Multiple Hydrogen-Bond Accepting Capacities of Polybasic Molecules: The Case of Cotinine

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Received: July 16, 2004; In Final Form: August 30, 2004

The hydrogen-bond (HB) basicities of the carbonyl oxygen and pyridine nitrogen of the cotinine molecule, a long-lived metabolite of nicotine, have been measured in carbon tetrachloride and estimated in water. For the first time, the equilibrium constants of two coexisting 1:1 associations of a phenol on the basic centers of a bifunctional compound have been measured individually. The sum of these individual equilibrium constants closely corresponds to the global experimental constant obtained by the classical IR method based on the measurement of the free phenol OH absorption intensity. The solvation of the cotinine amide group has been examined in various mixed acetonitrile−water solutions revealing the presence of di- and tri-hydrogen-bonded carbonyl groups in pure water. Independently, the accepting strengths of the two sites of cotinine have been calculated from linear correlations between the pK_{HB} scale and the electronic energy of the reaction of hydrogen fluoride complexation on substituted pyridines and carbonyl model compounds using density functional theory calculations at the B3LYP/6-31+G** level. The agreement between the calculated and the experimental individual equilibrium constants of cotinine is well inside the experimental error. The knowledge of the individual acceptor strengths of cotinine in carbon tetrachloride enables the calculation of the octanol−water partition coefficient, this estimation exactly fits the experimental data. Contrary to the order of basicity measured by the pK_a scale, the HB basicity of the carbonyl group appears to be 1.6 pK units greater than the HB basicity of the pyridine moiety in water.

I. Introduction

The importance of the hydrogen bond (HB) in physicochemical and biological processes has long been recognized,[1−3] and a great wealth of thermodynamic and spectroscopic data has been collected for very diverse donor−acceptor couples.[4] Using *p*-fluorophenol (pFP) as a standard donor, Taft[5] and Arnett[6] defined in 1969−70 the first reference scale of hydrogen-bonding basicity, noted pK_{HB}. In the last 15 years, Berthelot and Laurence have further extended this scale to more than a thousand diversified bases[7] and pointed out its fundamental differences with the pK_a scale of aqueous protonation. Most of the thermodynamic data collected to date refers to the formation of simple HB dimers where the acceptor and the donor are monofunctional solutes. Furthermore, the number of analyses devoted to the association of monoacidic donors on polybasic compounds, the most common biologically active molecules, is very limited. To our knowledge, even in the simplest situation of an association between a phenol and a dibasic compound (O <> N) diluted in an apolar solvent, the independent evaluation of the HB interaction strengths of the two individual centers has never been carried out experimentally. The reason is that the IR,[6] UV,[8] or NMR[9] signal generally monitored for the evaluation of the association equilibrium constant is the donor intensity or the donor frequency shift, the variations of which yield the sum of the concentrations C_O and C_N of the two 1:1 complexes (eqs 1−3). Thus, in optimal experimental conditions, the only accessible value is the total equilibrium constant K_t, corresponding to the sum of the two individual

$$\mathrm{AH + O <> N} \leftrightarrows \mathrm{AH\cdots O <> N} \qquad K_O \tag{1}$$

$$\mathrm{AH + O <> N} \leftrightarrows \mathrm{O <> N\cdots HA} \qquad K_N \tag{2}$$

$$K_t = \frac{[\mathrm{AH\cdots O <> N}] + [\mathrm{O <> N\cdots HA}]}{[\mathrm{AH}][\mathrm{O <> N}]} = \frac{C_O + C_N}{C_a C_b} = K_O + K_N \tag{3}$$

constants K_O and K_N. Because the free energies of the associations involve the logarithms of the individual constants, log K_O and log K_N, they cannot be algebraically calculated from K_t. Consequently, the equilibrium constant measured in the usual way is totally deprived of any thermodynamical interest. Moreover, when the HB basicity data of weak and very weak bases such as nitro,[10] pi,[11] and halogen[12] bases became available, it became evident that some substituted representatives of general families of bases (pyridines, amines, ketones, etc.) should be carefully reexamined as possible polybasic solutes. This gives the scale of HB basicity, ranging on about 7 pK units, a very specific character that contrasts to the more extended pK_a scale where the large differences between the pK_a values of the different families of bases drastically limit the emergence of simultaneous protonation during a titration. For the pK_{HB} scale, it is therefore necessary to finalize dedicated techniques,

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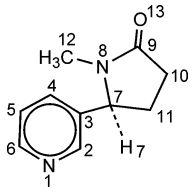
10.1021/jp046836w CCC: $27.50
Published on Web 11/06/2004

permitting the revelation of the polyfunctionality and the estimation of individual constants.

The molecule of cotinine **1**, a long-lived primary metabolite of nicotine, is an efficient cytoprotective agent of specific neuronal cells and is suspected to play a potential role in different aspects of ongoing behavior and cognitive functions despite its low affinity for the specific $\alpha_4\beta_2$ subtype of brain nicotinic acetylcholine receptors (nAChRs). Indeed, the nicotine-like pharmacological activities of cotinine are not fully understood, and this molecule is still the focus of active research in pharmaceutical science.[13] In contrast to most nAChRs ligands, it is not protonated at physiological pH so that it retains, in vivo, its two potential and well-characterized acceptor sites of hydrogen bonding, an amide carbonyl group and a pyridine nitrogen.



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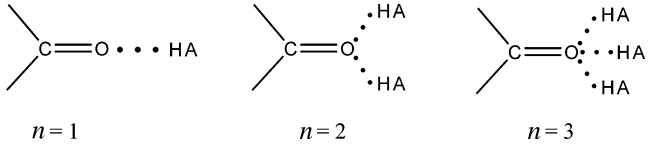
In this study, we present the direct experimental determination of the individual equilibrium constants of the association of pFP on the pyridine and carbonyl sites of cotinine in carbon tetrachloride. This splitting of the apparent equilibrium constant into its different components is a crucial step for the evaluation of the HB basicity in pure hydroxylic solvents because it has been shown that in these media, where the solute is completely surrounded by HB donor molecules, even the weakest basic secondary sites may contribute significantly to the solute−solvent interaction energy through specific hydrogen bonds, although their association equilibrium constants are found to be negligible when the acceptor and the donor are diluted in an apolar solvent.[14] For evident reasons, direct thermodynamic measurements of local HB complexes can hardly be carried out in donor solvents, for instance, in water, the relevant solvent for biochemical processes; yet, the necessity for the rigorous evaluation of a comprehensive parameter encoding all of the information related to the basicity of a multifunctional solute surrounded by a great excess of donor molecules has repeatedly been pointed out.[15−17] In a recent article, our group has shown that the octanol−water partition coefficient of a solute may reveal its HB polyfunctionality and that the partition coefficient can be calculated with precision when the exact contributions of all sites are known.[14] In this work, we will estimate the HB parameters of the two sites of cotinine relevant to the situation in which the solute is surrounded by water and we will compare the calculated partition coefficient with the experimental one.

One of the HB acceptor sites of cotinine is a carbonyl group. This organic functionality is known to accept several HB and coordination numbers, *n*, depending on the reactant conditions, CO basicity, steric (un)hindrance around the lone pairs, and steric effects of the HB donor. The coordination number *n* can therefore vary from 1 to 3; with *n* values of 1 and 2 being well known both in solution and in the solid state, whereas the triple HB acceptor property of a CO group has, to our knowledge, been observed in both environments only in the case of progesterone.[18] The successive steps of coordination of the carbonyl group by water molecules can be followed by infrared spectroscopy on mixed water/aprotic solvents because its vibration gives discrete absorptions corresponding to the different solvates.[19,20] We have thus carried out an analysis of the carbonyl absorptions of the cotinine solute dissolved in water/acetonitrile solutions with increasing amounts of water and identified its coordination number in pure water.



$n = 1$ $n = 2$ $n = 3$

To investigate the relations between the structure and HB properties of cotinine, we completed this experimental study by density functional calculations at the B3LYP/6-31+G** level. In nicotine-like molecules, the main sources of conformational uncertainties are (i) the syn or anti orientation of the *N*-methyl group relative to the pyridine ring, (ii) the relative orientation of the pyridine and pyrrolidine rings generally described through the H7−C7−C3−C2 dihedral angle, and (iii) the conformation of the pyrrolidine ring. We have, therefore, analyzed the conformational preferences of cotinine and compared the structures of the theoretical minima to the geometrical features obtained (i) in solution from the experimental dipole moment and (ii) in the solid state through the Cambridge Structural Database (CSD). We then independently estimated the hydrogen-bonding properties of the two HB acceptors of cotinine from linear Gibbs energy relationships between the experimental Gibbs energy of the *p*-fluorophenol complexation ΔG^0_{298} measured in CCl_4 and the calculated density functional ΔG^0_{298} of hydrogen fluoride complexation in vacuo.

II. Experimental Methods

Chemicals. (−)-Cotinine (Lancaster, 98%) was sublimed and kept over P_2O_5; its purity was checked by thin-layer chromatography and IR spectroscopy. The solvents were of spectroscopic grade and were kept several days over freshly activated 4-Å molecular sieves before use. *p*-Fluorophenol was sublimed over P_2O_5. Deuterium oxide (Aldrich, 99.9%) was used without further treatment.

Dipole Moments. The dielectric permittivities have been measured in tetrachloroethylene on a WTW dipolemeter DM 01 working at a frequency of 2 MHz. The DFL1 cell used in this work enables high precision dielectric measurements ($\Delta\epsilon/\epsilon = 10^{-5}$) in the permittivity range of 1 to 3.4. It was calibrated with cyclohexane ($\epsilon = 2.0228$), carbon tetrachloride ($\epsilon = 2.2326$), and benzene ($\epsilon = 2.2825$) at a temperature of 20 °C. The refractive indexes were obtained with an uncertainty of 2×10^{-5} on a Schmidt Haensch refractometer DNR-W2 thermostated at 20 °C. The dielectric constant and the refractive index measurements were carried out on three solutions of weight fractions $5.90\ 10^{-4}$, $2.66\ 10^{-4}$, and $1.32\ 10^{-4}$ and on the pure solvent.

FTIR Spectrometry. The IR spectra were recorded with a Fourier transform spectrometer Bruker Tensor 27 at a resolution of 1 cm^{-1} with 60 accumulations. An infrasil quartz cell of 1 cm was used for the K_{app} determinations on the *p*-fluorophenol OH absorption at 3614 cm^{-1}. The equilibrium constants on the carbonyl band at 1707 cm^{-1} and on the pyridine ring absorption ν_1 at 1026 cm^{-1} were carried out with KBr cell of 0.9-mm path length. The total equilibrium constant K_t was measured on the same sample for comparison with K_{app}. A CaF_2 cell of 0.1-mm thickness was used for the analysis of the carbonyl solvation in acetonitrile−water mixtures. The cells were thermostated at 25.0 ± 0.5 °C with a circulation bath or a Peltier-effect regulation.

All reference and sample cell temperatures were checked with a thermocouple just before scanning.

III. Computational Methods

All of the calculations were performed at the B3LYP/6-31+G** level using the Gaussian 98 package[21] supported on the IDRIS, CINES, and CCIPL supercomputers.

Conformational Profile. *Geometries.* HB features are clearly dependent on the geometries of the molecules involved. A preliminary investigation of the conformational preferences of the various compounds studied appears, therefore, as a prerequisite to analyze the HB properties of the most stable structures. Species (19 total) corresponding to cotinine, 11 to pyridine, and 7 to carbonyl model compounds were, respectively, considered in this work. A systematic conformational search around the C3−C7 bond of cotinine has been performed by using a step of 15°. For all of the compounds, frequency calculations were performed on the optimized geometries to ensure that they corresponded to true minima. The structural features of the cotinine minima were then compared to similar systems through a search in the 5.25 version (November 2003) of the Cambridge Structural Database (CSD).[22]

Hydrogen-Bonded Complexes of Hydrogen Fluoride. The geometries of both monomers and HB complexes have been fully optimized at the above level of theory. All stationary points were confirmed as true minima via vibrational frequency calculations. Hydrogen fluoride (HF) was selected as the simplest HB donor, allowing the lowest computational cost since Lamarche and Platts[23] recently found good linear relationships between the pK_{HB} values of approximately 65 different bases and the HB Gibbs free energies of hydrogen fluoride complexation computed at the B3LYP/6-31+G** level. In the initial geometries of complexes of the various HB acceptors (denoted B) investigated, substituted pyridines, amides and cotinine, the HF molecule was placed in the direction of the lone pair(s) of the acceptor. The interaction energies were computed as the difference between the energy of the HB complex and the sum of the monomers energies. The electronic energy ΔE_{el}, the enthalpy ΔH^0_{298}, and the Gibbs free energy of complexation ΔG^0_{298} were, respectively, computed from eqs 4−6. The enthalpy includes the zero-point vibrational energies ΔE_{ZPVE}, the thermal energies, which comprise the effects of molecular

$$\Delta E_{el} = E_{el}(B\cdots HF) - [E_{el}(B) + E_{el}(HF)] \quad (4)$$

$$\Delta H^0_{298} = \Delta E_{el} + \Delta E_{ZPVE} + \Delta E_{tr} + \Delta E_{rot} + \Delta E_{vib,therm} - RT \quad (5)$$

$$\Delta G^0_{298} = \Delta H^0_{298} - T\Delta S^0_{298} \quad (6)$$

translation ΔE_{tr}, rotation ΔE_{rot}, and vibration $\Delta E_{vib,therm}$ at 298.15 K and 1 bar, and the ΔPV correction (equal to $-RT$ in the usual assumption of ideal gas behavior). All of the thermal energies and entropy terms were calculated within the harmonic approximation. The basis set superposition error (BSSE) was not accounted for because it is expected to be quasi-constant inside the two homogeneous families of pyridines and carbonyl model compounds, which are considered separately in this study.

IV. Experimental Results

IV. A. Dipole Moments. The experimental dipole moment was calculated with the Guggenheim−Smith[24,25] equation (eq 7) using the slopes of the linear variations $a(\epsilon)$ and $a(n^2)$ of the dielectric permittivity and of the square of the refractive index of the solution with the weight fraction of the solute.

$$\frac{\mu^2}{D^2} = \frac{27kT}{4\pi N}10^{-38}\frac{M_2}{d_1}\left[\frac{a(\epsilon) - a(n^2)}{(\epsilon_1 + 2)^2}\right] = 0.144\frac{M_2}{d_1}\left[\frac{a(\epsilon) - a(n^2)}{(\epsilon_1 + 2)^2}\right] \quad (7)$$

In this equation, k is the Boltzman constant, N is Avogadro's number, M_2 is the molar mass of the solute, and d_1 and ϵ_1 are, respectively, the measured density and dielectric permittivity of the solvent. The experimental slopes, $a(\epsilon) = 14.87$ and $a(n^2) = 0.74$, yield a value of 3.48 D (1 D = 3.336 10^{-30} C m) for the cotinine dipole moment in C_2Cl_4.

IV. B. Total and Individual Equilibrium Constants. *Measurement of K_t from the Free OH Absorption of pFP.* The widespread IR method of measuring the hydrogen-bond association equilibrium constant K (eq 8) is based on the determination of a unique unknown variable, the equilibrium concentration C_a of the donor AH. This concentration is easily determined from the intensity of the AH vibration, provided that a preliminary calibration is done with the free donor alone in the solvent. The other equilibrium concentrations of complex C_c and of base C_b are then deduced from the initial concentrations of the weighted acid and base C^0_a and C^0_b (eq 9).

$$AH + B \rightleftarrows AH\cdots B \quad (8)$$

$$K = \frac{C_c}{C_a C_b} = \frac{C^0_a - C_a}{C_a(C^0_b - C^0_a + C_a)} \quad (9)$$

This method has been successfully used for thousands of bases with various OH, NH, SH, CH, etc. donors[4] and can yield very accurate equilibrium constants ($\Delta K/K \approx 5-7\%$) when careful attention is paid to the experimental conditions, not only to the purities of the solutes and the solvent and to the temperature calibration but also, more specifically, to the dilutions of the donor and the acceptor and to the concentration ratio between the acceptor and the donor. When the base is polyfunctional and when diluted solutions are used, the absorbance decrease in the free-donor band is regulated by the formation of all 1:1 complexes. For a bifunctional base such as cotinine, equilibria eqs 1 and 2 can be set up. Provided that C_O and C_N are the equilibrium concentrations of the two complexes, the apparent constant K_{app} measured from the absorbance of the donor should be equal to the sum K_t of the two 1:1 equilibrium constants on the two basic centers K_O and K_N (eq 3) in ideal conditions where no side equilibrium exists between the different species in solution. In Table 1, we report the results found for the complex between pFP and cotinine in CCl_4. The initial concentration of donor is kept approximately constant in such a low value that its dimerization is negligible and the ratio r of the acceptor and donor initial concentrations is changed through the cotinine concentration. Clearly, the range of variation of the apparent equilibrium constant ($\Delta K = 55$ dm^3 mol^{-1}) is well outside the experimental error on a constant K_t, and Table 1 shows the regular decrease in the apparent equilibrium constant when the ratio r increases. A rather stable K_{app} value can be obtained only when the acceptor is in significant excess over the donor ($r > 2$). When the relative concentration of the acceptor is low ($r < 1$), the formation of a 2:1 complex (eqs 10 and 11) is no longer negligible with regard to the formation of the two 1:1

TABLE 1: Variation of the Apparent Equilibrium Constant between pFP and Cotinine[a]

solution	C_a^0	C_b^0	r	C_a	K_{app} dm^{3}mol^{-1}
1	5.11	1.01	0.20	4.57	249.5
2	5.07	1.67	0.33	4.21	246.5
3	5.00	3.39	0.68	3.51	224.2
4	4.97	5.08	1.02	2.97	220.3
5	5.01	6.83	1.36	2.58	214.1
6	5.05	8.22	1.63	2.30	217.5
7	4.96	10.09	2.05	2.01	203.3
8	5.02	13.71	2.73	1.63	200.9
9	5.03	14.56	2.89	1.58	196.2
10	4.93	20.64	4.18	1.14	197.0
11	4.86	26.47	5.45	0.91	193.1
12	4.86	34.06	7.00	0.72	193.7

[a] Calculated from the OH absorption of pFP in 1-cm cells. Estimated relative error: ±7%. C_a^0 and C_b^0: initial concentrations of pFP and cotinine; $r = C_a^0/C_b^0$; C_a = equilibrium concentration of pFP (all concentrations are in mmol dm^{-3})

species. The consumption of free donor due to the formation of the 2:1 complex contributes more and more significantly to

$$AH + AH\cdots O <> N \rightleftarrows AH\cdots O <> N\cdots HA \quad (10)$$

$$AH + O <> N\cdots HA \rightleftarrows AH\cdots O <> N\cdots HA \quad (11)$$

the absorbance decrease in the free OH band when the r values get smaller, giving increasingly overestimated K_t values. At the other extreme, larger concentrations of the polar acceptor gradually enhance the solvent permittivity (see above, the variation a(ϵ)), leading to a small but regular decrease in the total equilibrium constant.[26−28] Thus, the existence of a limiting K_t value that could be obtained by extrapolation toward infinite ratio r does not make sense. Therefore, we will retain for K_t the mean values of all six K values obtained for $r > 2$: K_t = 197.4 dm^3 mol^{-1}, remarking that, in this reasonably large range of complexation of the donor (59−85%) and of the acceptor (12−29%), no experimental value differs by more than 3% from the mean.

Measurement of K_O and K_N. Diverse algebraic equations derived by Clotman et al.[29] and Roland[30] from numerical analysis of equilibria eqs 1, 2, 10 and 11 may yield the individual constants K_O and K_N from the variation of the constant K_{app} with the concentration ratio r. An adaptation of these methods has successfully been used in the case of nicotine,[31] and in this study for the molecule cotinine, the K_{app} variation presented in Table 1 permits the calculation of the values K_O = 157 and K_N = 28 dm^3 mol^{-1} of the association constants on the carbonyl and pyridine sites. Although the sum of these two individual constants compares favorably with the K_t value, the results obtained by this method must be regarded as rough estimates of the individual basicities mainly because the equations are based on several approximations, such as the independence of the two sites (the association on one site does not alter the HB basicity of the second site). Moreover, the two constants K_O and K_N that were obtained in this way cannot be assigned a priori to their respective site of association. We thus turned to the direct determination of the individual association constants in the two basic centers. In the spectrum of cotinine (Figure 1), two characteristic absorptions involving the respective acceptor sites are found to be sensitive to the hydrogen-bond association: the carbonyl stretching, the most intense absorption of the spectrum is red shifted by 26 cm^{-1} by association with pFP, and the ν_1 band of the pyridine moiety corresponding to a breathing cycle deformation[32] is blue shifted by 5 cm^{-1}. In the

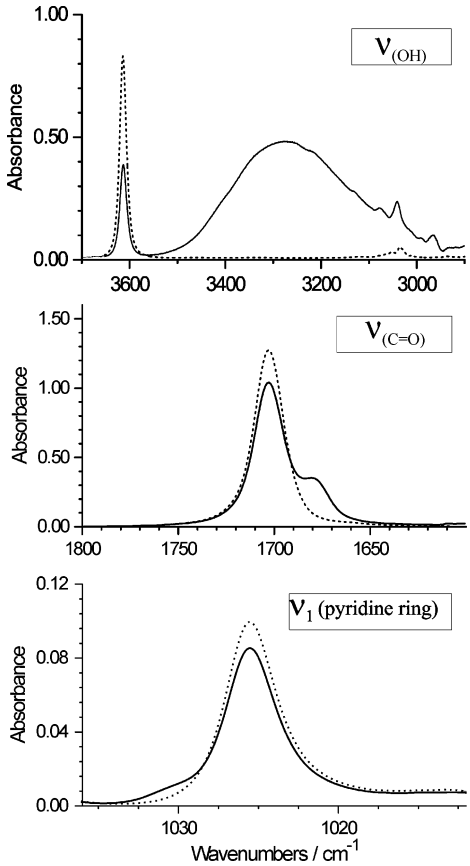


Figure 1. Partial views of the IR spectrum of a mixture of pFP (C_a^0= 4 10^{-3} M) and cotinine (C_b^0 = 1 10^{-2} M). The corresponding spectra of the free donor (acceptor) absorptions are shown for comparison as dashed lines.

TABLE 2: Simultaneous Evaluation of the Total and Individual Equilibrium Constants[a]

spectral characteristic	absorptions		
vibration	OH	C═O	ν1
wavenumber/cm^{-1}	3613.6	1702.9	1025.5
absorption coefficient dm^3 mol^{-1} cm^{-1}	235.5	1072.7	80.5
frequency shift by association	−338	−23.1	+5.3

initial concentrations[b]		equilibrium concentrations[b] and equilibrium constants[c]					
C^0_a	C^0_b	C_c	K_t	C_O	K_O	C_N	K_N
4.99	8.11	2.57	192	1.90	142	0.52	39
4.96	9.88	2.89	199	2.12	146	0.65	45
5.06	13.2	3.37	204	2.42	147	0.68	41

[a] Calculated from the OH, CO and ν_1 absorptions in 0.9-mm cells. Estimated relative errors are K_O: ±7%, K_t: ±15%, and K_N: ±30%; [b] In units of mmol dm^{-3} [c] In units of dm^3 mol^{-1}

spectrum of a mixture of pFP and cotinine, the equilibrium concentration C_a of the free donor directly taken from the intensity of the OH absorption gives the total concentration of the complexes ($C_N + C_O$) and the global equilibrium constant K_t, provided that the acceptor is in excess. In the same way, the decrease in the carbonyl band intensity upon association is proportional to the concentration C_O of the complex formed on the carbonyl oxygen, and the decrease in ν_1 pyridine band intensity gives the concentration of the complex on the pyridine nitrogen. These results are presented in Table 2. Despite the large difference between the absorption coefficients of the ν-(C═O) and ν_1 absorptions, both K_O and K_N determinations are

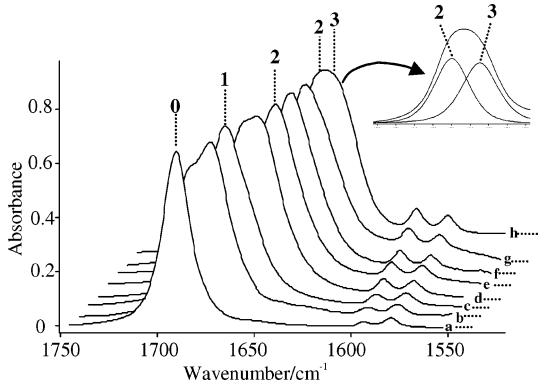


Figure 2. IR spectra ($\nu_{C=O}$) for cotinine in CH_3CN-D_2O mixed solvents. Mole fractions of D_2O (a) 0, (b) 0.13, (c) 0.49, (d) 0.74, (e) 0.90, (f) 0.98, (g) 0.99, and (h)1. Intensities are arranged for clarity; the numbers 0, 1, 2, and 3, respectively, denote the absorptions corresponding to the free, mono-, di-, and trihydrated molecule. The band fitting of the absorption in pure D_2O is shown separately.

found to be reliable because their sum is in excellent agreement with the mean value of K_t selected through independent measurements. Taking the mean values of the three experimental determinations, we found that the individual HB strengths of the two sites are $K_N = 42$ ($pK_{HB} = 1.62$; $\Delta G^0_{298} = -9.2$ kJ mol^{-1}) and $K_O = 145$ ($pK_{HB} = 2.16$; $\Delta G^0_{298} = -12.3$ kJ mol^{-1}).

Polyassociation of Water on the Carbonyl Group. Following the work of Symons and Eaton[19,20] on the solvation of acetone and dimethylacetamide with water and methanol, we carried out the analysis of the solvation state of the cotinine carbonyl group in pure water. To determine the solvation of this HB acceptor site, we followed the progression of the number of water molecules bonded on the carbonyl group by using mixed acetonitrile−heavy water mixed solvents with increasing proportions of heavy water in the full range of 0−100%. Figure 2 represents the key spectra, showing the free band ($n = 0$) at 1690 cm^{-1} and the successive bonding of a first and second molecule of water leading to the appearance of new absorptions at 1676 ($n = 1$) and 1658 cm^{-1} ($n = 2$) when the intensities of the $n - 1$ solvate decrease. These absorptions are gradually red shifted by the nonspecific solvent effect and secondary hydrogen bonds on the water molecules of the first solvation shell. The third hydrogen bond only appears as a shoulder in the last mixtures, where the molar fraction of water is over 98%. In pure heavy water, a fitting of the broad unresolved spectrum yields two bands at 1654 ($n = 2$) and 1641 cm^{-1} ($n = 3$) of nearly identical relative intensities indicating the presence in equal amounts of di and trihydrogen-bonded carbonyl groups.

V. Theoretical Calculations

V. A. Rotational Profile of Cotinine around the C3−C7 Bond. Earlier experimental and theoretical investigations in various physical states of nicotinic ligands (e.g., nicotine and epibatidine) have predicted the existence of two conformers, both of which have the two rings roughly perpendicular to one another.[33−36] In the case of nicotine, these minima, labeled A and B by Elmore and Dougherty, have dihedral angles H7−C7−C3−C2 close to 0 and 180°, respectively.[35] The rotational profile of cotinine calculated from fully optimized structures reported in Figure 3 shows that it adopts the same structural features as nicotine. The A and B conformers have nearly the same energies, the rotational barrier being about 30 kJ mol^{-1}, a height close to those found for other nicotinic ligands (e.g., epibatidine and nicotine) in their neutral form.[34,35]

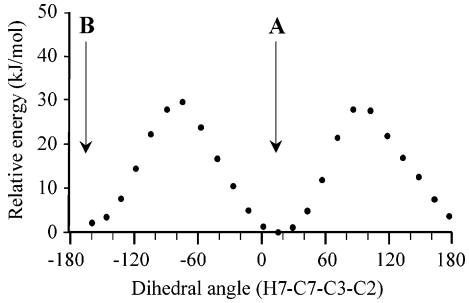


Figure 3. Rotational profile of the cotinine molecule around the C3−C7 bond linking the two cycles.

TABLE 3: Comparison of the Conformational Features (deg) of the Gas-Phase Theoretical Minima of Cotinine and Nicotine with Comparable Molecular Fragments Observed in the CSD

compound or CSD refcode	ϕ_1[a]	ϕ_2[b]	ϕ_3[c]	ϕ_4[d]	ref
cotinine A[e]	12.8	23.2	−6.2	−11.4	this work
cotinine B[e]	167.7	−23.2	6.6	11.2	this work
nicotine A[f]	16.1	−1.8	−42.7	26.4	37
nicotine B[f]	−165.7	−3.0	−43.1	27.3	37
BMPBFP	−178.8	−22.4	8.5	9.3	38
IDAZAO	31.9	26.0	−7.3	−13.0	39
IDAZES	−147.6	21.5	−0.1	−14.3	39
JUHGUO	−166.8	22.6	−0.8	−13.9	40
JUHGUO	18.2	26.1	−5.6	−13.4	40
KOPZEU	37.2	−22.5	−4.3	17.2	41
LUHCAS	−19.9	−28.0	2.0	16.8	42
LUHCEW	−3.9	−14.7	4.0	7.2	42
LUHCEW	−4.2	15.5	−1.9	−9.0	42

[a] ϕ_1= C2−C3−C7−H7. [b] ϕ_2 = C7−C11−C10−C9. [c] ϕ_3=C11−C10−C9−N8. [d] ϕ_4=C10−C9−N8−C7. [e] B3LYP/6-31+G**. [f] B3LYP/6-31G**.

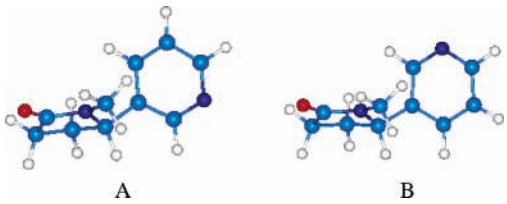


Figure 4. A and B isomers of cotinine.

V. B. Structural Features of the Cotinine Minima. The presence of the lactam moiety in cotinine must induce specific structural features to the two other conformational aspects of nicotinic ligands: (i) the syn or anti orientation of the *N*-methyl group relative to the pyridine ring[36] and (ii) the conformation of the pyrrolidine ring. To investigate more deeply the cotinine conformational features, we searched the CSD for corresponding molecular fragments. Because no cotinine structure was found, we searched substructures containing an *N*-methylpyrrolidinone moiety substituted in position 7 by an aromatic ring. To analyze the various conformational aspects of cotinine in the solid state, we measured four dihedral angles: ϕ_1 (H7−C7−C3−C2), ϕ_2 (C7−C11−C10−C9), ϕ_3 (C11−C10−C9−N8), and ϕ_4 (C10−C9−N8−C7). ϕ_1 describes (vide supra) the relative orientation of the two rings, whereas ϕ_2, ϕ_3, and ϕ_4 are devoted to the description of the five-membered-ring conformation. These parameters are presented in Table 3. We have also included in Table 3 the corresponding values of the two gas-phase minima of nicotine[37] and cotinine.

The 3D structures of the A and B cotinine conformers are depicted in Figure 4. The ϕ_1 values reported in Table 3 show that, in the solid state, the two conformations are observed. This

TABLE 4: Theoretical and Experimental Dipole Moments (D) of Substituted Pyridine and Carbonyl Bases

pyridine models			carbonyl models		
compound	μ_{theor}[a]	μ_{exptl}[b]	compound	μ_{theor}[a]	μ_{exptl}[b]
s-triazine	0.00	0.00	*N*,*N*-dimethylcarbamoyl chloride	4.62	4.08
3,5-dichloropyridine	0.79	0.95	propanone	3.19	2.78
pyrazine	0.00	0.00	*N*,*N*-dimethylformamide	4.30	3.85
pyrimidine	2.48	2.28	*N*,*N*-dimethylacetamide	4.10	3.91
3-chloropyridine	2.18	2.02	1-methyl-2-pyrrolidinone	4.23	4.07
3-fluoropyridine	2.19	2.04	1-methyl-2-pyridone	4.31	4.07
pyridine	2.38	2.20	3-dimethylamino-5,5-dimethyl-2-cyclohexene-1-one	6.41	6.24
3- methylpyridine	2.65	2.40	cotinine		3.48
3,5-dimethylpyridine	2.84	2.54	isomer A	2.23	
4-aminopyridine	4.12	3.94	isomer B	4.99	
4-(dimethylamino)pyridine	4.88	4.32			

[a] B3LYP/6-31+G** [b] Experimental dipole moment in benzene.

is expected because the A conformer is more stable than B by only 2.2 kJ mol^{-1}. Conversely, the structural features of the five-membered ring are very different because the ϕ_2 dihedral angle measured in the structures found in the CSD ranges from -28.0 to $+26.0°$, whereas in nicotine, ϕ_2 is close to 0°. Actually, the pyrrolidinone ring of cotinine adopts an envelope conformation in which the C7 atom (and not the N8 atom) is located out of the plane. In contrast to class C nicotinic ligands, which contain an aromatic moiety with an HB acceptor and a ring carrying a protonable nitrogen, the quasi-planarity of the lactam fragment in cotinine leads to a location of the *N*-methyl group in the envelope plan. This feature is confirmed by the ϕ_3 values, which range from about -7 to 9°, the theoretical ϕ_3 values, respectively, of -6 and $+6$ for the two minima, being in good agreement with these data. The values of ϕ_4 reflect the same tendencies.

V. C. Dipole Moment. Figure 4 shows that the relative orientations of the pyridine and carbonyl dipoles in the A and B conformers are very different. In conformer A, the two vectors cooperate to give a polar molecule ($\mu_A = 4.99$ D), whereas structure B is found to be moderately polar with $\mu_B = 2.23$ D. The value of the experimental dipole moment, μ_{exptl} (C_2Cl_4) = 3.48 D, approximately situated midway between these theoretical values provides a first indication that the two conformers are present in apolar solvents, a result in agreement with the low energy difference found between the two isomers. To get a rough estimation of the conformer populations, it is necessary to calibrate the calculated dipole moments in the gas phase with the experimental values in solution. Unfortunately, experimental data in CCl_4 or C_2Cl_4 are very scarce, and we turned to the dipole moments in benzene solutions[43−45] because the differences between the values in perchlorinated and benzene solvents are generally less than 0.14 D, in our range of 6.20 D. The data presented in Table 4 correspond to these dipole moments measured in benzene. The statistics of regression eq 12 indicate that the DFT calculations can predict the experimental dipole moments in solution with a standard error of 0.14 D, a value in agreement with previous theoretical investigations at a comparable level of theory.[46] From the theoretical dipole moments (Table 4), one can now use eq 12 to calculate the dipole moments of the A and B isomers in benzene ($\mu_{B(calcd)} = 4.72$ D; $\mu_{A(calcd)} = 2.06$ D) as good approximations of their values in perchlorinated solvents. Finally, by using the additivity rule of the molar polarizations,[47] a proportion of 56% was calculated for isomer A.

$$\mu_{exptl}\,(\text{benzene}) = -0.007 + 0.931\mu_{theor} \qquad r^2 = 0.992 \qquad n = 18 \quad s = 0.14 \quad (12)$$

V. D. Hydrogen Fluoride HB Complexes. Table 5 compiles the energetic parameters (ΔE_{el}, ΔH^0_{298} and ΔG^0_{298}) computed for the HB complexation of HF on the carbonyl oxygen and the pyridine nitrogen of cotinine and model compounds together with the experimental Gibbs energies ΔG^0_{298} of *p*-fluorophenol HB complexation deduced from the pK_{HB} values ($\Delta G^0_{298} = -5.71$ pK_{HB}). For carbonyl model compounds, the HB energetics reported correspond to the most stable HB complex found by the calculations. The electronic energy preference relative to the less stable association on the second lone pair ranges from 1.2 kJ mol^{-1}(*N*,*N*-dimethylchloroacetamide) to 6.3 kJ mol^{-1} (*N*,*N*-dimethylacetamide). Note that these data cover a wide HB energetic range in both the pyridine (15 kJ mol^{-1}, 2.5 pK_{HB} units) and the carbonyl (11 kJ mol^{-1}, 2.1 pK_{HB} units) series. Table 5 shows that all of the computed energetic parameters follow the experimental order of HB strengths.

Table 6 compares the correlations obtained between the experimental ΔG^0_{298} and the various theoretical energetic descriptors. In contrast to the analysis of Lamarche and Platts in their recent theoretical investigation on the pK_{HB} scale,[23] we found that for both series of model compounds, the best statistics are obtained with ΔE_{el} and ΔH^0_{298}. Inside the homogeneous series of pyridines, the correlations with these two descriptors are remarkable because their standard estimates of $s = 0.15$ correspond to the magnitude of the error in the experimental determination of ΔG^0_{298}. Surprisingly, when the theoretical free energy is taken to be the descriptor, the predictive power of the correlation is dramatically lower ($s = 0.65$). This discrepancy is attributed to the vibrational component of the entropic terms: the harmonic approximation leads to strong errors in the calculation of low-frequency vibrational modes, which are likely to be the least harmonic in character.[48] In favorable cases, cancellations occur when the entropic terms of the dimer and the monomers are subtracted in the supermolecule approach. However, some substituents may introduce several supplementary low vibrational modes, such as weakly hindered torsions, creating badly compensated errors in the equilibrium entropy. Table 6 also shows that the standard errors of the estimates in the carbonyl series are about five times greater than the experimental error, regardless of the theoretical energetic descriptor used. This loss of precision could be a consequence of the smaller distance between the substituent and the donor molecule (Figure 5), which may induce nonproportional proximity effects such as lone pair−lone pair interactions, steric effects, or secondary hydrogen bonds with hydrogen fluoride or *p*-fluorophenol.

For these reasons, we selected the correlations established with ΔE_{el} to predict the experimental ΔG^0_{298} and, conse-

TABLE 5: Theoretical and Experimental HB Energetics of Cotinine and Model Compounds

	theoretical (HF) kJ mol^{-1}			experimental (pFP) kJ mol^{-1}
compound	$-\Delta E_{el}$	$-\Delta H^0_{298}$	$-\Delta G^0_{298}$	$-\Delta G^0_{298}$ [a]
pyridine models				
s-triazine	45.1	39.0	5.5	1.8
3,5-dichloropyridine	49.5	43.3	9.1	4.6
pyrazine	51.6	45.2	11.1	5.4
pyrimidine	52.6	46.4	12.3	6.0
3-chloropyridine	54.4	48.2	13.8	7.4
3-fluoropyridine	54.9	48.5	14.1	7.7
pyridine	59.9	53.5	18.9	10.6
3-methylpyridine	61.5	55.1	19.9	11.6
3,5-dimethylpyridine	62.8	56.5	22.1	12.4
4-aminopyridine	66.1	60.0	25.6	14.4
4-(dimethylamino)pyridine	68.4	62.2	31.1	15.8
cotinine				
isomer A	58.2	52.0	17.6	
isomer B	57.8	51.4	16.5	
carbonyl models[b]				
N,*N*-dimethylcarbamoyl chloride	38.9	33.1	1.6	5.6
propanone	47.0	40.7	6.1	7.1
N,*N*-dimethylformamide	54.7	47.8	14.2	11.9
N,*N*-dimethylacetamide	58.7	51.8	15.2	13.9
1-methyl-2-pyrrolidinone	58.6	52.0	17.7	14.0
1-methyl-2-pyridone	60.0	53.0	18.0	14.7
3-dimethylamino-5,5-dimethyl-2-cyclohexen-1-one	65.8	59.3	24.7	16.7
cotinine				
isomer A	56.4	49.8	15.2	
isomer B	56.4	49.8	15.3	

[a] $-\Delta G^0_{298} = 5.71\ pK_{HB}$. [b] Only the values of the most stable HB complex are reported.

TABLE 6: Linear Relationships $-\Delta G^0_{298} = aX + b$ between the Experimental Free Energy of Association with *p*-Fluorophenol and the Theoretical Energetic Descriptors X

series	X	*a*	*b*	*n*	r^2	*s*
pyridine	$-\Delta E_{el}$	0.603	−25.46	11	0.999	0.15
	$-\Delta H^0_{298}$	0.603	−21.67	11	0.999	0.15
	$-\Delta G^0_{298}$	0.576	−0.664	11	0.980	0.65
carbonyl	$-\Delta E_{el}$	0.447	−12.46	7	0.973	0.74
	$-\Delta H^0_{298}$	0.458	−10.21	7	0.973	0.73
	$-\Delta G^0_{298}$	0.517	4.710	7	0.969	0.79

quently, the equilibrium constants of *p*-fluorophenol complexation K_O and K_N of cotinine. For the O and N sites of the A and B isomers, the calculated ΔG^0_{298} values of 12.6 and 9.6 kJ mol^{-1} ($K_O = 162$ and $K_N = 49$ dm^3 mol^{-1}) and 12.6 and 9.4 kJ mol^{-1} ($K_O = 162$ and $K_N = 44$ dm^3 mol^{-1}), respectively, appear to be very satisfactory because they give the two sites very similar HB accepting strengths in both isomers, indicating that they are internally independent, a behavior that agrees with the observed infrared spectra. Moreover, the predicted mean individual equilibrium constants calculated from the populations of the two isomers ($K_O = 162$ and $K_N = 47$ dm^3 mol^{-1}) are in complete agreement with the experimental values.

V. E. Substituent Effects in the Pyridine Ring. The electron attracting strength of the 3-pyridyl substituent is now well established,[49] but the lack of data on a family of substituted

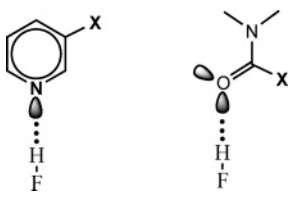


Figure 5. HF associations on substituted pyridines and amides.

N-methylpyrrolidinones or structurally homogeneous compounds does not allow any quantitative prediction of the carbonyl basicity of cotinine from linear free-energy relationships using substituent constants. The situation is more favorable for the pyridine nitrogen because the influence of the field, resonance, and polarizability effects of the substituent, represented, respectively, by the σ_F, σ_R, and σ_α constants have already been precisely quantified in meta-substituted pyridines by the Taft−Topsom[50] equation (eq 13). In this series, the unknown σ parameters of the 5-pyrrolidinonyl substituent may be calculated using the theoretical model of Topsom,[51] which was validated by Exner and Carsky.[52,53] In the cotinine molecule, the HB basicity decrease in the pyridine nitrogen is found to be mainly

$$pK_{HB}\ (\text{meta-substituted pyridines}) = 1.86 - 0.10\sigma_\alpha - 1.79\sigma_F - 1.14\,\sigma_R \quad (13)$$

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

due to the medium electron attracting field effect of the pyrrolidinone moiety ($\sigma_F = 0.165$, $\Delta pK_{HB} = -0.30$), which is partially attenuated by the small opposing resonance ($\sigma_R = -0.05$, $\Delta pK_{HB} = 0.06$) and polarizability ($\sigma_\alpha = -0.85$, $\Delta pK_{HB} = 0.09$) effects. The equation yields a pK_{HB} value of 1.70 so that the equilibrium constant of the pyridine site $K_N = 50$ is not only correctly estimated but also explained by the dominating electron withdrawing field effect of the carbonyl group.

The comparison of the different values obtained by the experiment and the theoretical calculations (Table 7) indicates that the theoretical results obtained by modeling the association equilibrium by using HF as the donor in place of pFP and the gas-phase instead of CCl_4 yield very consistent results. However, the differences in the slopes and intercepts presented in Table 6 show that the relationship between the experimental and theoretical basicity scales is family dependent so that a new calibration equation is necessary whenever a new type of accepting site is studied.

TABLE 7: Independent Measurements and Calculations of the Basicities of the Cotinine Molecule

	experimental	theoretical			
		HF complexes[a]			substituent effects[b]
		A	B	C[c]	
K_N	42 ± 12	48 ± 3	44 ± 3	46 ± 3	50 ± 3
K_O	145 ± 10	162 ± 50	162 ± 50	162 ± 50	-
K_i[c]	197 ± 14[d]				

[a] Equilibrium constants and errors calculated from electronic energies given in Table 5 and corresponding relationships of Table 6. [b] Equilibrium constant and error calculated from eq 13. [c] Mean equilibrium constants calculated from the populations of two conformers A and B. [d] Calculated from measurements on the OH vibration in 1-cm cells (see text).

In Figure 6 are represented the mutual deactivations of the carbonyl and pyridine basicities in the cotinine molecule by comparison with the parent compounds 1-methylpyrrolidinone and pyridine. Because these deactivations are equivalent and relatively moderate, both sites keep significant basicities in the molecule of cotinine where the carbonyl group is 2.7 kJ mol^{-1} more basic than the pyridine nitrogen on the free-energy scale.

VI. Prediction of the Partition Coefficient

The separation of the global HB association constant into two contributions from the pyridine and the carbonyl fragments finds its importance when the molecule is dissolved in hydrogen-bond donor solvents such as chloroform or alcohol and, more importantly, in water. We have shown[14] that, in the absence of steric effects, the bulk basicity of the molecule in these media is precisely evaluated by a new parameter noted as $\Sigma\lambda pK_x(HB)$, where the index x signifies that the pK_{HB} scale is used in mole fraction units and the Σ operator indicates a summation over all basic centers. The multiplicative factor λ is a family-dependent parameter that may have different values depending on the nature of the basic site. As a first approximation, λ can be taken to be 0.70 for the pyridine and amine nitrogen accepting groups, $\lambda = 0.87$ for the ether oxygens, and 1.07 is suitable for not only nearly all polar bases, such as carbonyl, phosphoryl, or nitrile groups, but also π bases. This basicity term, together with the molar volume term measuring approximately all of the nonspecific inductive, dispersive, and polarization interactions, has been found to be the only robust parameter able to change the partitioning of a solute between water and octanol, leading to eq 14.

$$\log P = 0.041 + 3.827\, V_x/100 - 0.988\Sigma\lambda pK_x(HB) \quad (14)$$

$$r^2 = 0.993 \quad n = 266 \quad s = 0.2$$

In this equation, the molar volume $V_x/100$ is a parameter easily calculated from atomic and bond increments[54,55] and $pK_x(HB) = pK_{HB} + 1.01$. For the cotinine molecule, the molar volume is calculated to be 138.7 cm^3 mol^{-1} and the global basicity is obtained via eq 15, where the first term of the summation represents the contribution of the pyridine nitrogen and the second term, the contribution of the pyrrolidinone carbonyl oxygen.

$$\Sigma\lambda pK_x(HB) = 0.70\,(1.62 + 1.01) + 1.07\,(2.16 + 1.01) = 5.23 \quad (15)$$

The value calculated from eq 14 ($\log P_{calc} = 0.18$) nicely matches the experimental value $\log P_{exptl} = 0.07$ determined by Li et al.

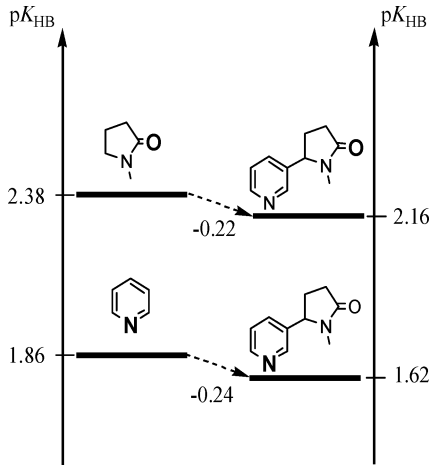


Figure 6. Deactivation of *N*-methylpyrrolidinone and pyridine HB strengths in cotinine.

in neutral pH conditions.[56] Conversely, once the calculated log P is validated by the experiment, the λ values of 0.70 and 1.07 used in eq 15 indicate that, in these solvent conditions, the carbonyl HB basicity of the cotinine molecule is notably reinforced relative to that of the pyridine site by comparison of their accepting strengths in apolar solvents. The formation of multiple associations with the small water molecule (see above) may be one of the main factors contributing to this relative strengthening of the oxygen accepting group.

VII. Concluding Remarks

Although the aqueous protonation scale shows a difference of about 6 pK_a units in favor of the basic pyridine nitrogen site (pyridine $pK_a = 5.22$)[57] over the carbonyl group (*N*-methylpyrrolidinone $pK_{BH+} = -0.71$),[58] the cotinine molecule appears to be a bifunctional HB acceptor where the carbonyl group is in all solvents the major site of HB association. The difference in HB basicity is in favor of the carbonyl group by 0.47 pK_{HB} units in tetrachloromethane, where two 1:1 complexes coexist in dilute conditions. Supplementary specific associations occur on the carbonyl group when the solute is surrounded by a great excess of donor solvent. In biological media, the carbonyl group is found to be more basic than the pyridine group by 1.6 pK units ($\Delta G^0_{298} = 9.1$ kJ mol^{-1}). If the transport properties toward a biological target and the binding to a receptor are principally due to multiple hydrogen-bonding interactions, then they must be interpreted exclusively in terms of the pK_{HB} scale after identification and quantification of all of the basic sites.

Acknowledgment. We thank Petr Nauš (Charles University, Praha, Czech Republic) for the calculation of the polarizability parameter of the 5-pyrrolidinonyl substituent. We gratefully acknowledge the IDRIS (Institut du Développement et des Ressources en Informatique), the CINES (Centre Informatique National de l'Enseignement Supérieur) and the CCIPL (Centre de Calcul Intensif des Pays de la Loire) for grants of computer time.

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