achieved. Therefore, we have lowered the computational difficulty by (i) using hydrogen fluoride as hydrogen-bond donor instead of 4-fluorophenol, (ii) putting the species in the gas phase in place of CCl_4, and (iii) considering only *variations* of Gibbs energies of complexation; thus, we expect the cancellation of model and calculation errors. Then, we have searched for relationships between the experimental Gibbs energies of complexation of 4-fluorophenol in CCl_4, i.e., pK_{HB}, with the series of pyridines **c** and pyrrolidines **a** and **b**, and the corresponding calculated quantities for hydrogen fluoride in the gas phase. The results of our calculations are presented in Table 7 for the pyridine series, nornicotine, nicotine, and their Nsp³-protonated forms. We find a good correlation (eq 34) between pK_{HB} and the Gibbs energy of hydrogen-bonding of hydrogen fluoride to

$$pK_{HB} = -0.100(\pm 0.004)\Delta G^\circ_{298} + 0.97(\pm 0.03) \quad (34)$$

$$n = 6 \quad r^2 = 0.993 \quad s = 0.05$$

pyridines (correlations of similar qualities are found with ΔH°_{298} and ΔE_{el} because of isoentropism and small variation of the thermal and zero-point vibration terms). The pK_{HB} (Nsp²) of neutral nicotine and nornicotine, and of their Nsp³ protonated forms, can then be calculated from their Gibbs energy of complexation with hydrogen fluoride. The results are given in Table 5. They agree satisfactorily with the results of previous methods for neutral forms.

In the pyrrolidine series **a** and **b** we were unable to find satisfactory correlations between pK_{HB} and ΔG° for hydrogen-bonding to hydrogen fluoride, probably because of the greater number of degrees of freedom (and consequent difficulties in the geometry optimization) for the complexes of hydrogen fluoride with the flexible pyrrolidine ring than with the rigid pyridine ring.

4.5. Enthalpic and Entropic Contributions to the Hydrogen-Bonding Selectivity. If we retain the mean of the results (Table 5) of the various methods, we find $K(Nsp^2) = 108$ and 122 L mol^{-1} and $K(Nsp^3) = 13$ and 33 L mol^{-1} for nicotine and nornicotine respectively; i.e., ca. 90% of complexes for nicotine and ca. 80% for nornicotine are formed on the pyridine nitrogen. On the Gibbs energy scale, the fixation of 4-fluorophenol on the pyridine nitrogen is favored relative to fixation on the pyrrolidine nitrogen by 5.25 kJ mol^{-1} for nicotine and 3.24 kJ mol^{-1} for nornicotine. These values correspond to the Gibbs energy of the isomerism of complexation (6) (AH = 4-fluorophenol) of equilibrium constant $K(Nsp^3)/K(Nsp^2)$ (0.12 for nicotine and 0.27 for nornicotine). Is this selectivity driven by enthalpy and/or entropy?

This question can be answered by estimating the complexation enthalpy and entropy of each hydrogen-bonding site, i.e., $\Delta H°(Nsp^3)$, $\Delta H°(Nsp^2)$, $\Delta S°(Nsp^3)$, and $\Delta S°(Nsp^2)$, from the thermodynamic data of model compounds (Table 2) in the following way:

(i) $\Delta H°(Nsp^3)$. Since the field effect of the 3-pyridyl substituent ($\sigma_F = +0.143$) is closely bracketed by those of 3-fluorophenyl (+0.126) and 3-trifluoromethylphenyl (+0.166), and since these groups have quite similar steric and polarizability effects, we have interpolated this enthalpy from the line $\Delta H°$ vs σ_F drawn with the 3-fluorophenyl and 3-trifluoromethylphenyl substituents.

(ii) $\Delta S°(Nsp^2)$. The value of $\Delta S°$ is essentially constant within the family of 3-substituted pyridines, since the standard deviation (1.0 J K^{-1} mol^{-1}) of the mean (44.1 ± 1.0 J K^{-1} mol^{-1}) is within the experimental error (5%). This isoentropic behavior was already noted on a different sample of substituted pyridines complexed with 4-fluorophenol.[38,62]

(iii) $\Delta H°(Nsp^2)$. The logical consequence of isoentropy is that $\Delta G°$ is controlled by $\Delta H°$; thus, $\Delta H°$ is correlated to, and can be calculated from, $pK_{HB}(Nsp^2)$.

(iv) $\Delta S°(Nsp^3)$. The hydrogen bonding of 4-fluorophenol with the three 2-phenyl substituted pyrrolidines (**10**−**12**) shows nearly constant $\Delta S°$ within −53.1 to −56.2 J K^{-1} mol^{-1}, so we can retain their mean (−54.8 J K^{-1} mol^{-1}) for nornicotine. Likewise, on the basis of the similarity of the $\Delta S°$ values for the three 2-phenyl substituted *N*-methylpyrrolidines (**14**−**16**), their mean value of −62.8 J K^{-1} mol^{-1} can be used for nicotine.

The details of the calculations are given in Table 8. These results show that the enthalpy of hydrogen-bonding is nearly the same for the two nitrogens of nicotine and nornicotine and that the selectivity of complexation is entirely controlled by entropy, which disfavors hydrogen-bonding to Nsp³ with respect to Nsp², by 3.19 kJ mol^{-1} in nornicotine and by 5.58 kJ mol^{-1} in nicotine. The greater entropic penalty in nicotine than in nornicotine is probably explained by the steric effect of the *N*-methyl group. This effect is clearly enhanced in 2-aromatic substituted-*N*-methylpyrrolidines compared to the demethylated compounds (compare in Table 2 the insignificant difference $\Delta S°_9$- $\Delta S°_{13}$ to the significant $\Delta S°_{10to12}$- $\Delta S°_{14to16}$), as expected for steric effects which are well-known to be nonadditive.[72]

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TABLE 8. Nicotine and Nornicotine Complexes with 4-Fluorophenol in CCl_4 at 298 K: Partition of the Gibbs Energy (kJ mol^{-1}) of Isomerism of Complexation, OH···Nsp^2 ⇌ OH···Nsp^3, into Enthalpic (kJ mol^{-1}) and Entropic (J K^{-1} mol^{-1}) Contributions

reaction	from the partition of the total constant: K	from the partition of the total constant: pK_{HB}	from the partition of the total constant: ΔG°_{298}	from models: ΔH°	from models: ΔS°_{298}	from models: $-T\Delta S^\circ_{298}$
			Nicotine			
OH + Nic. ⇌ OH ··· Nsp^3	13[a]	1.11		−30.20[b]	−62.8[c]	
OH + Nic. ⇌ OH ··· Nsp^2	108[a]	2.03		−30.52[d]	−44.1[e]	
OH ··· Nsp^2 ⇌ OH ··· Nsp^3	0.12		+5.25[f]	+0.32	−18.7	+5.58
			Nornicotine			
OH + Nor. ⇌ OH ··· Nsp^3	33[a]	1.52		−30.85[g]	−54.8[h]	
OH + Nor. ⇌ OH ··· Nsp^2	122[a]	2.09		−30.80[d]	−44.1[e]	
OH ··· Nsp^2 ⇌ OH ··· Nsp^3	0.27		+3.24[f]	−0.05	−10.7	+3.19

[a] L mol^{-1}. Mean values of Table 5. [b] Value interpolated from the line $-\Delta H^\circ = 36.36-42.5\ \sigma_F$ drawn from **15** and **16**. [c] Mean of complexation entropies of **14**−**16**. [d] Calculated from the relation $-\Delta H^\circ = 18.79 + 5.77 pK_{HB}$, $n = 6$ (**17**−**22**), $r^2 = 0.95$, $s = 0.78$. [e] Mean of complexation entropies of the pyridine series **17**−**22**. [f] $\Delta G^\circ_{298} = -RT \ln[K(Nsp^3)/K(Nsp^2)]$. [g] Value interpolated from the line $-\Delta H^\circ = 32.99-15\sigma_F$ drawn from **11** and **12**. [h] Mean of complexation entropies of **10**, **11**, and **12**.

TABLE 9. Complexation of Hydrogen Fluoride with Nicotine and Nornicotine in the Gas Phase (B3LYP/6-31+G(d,p)//B3LYP/6-31G(d,p) Calculations): Partition of the Gibbs Energy (kJ mol^{-1}) of Isomerism of Complexation, FH···Nsp^2 ⇌ FH···Nsp^3, into Electronic, Enthalpic (kJ mol^{-1}), and Entropic (J K^{-1} mol^{-1}) Contributions

compd	ΔE_{el} [a]	ΔH°_{298}	ΔS°_{298}	$-T\Delta S^\circ_{298}$	ΔG°_{298}
nicotine	−1.07	0.61	−23.9	7.13	+7.74
nornicotine	−1.22	0.49	−21.0	6.27	+6.76

[a] Counterpoise correction included.

We have further studied theoretically this isomerism of complexation (6), in the gas phase, with hydrogen fluoride as the hydrogen-bond donor. We expected a cancellation of calculation errors in this isodesmic reaction. Our prediction was justified, since the theoretical results presented in Table 9 confirm those obtained experimentally (Table 8): hydrogen fluoride prefers to be hydrogen-bonded to the pyridine nitrogen and this selectivity is almost entirely controlled by entropy.

4.6. Lipophilicity of Nicotine and Nornicotine. The equilibrium constant P_{ow}, for a solute partitioning between wet octanol and water, is important in correlating biological activities for drug design.[73] Fundamentally, $-RT \ln P_{ow}$ measures the differential of drug-octanol and drug-water interactions on the Gibbs energy scale.[74] Attempts to unravel and quantify the various interactions contributing to the differential between wet octanol and water phases are numerous. They all conclude[33,34,75,76] that the two main terms governing the partitioning are a hydrophobic volume term, and an opposing hydrophilic hydrogen-bond acceptor ability term. We have recently proposed[77] the simple eq 35. In this equation, the first term tries to gather different contributions assumed to be roughly collinear with volume, i.e., the endoergic cavity creation and the exoergic dispersion and induction energies. The molecular volume V for any solute is obtained using McGowan's atomic volumes and the Abraham−McGowan algorithm.[78] The second term corresponds to the effective hydrogen-bond basicity. It sums the basicities of the various hydrogen-bond acceptor sites of the solute. These are measured by the pK_x(HB) scale, which has the same definition as the pK_{HB} scale, but is recalculated in terms of mole fractions instead of molar concentrations (advantages of this change of standard state are explained in ref 77). λ is a family-dependent term which is required for employing the simple pK_{HB} scale to describe a more complex hydrogen bonding with bulk water and octanol.

$$\log P_{ow} = 3.827(0.01V) - 0.988\Sigma\lambda pK_x(HB) + 0.046 \quad (35)$$

Despite the many assumptions and simplifications introduced in this model, eq 35 explains[77] 98.6% of the variance of log P_{ow} in a sample of 266 solutes (about 20% of non-hydrogen-bond acceptors and all the hydrogen-bond acceptors for which both P_{ow} and pK_{HB} have been measured), with a standard deviation of the estimate of 0.20 log unit. Its main weakness lies in the prediction of the lipophilicity of solutes with sterically hindered hydrogen-bond acceptor sites, for which the calculated log P_{ow} are systematically and significantly too high. Table 10 illustrates the application of eq 35 to the octanol−water partition of amines and pyridines ($\lambda = 0.703$)[77] studied here. The differences between experimental and calculated values range from −0.39 to +0.31. The smallest compound and the best hydrogen-bond acceptor, pyrrolidine (**9**), shows the greatest hydrophilicity, while the most voluminous compound, 3,5-dimethylpyridine (**17**), is the most lipophilic.

In the case of nicotine and nornicotine the prediction is less satisfactory, possibly because of the steric effect of the 2-(3-pyridyl) substituent on the Nsp^3 nitrogen. However, eq 36, an explicit writing of (35) for nicotinoids,

$$\log P_{ow} = 3.827(0.01V) - 0.695[pK_x(HB)(Nsp^2) + pK_x(HB)(Nsp^3)] + 0.046 \quad (36)$$

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TABLE 10. Partition of the Octanol−Water Partition Coefficient, P_{ow}, of Nicotine, Nornicotine, and Model Amines and Pyridines into Volume and Hydrogen-Bonding Terms, According to eq 35

no.	compd	V[a]	vol term[b]	pK_x(HB)[c] Nsp^3	pK_x(HB)[c] Nsp^2	HB term[d] Nsp^3	HB term[d] Nsp^2	log P_{ow}[e] calcd	log P_{ow}[f] expt	Δlog P_{ow} expt − calcd
9	pyrrolidine	66.4	2.541	3.61		−2.507		0.08	0.47	−0.39
13	*N*-methylpyrrolidine	80.4	3.077	3.19		−2.216		0.91	0.92	+0.01
17	3,5-dimethylpyridine	95.7	3.662		3.22		−2.336	1.47	1.78	+0.31
18	3-methylpyridine	91.6	3.506		3.01		−2.091	1.46	1.20	−0.26
19	pyridine	67.5	2.583		2.87		−1.993	0.64	0.65	+0.01
20	3-fluoropyridine	69.3	2.652		2.36		−1.639	1.06	0.77	−0.29
21	3-chloropyridine	79.8	3.054		2.32		−1.611	1.49	1.33	−0.16
1	nicotine	137.1	5.247	2.13	3.05	−1.479	−2.118	1.70	1.17	−0.53
2	nornicotine	123.0	4.707	2.53	3.10	−1.757	−2.153	0.84	0.17	−0.67

[a] In mL mol^{-1}. [b] 3.827(0.01*V*). [c] K_x(HB) = 10.36K_c. [d] −0.988 (0.703pK_x). [e] Equation 36. [f] Reference 77.

remains useful in this important series. It shows that even if only 10% of 4-fluorophenol is hydrogen-bonded to the pyrrolidine nitrogen of nicotine in CCl_4, this hydrogen-bonding site contributes to 41% to the hydrogen-bonding term of the octanol−water partition. This behavior appears as a leveling effect of hydroxylic solvents on the relative hydrogen-bond basicities of various sites of polyfunctional molecules. Equation 36 also expresses, at least semiquantitatively, the three main factors controlling the lipophilicity of nicotinic ligands: their volume, the hydrogen-bond basicity of their pyridine nitrogen, and the hydrogen-bond basicity of their amino nitrogen. The consequences on lipophilicity of structural modulations of the lead compound, nicotine, can now be understood and semiquantitatively predicted.

4.7 Molecular Recognition of Nicotine. The existence of two active hydrogen-bond acceptor sites in nicotine means that, in nonprotonating media, the molecular recognition of nicotine can be made through two hydrogen bonds. Such a recognition was evidenced[79] between nicotine and the diol $HO(Ph)_2C-C\equiv C-C\equiv C-C(Ph)_2OH$. In the 2:2 solid complex,[79] two molecules of diol are linked to two molecules of nicotine through four hydrogen bonds: two OH···Nsp^2 and two OH···Nsp^3. The hydrogen bonds to the Nsp^3 nitrogen are found longer [d(Nsp^3···O) = 2.88 Å], i.e. weaker, than the ones on the Nsp^2 nitrogen [d(Nsp^2···O) = 2.80 Å]. The weaker hydrogen bond to the Nsp^3 nitrogen can again be explained by steric effects which are greater around Nsp^3 than around Nsp^2 and are here revealed by the fixation of a sterically hindered tertiary hydroxyl group (Figure 3).

4.8. Hydrogen-Bond Basicity of Monoprotonated Nicotine and Nornicotine. It is the protonated form of nicotine (nornicotine) that interacts with nAChRs, since this is the major form at physiological p*H* (nicotine and nornicotine have pK_a = 8.05 and 9.12, respectively)[65] and that which mimics the quaternary nitrogen of ACh.[17,18] Another similarity between ACh and protonated nicotine (nornicotine) is their ability to form hydrogen bonds with nAChRs, through the carbonyl oxygen for ACh and the pyridine nitrogen for protonated nicotine (nornicotine).[17,18] It therefore seems important to estimate the hydrogen-bond basicity of protonated nicotine (nornicotine) and to compare our result to that of ACh. A preliminary study of acetylcholine chloride, through electrostatic potential calculation around the carbonyl

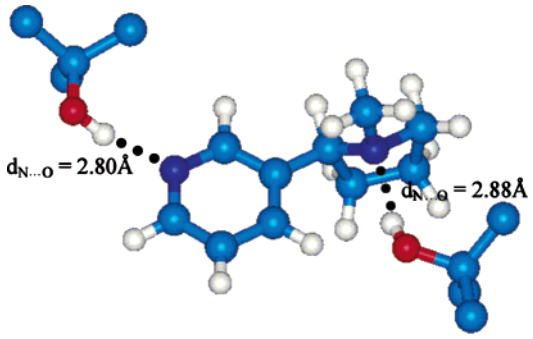

FIGURE 3. Hydrogen bonding to the two nitrogens of nicotine in the 2:2 nicotine−diol complex (truncated).[79]

oxygen ($V_{S,min}$ = −123.6 kJ mol^{-1} at B3LYP/6-31+G(d,p)//B3LYP/6-31G(d,p) level) and the establishment of a correlation between the pK_{HB} scale of esters[80] and their carbonyl oxygen $V_{S,min}$ (n = 4, r^2 = 0.950, s = 0.11) gives a calculated pK_{HB} = 0.18 for acetylcholine chloride, i.e., K_c = 1.5 L mol^{-1}, for the hydrogen-bond fixation of 4-fluorophenol to the neurotransmitter.

The K_c values, calculated for nicotinium and nornicotinium chloride from their Nsp^2 electrostatic potentials (Table 4) and eq 26, are 18 and 17 L mol^{-1}, respectively. Those calculated from their HF complexes (Table 7) and eq 34 are significantly greater (57 and 45 L mol^{-1}, respectively). A third estimate of the pK_{HB} value of nicotinium (nornicotinium) chloride can be made from the second ionization constant of nicotine (nornicotine) in water. Although there is no general relationship between the pK_{HB} and pK_a scales,[39,81] nevertheless, local relationships can be found in series of closely related bases.[39] Such is the case for the series of 3-substituted pyridines, which obey eq 37. From this correlation, shown in Figure

$$\text{p}K_{HB}(\text{3-substituted pyridines}) = 0.237(\pm 0.007)\text{p}K_a + 0.66(\pm 0.03) \quad (37)$$

$$n = 6\ (\mathbf{17}-\mathbf{22}) \quad r^2 = 0.996 \quad s = 0.03$$

4, and the second ionization constant of nornicotine (pK_a = 3.50),[65] we calculate pK_{HB} = 1.49, i.e. K_c = 31 L mol^{-1}. For nicotine, several pK_a values, ranging from 2.87 to

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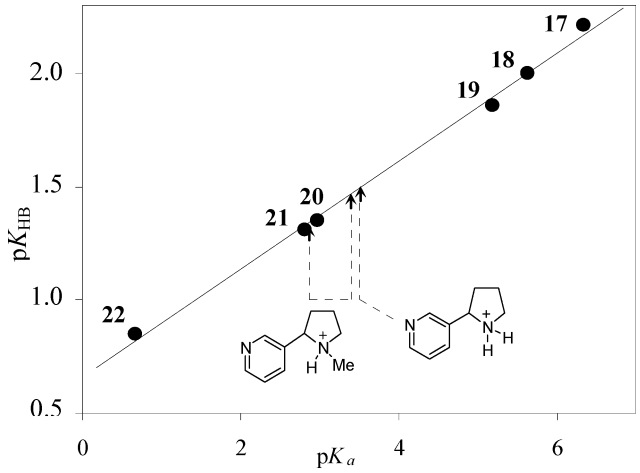

FIGURE 4. Correlation between the hydrogen-bond basicity scale pK_{HB} and the proton basicity scale pK_a of 3-substituted pyridines (**17**−**22**). If charged nicotine (nornicotine) obeys the relationship of neutral pyridines, the pK_{HB} can be interpolated from the second ionization constant.

TABLE 11. Complexation Constants K_c (L mol^{-1}) for Hydrogen Bonding of 4-Fluorophenol to the Pyridine Nitrogen of Nicotinium and Nornicotinium Chloride, Estimated from Various Methods

method	Nic$^+$ Cl$^-$	Nornic$^+$ Cl$^-$
electrostatic potentials	18	17
hydrogen fluoride complexes	57	45
second ionization constant	22−30	31

3.41, are found in the literature.[64,65,82] They give pK_{HB} values between 1.34 and 1.47, i.e., K_c = 22−30 L mol^{-1}.

The complexation constants obtained by the three methods are gathered in Table 11. The discrepancies found are not entirely unexpected, since all three methods include charged (unipolar) substituents in correlations established with neutral (dipolar) ones. It is well-known in correlation analysis of chemical data that charged substituents do not affect the reactivity in different reactions in a regular manner.[83,84] The main reason for this is the dependence on solvent and distance to the reaction center, which differs from the dependence for neutral substituents.[50] Another reason, which might explain the surprisingly high results of the second method, comes from the strong polarization of the C_2−H pyridine bond by the positive charge of nitrogen in the (nor)nicotinium chloride ion pair: while the electrostatic potential on this hydrogen is about + 50 kJ mol^{-1} in neutral (nor)nicotine, it rises to + 130 kJ mol^{-1} in (nor)-nicotinium chloride. As a consequence, a secondary hydrogen bond C_2−H···F (length 2.45 Å, significantly shorter than the sum of van der Waals radii, 2.57 Å) is established in the complex of HF with (nor)nicotinium chloride (Figure 5). This gives a stabilization of the HF complex peculiar to (nor)nicotinium chloride in the series of HF complexes with 3-substituted pyridines.

However, the comparison of the data in Tables 5 and 11, and the comparison of ACh (K_c = 1.5 L mol^{-1}) to the

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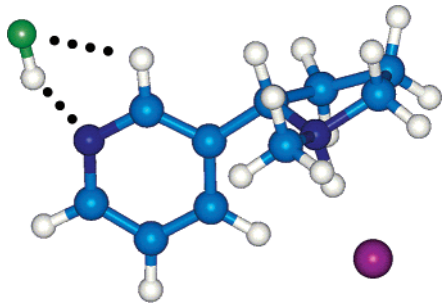

FIGURE 5. B3LYP/6-31G(d,p) geometry of the hydrogen-bonded complex of hydrogen fluoride with nicotinium chloride showing the main FH···N hydrogen bond (1.72 Å) and the C_2−H···F secondary hydrogen bond (2.45 Å).

data in Table 11, allows two conclusions to be drawn on the hydrogen-bond acceptor properties of neutral and charged (nor)nicotine and ACh (toward a phenol). First, the Gibbs energy of hydrogen-bonding complexation is reduced by at least 1.6 (2.5) and at most 4.4 (4.9) kJ mol^{-1} in going from neutral to protonated nicotine (nornicotine). This was expected from the strong electron-withdrawing effect of positively charged substituents.[50] Second, ACh is a worse hydrogen-bond acceptor than nicotine (nornicotine) as chloride salt by 6 to 9 kJ mol^{-1} on the Gibbs energy scale. If ACh and nicotine bind to the same hydrogen-bond donor of the receptor, the hydrogen-bonding contribution to the binding to nAChRs will therefore be greater for nicotine than ACh.

Conclusions

(a) A number of reliable thermodynamic parameters of hydrogen bonding have been measured for substructures of nicotinic ligands: 3-substituted pyridines, 2-substituted pyrrolidines, and *N*-methylpyrrolidines.

(b) We have proposed various experimental and theoretical methods for calculating the hydrogen-bond basicity of each site of polybasic molecules. These methods will be useful in hydrogen-bonding studies on nAChR ligands, which contain a basic amino nitrogen, and a second hydrogen-bond acceptor site (oxygen as in cytisine or Nsp^2 as in nicotinoids).

(c) We have shown that neutral nicotine and nornicotine have two active hydrogen-bond acceptor sites, the pyridine and the pyrrolidine nitrogens, and that ca. 90%, for nicotine, and ca. 80%, for nornicotine, of the 1:1 hydrogen-bonded complexes with a phenol, are formed to the pyridine nitrogen. This result is the reverse of the aqueous proton basicity order, according to which the pyrrolidine nitrogen is the first protonation site. Accordingly the hydrogen-bonding contribution to the binding of ligands to nAChRs must not be interpreted in terms of the pK_a scale, but of hydrogen-bonding basicity scales, such as the pK_{HB} scale.

(d) The low hydrogen-bond basicity of the pyrrolidine nitrogen in nicotine and nornicotine is mainly explained by the electron-withdrawing field-inductive and steric effects of the 2-(3-pyridyl) substituent. In nicotine, this steric effect is reinforced by the methyl group.

(e) The selectivity in favor of the pyridine nitrogen is controlled by the entropy, and more importantly in nicotine than in nornicotine. While the enthalpies of

hydrogen bonding with a phenol are about the same for the two nitrogens of nicotine (nornicotine), ca. −30.5 kJ mol^{-1}, the entropies are more negative, by ca. 19 (in nicotine) and ca. 11 (in nornicotine) J mol^{-1} K^{-1}, for hydrogen bonding to the pyrrolidine than to the pyridine nitrogen. These experimental results are confirmed by ab initio calculations on hydrogen-bonded complexes of nicotine and nornicotine with HF.

(f) A leveling effect of hydrogen-bond basicity in hydroxylic solvents explains the importance, for the octanol−water partition, of secondary hydrogen-bond acceptor sites, as in nicotine and nornicotine. In the same way, even the secondary hydrogen-bond acceptor site is important for the molecular recognition of nicotine by a diol.

(g) The form of nicotine (nornicotine) which binds to nAChRs (that protonated on the sp^3 nitrogen) is a worse hydrogen-bond acceptor than neutral nicotine (nornicotine). Nevertheless this form remains a significantly stronger base in hydrogen bonding than acetylcholine.

Chemists have now at hand a set of methods for studying the hydrogen-bond properties of nAChR ligands and a set of thermodynamic data on nicotine and nornicotine for understanding and modulating (i) their lipophilicity and (ii) the hydrogen-bond contribution to their binding to receptors.

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Supporting Information Available: Cartesian coordinates of the monomers and hydrogen-bonded complexes optimized at the B3LYP/6-31G(d,p) level. Electronic energies at the B3LYP/6-31+G(d,p) level are specified. This material is available free of charge via the Internet at http://pubs.acs.org.

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