Conformational analysis. Part 34.[1] An NMR investigation of the conformational equilibrium and intramolecular hydrogen bonding in nipecotic acid derivatives

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The ^{1}H NMR spectra of nipecotic acid (piperidine-3-carboxylic acid), ethyl nipecotate, nipecotamide and some of their *N*-methyl derivatives are reported and analysed. At −80 °C the interconversion between the two chair conformations is so slow that the spectra of the two conformers can be resolved and the conformer populations and free energy differences obtained. The proton couplings found for the individual conformers were used together with the measured couplings at room temperature to obtain the conformer free energy differences for these compounds in a variety of solvents.

The intramolecular hydrogen bonding interaction between the side chain and the ring nitrogen atom in the axial conformation may be obtained from the conformer energy differences. For nipecotic acid in D_2O $\Delta G_{A-E} = 0.41$ kcal mol^{-1}. From these data the hydrogen bond energy between the CO_2^- and NH_2^+ groups in the nipecotic acid zwitterion is obtained as *ca.* 1.7 kcal mol^{-1} in the axial conformer even in the protic solvents methanol and water. The corresponding interactions in the cation and anion are much less (*ca.* 1 kcal mol^{-1}) and also do not show a large solvent effect.

In contrast the H-bond interaction between the neutral species is very solvent dependent. In nipecotamide the $CONH_2 \cdots N$ hydrogen bond energy is >2 kcal mol^{-1} in nonpolar solvents, in which the axial conformer is the major form ($\Delta G_{A-E} = -0.46$ kcal mol^{-1}), but decreases to almost zero in aqueous solution in which the equatorial conformer predominates ($\Delta G_{A-E} = 1.4$ kcal mol^{-1}). The $C{=}O \cdots HN$ hydrogen bond is less affected by the solvent varying from *ca.* 1.8 kcal mol^{-1} in nonpolar solvents to 1.0 kcal mol^{-1} in D_2O in *N*,*N*-diethylnipecotamide and from 0.9 to 0.6 kcal mol^{-1} in ethyl nipecotate.

Introduction

Jeffrey and Saenger in their classic text on the hydrogen bond[2] noted that "the hydrogen bond is the most important intra- and intermolecular cohesive force determining geometry, mode of recognition and association of biological molecules." They also observed that the intramolecular hydrogen bonds stabilising the three-dimensional structure of these molecules are in competition with those to the water solvent and the competing effect of the solvent is *the* central problem in all investigations of hydrogen bonding. For this reason, despite a large number of investigations there is still a lack of good data on hydrogen bonding energies in solution.

The use of substituted cyclohexanes as conformational probes for a variety of non-bonded interactions has recently been promoted in this series[3,4] and by others.[5] Cyclohexanes have well defined geometries, are small enough for theoretical calculations and can be "frozen out" at low temperatures so that the separate conformers can be observed by NMR thus allowing a precise determination of the conformer free energy differences. An NMR study of *cis*-1,3-dihydroxycyclohexane[3] showed that the diequatorial conformer is favoured in polar solvents (including water) by *ca.* 2.0 kcal mol^{-1}, which is as expected from the conformational preference of the OH group in cyclohexanol (*ca.* 1.0 kcal mol^{-1}). In the nonpolar CCl_4 solvent the conformer energy difference is reduced to 0.10 kcal mol^{-1} giving a value for the energy of the intramolecular $OH \cdots O$ hydrogen bond of 1.6 kcal mol^{-1}. A similar study of *trans*-2-fluorocyclohexanol and the methyl ether gave the $OH \cdots F$ attraction in the eq–eq conformer as 1.6 kcal mol^{-1} compared to zero for the $OMe \cdots F$ interaction.[4a] This confirmed previous theoretical interpretations of $OH \cdots F$ hydrogen bonding[4b] and showed that the discrepancy between experimental measurements in the condensed phase and theoretical studies in the gas phase was due to solvation.

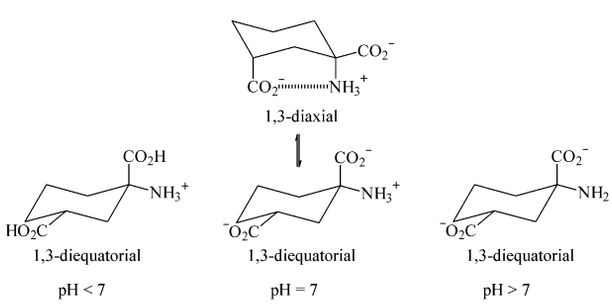

Fig. 1 Conformations of *trans*-1-aminocyclohexane-1,3-dicarboxylic acid in aqueous solution.

The pH of the medium is also a factor in determining the conformation of cyclohexane derivatives in solution. The conformations of *cis*-and *trans*-1-aminocyclohexane-1,3-dicarboxylic acid were investigated by X-ray crystallography and ^{1}H and ^{13}C NMR spectroscopy.[5] Steric interactions favoured the 1,3-diequatorial conformers in acid and alkaline media, whereas at intermediate pH a 1,3-electrostatic attraction stabilises the 1,3-diaxial conformer (Fig. 1).

The introduction of a nitrogen atom into the cyclohexane ring gives rise to further non-bonding interactions including in substituted piperidines possible intramolecular hydrogen

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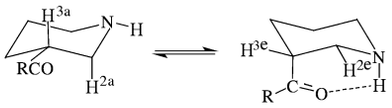


Fig. 2 Conformational equilibrium of nipecotic acid (R = OH), ethyl nipecotate (R = OEt) and nipecotamide (R = NH_2).

bonding between the substituent and the NH atom. The conformation of the NH in piperidine was the subject of a number of investigations and some controversy but there is now agreement that the NH equatorial conformer is favoured.[6] A gas phase microwave study[7] gave an energy difference of 0.74 kcal mol^{-1} and two stable conformers were observed in the ^{13}C NMR spectrum[8] at 101 K in a 1 : 1 solvent mixture of $CHFCl_2$ and CHF_2Cl to give ΔG° 0.36 kcal mol^{-1}. The difference in these values may well be due to solvation (the axial conformer has a larger dipole moment (1.19 *vs.* 0.82 D)[7] and would therefore be more favoured in polar media). We will use the average value of 0.5 kcal mol^{-1} for our $CDCl_3$ solutions henceforth. The conformational analysis of substituted piperidines has been well documented.[6,9,10] There is a large effect on the conformational equilibrium of 4-substituted piperidines on protonating the ring nitrogen atom.[11] For polar substituents (Br, F) the conformational preference was reversed on protonation. ΔG_{A-E} changes from 0.4→−0.4 and 0.2→−0.8 kcal mol^{-1} for 4-bromo- and 4-fluoropiperidine and this was quantitatively explained by the electrostatic interaction of the substituent and the protonated N atom.

Recently 3-fluoro- and *cis*-3,5-difluoropiperidine were shown to exhibit unusual conformational properties.[12] 3-Fluoropiperidine free base exists as the equatorial conformer but in the hydrochloride salt the fluorine axial conformer is preferred.[12a] In *cis*-3,5-difluoropiperidine the diaxial conformer is preferred in aqueous solution and this unusual conformation was explained by a favourable charge–dipole interaction between the N^+–H and C–F bonds.[12b]

Intramolecular hydrogen bonding in nipecotamide and some methyl derivatives has been investigated by IR spectroscopy.[13] The intramolecular hydrogen bond between the ring nitrogen and the amide substituent in the axial conformer was clearly identified by IR and the authors noted that the *N*-methylated compounds were more intramolecularly hydrogen bonded than the free amines (see later).

We present here a ^1H NMR study of some nipecotic acid derivatives (piperidine-3-carboxylic acid, see Fig. 2) and show that the intramolecular hydrogen bonds between the substituent and the nitrogen atom in the axial conformer can be characterised and quantified by NMR. The conformational equilibrium has been determined in a range of solvents of different polarity and also in aqueous solution at different pH in order to determine the energy of the hydrogen bonds in these systems. Whilst this work was in progress Roberts and co-workers reported the full analysis of the proton spectrum of nipecotic acid in D_2O at different pH in the course of a study on the conformational equilibrium in β-alanine and related compounds.[14] They did not report any VT or solvent studies. A preliminary account of the work presented here has been given.[15]

Theoretical

The free energy ΔG_{A-E} of the equilibrium of Fig. 2 is given directly by the conformer populations n_E and n_A (eqn. (1)).

$$\Delta G_{A-E} = RT \ln (n_E/n_A) \quad (1)$$

The conformer populations were obtained in two ways. If the conformational equilibrium could be frozen out at low temperature (190 K) direct integration of the proton peaks gives immediately the conformer populations. The conformer populations were also obtained at room temperature for those solvents such as water which are solid at low temperatures by measurement of the observed coupling constant ($^3J_{obs}$) between protons H^2 and H^3 (Fig. 2) using eqns. (2) and (3).

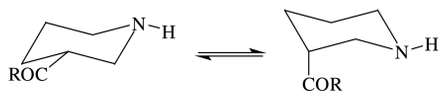


Fig. 3 Conformational equilibrium of nipecotic acid derivatives. $\Delta G = \Delta G_{CORax-eq.}$

$$^3J_{obs} = n_E{}^3J_{2a-3a} + n_A{}^3J_{2e-3e} \quad (2)$$

$$n_E + n_A = 1 \quad (3)$$

Vicinal HH couplings are known to be dependent on the substituents in the CHCH fragment.[16] It is therefore necessary to obtain the conformer couplings in eqn. (2) from CHCH fragments with the same substituents as the measured fragment. The conformer couplings may be calculated by means of a number of semi-empirical equations of which the Altona–Haasnoot equation is one of the most popular.[17] All such equations are prone to error. Roberts *et al.*[14] noted that the use of the Altona–Haasnoot equation for nipecotic acid gave conformer percentages >100%. Here the appropriate couplings were measured from the low temperature spectra of the conformers to remove this source of error. The coupling selected was J_{2-3} *trans* (Fig. 2). It was selected as the large axial–axial coupling of conformer E ($^3J_{2a-3a}$ = 11.6 Hz) could be measured directly from the low temperature spectrum of ethyl nipecotate in $CFCl_3$ (see Fig. 5). The $^3J_{2e-3e}$ coupling of conformer A could not be measured from the low temperature spectrum due to line broadening but the eq–ax coupling of conformer A ($^3J_{2a-3e}$ = 3.2 Hz) was resolved. Assuming that the $^3J_{2e-3e}$ and $^3J_{2a-3e}$ couplings in conformer A are very similar allows these values to be inserted directly into eqn. (2). We note that the majority of the conformer populations obtained favour conformer E, thus any small error in the eq–eq coupling will have little effect on the estimated conformer populations.

In the protonated amine the value of both coupling constants changes to $^3J_{2a-3a}$ = 12.3 Hz and $^3J_{2e-3e}$ = 2.8 Hz. These were obtained from the spectrum of ethyl 1-methylnipecotate salt in methanol at room temperature. In this equilibrium the exchange rate is decreased by an amine protonation–deprotonation process and both the *cis* and *trans* isomers are observed separately at room temperature. Inserting the conformer couplings into eqns. (2) and (3) gives eqns. (4) and (5).

Free base and anion salt: $n_E = (^3J_{obs} - 3.2)/8.4$ (4)

Zwitterion and cation salt: $n_E = (^3J_{obs} - 2.8)/9.5$ (5)

The hydrogen bond energy in the axial conformer may be obtained from the value of ΔG_{A-E} by the analysis of eqn. (6).

$$\Delta G_{A-E} = \Delta G_{CORax-eq} + \Delta G_{Hax-eq} + \Delta G_{Hbond} \quad (6)$$

$\Delta G_{CORax-eq}$ is the free energy difference of the substituent between the axial and equatorial positions (Fig. 3).

ΔG_{Hax-eq} is the free energy difference of the eq–ax NH conformation (Fig. 4) for which the value of 0.5 kcal mol^{-1} is taken.

Inserting these terms into eqn. (6) allows the energy involved in the hydrogen bond formation (ΔG_{Hbond}) for each system to be deduced.

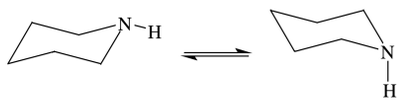


Fig. 4 Conformational equilibrium of piperidine.

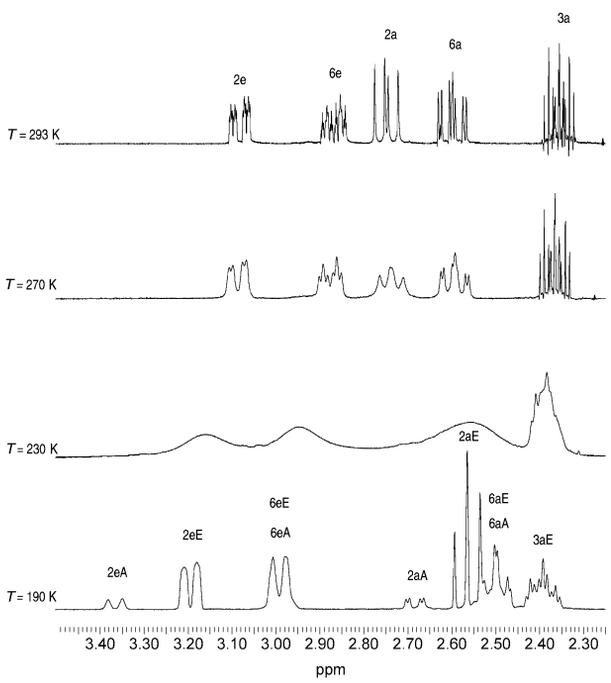


Fig. 5 Part of the ^{1}H NMR spectrum of ethyl 1-methylnipecotate in $CFCl_3$ at the temperatures shown.

Experimental

Nipecotic acid, nipecotamide, *N*,*N*-diethylnipecotamide, ethyl nipecotate and ethyl 1-methylnipecotate were obtained commercially (Aldrich). The other compounds were all synthesised according to literature methods.[18] The ^{1}H NMR spectra were obtained on a Bruker AMX 400 spectrometer. Typical conditions for the ^{1}H NMR spectra were 256 transients accumulated in 32 K data points with a pulse width of 7.5 μs (45° flip-angle) and a sweep width of *ca*. 2500 Hz, giving an acquisition time of *ca*. 4.5 s. The FID was zero filled to 512 K data points giving a digital resolution of 0.01 Hz point^{-1}. Probe temperature was 22 °C. Samples were of *ca*. 4 mg of compound in 0.7 ml of solvent using TMS as internal reference for the non-aqueous solvents and TSP (trimethylsilyl sodium propionate) for the aqueous solutions. Solvents were stored over molecular sieves in airtight containers.

Most FIDs were processed with Gaussian multiplication, typically of lb = −0.8 and gb = 0.3 for spectral resolution improvement.

H–H COSY experiments using COSY45[19] were performed on a Varian GEMINI 300 spectrometer for the complete assignment of some of the ^{1}H NMR spectra. Typical conditions were 128 transients, accumulated into 1 K data points with 512 experiments, a 7.5 μs pulse and a spectral width of 2400 Hz. The FID was zero filled to 1 K (F1) and 2 K (F2) data points. Solutions were of *ca*. 25 mg of sample in 0.7 ml of solvent using TMS as internal reference.

Low temperature spectra were recorded as above for the ^{1}H and COSY experiments.

Results

A typical series of VT experiments is illustrated in Fig. 5 which shows part of the ^{1}H spectrum of ethyl nipecotate containing the H^2, H^3 and H^6 protons, which are the most resolved and most informative signals. The room temperature spectrum is easily assigned on the basis that the equatorial (E) conformer is the major form. Thus the equatorial and axial H^2 and H^6 protons are clearly differentiated into 2e and 2a (and 6e and 6a) by both their chemical shifts and coupling constants.

On cooling the spectrum broadens ($T_c \sim 230$ K) and at 190 K the separate spectra of the E and A conformers are clearly observed. Integration of either the 2e pair of signals or the 2a pair gives directly the conformer populations. The small signal of H^{3e} in the A form is under the 6a peak. The ax–ax coupling (J_{2a-3a}) is clearly resolved at low temperature but the corresponding eq–eq coupling was not resolved. However the 2a–3e coupling is resolved in the 2aA signal and the value of this coupling was used in eqn. (2). In many cases two or more couplings are not completely resolved. In Fig. 5 the H^3 proton is a characteristic triplet of triplets in all the spectra from which only the average couplings $\langle J_{2a-3} + J_{3-4a} \rangle$ and $\langle J_{2e-3} + J_{3-4e} \rangle$ can be obtained. If one of these couplings can be measured separately (which was the case for these spectra) both the couplings can be deduced. Often this was not possible and in these cases the average coupling is recorded in the Tables.

The results from experiments of this type and also in different solvents are given in Tables 1–9. Both the proton chemical shifts and as many couplings as could be clearly resolved were measured and recorded together with, where possible, the integration of the separate conformers at low temperature.

Nipecotic acid was analysed in neutral, acidic and basic media to study the hydrogen bonding interactions in the zwitterion, cation and anion. Variable temperature experiments were also performed on the zwitterion and the cation in methanol solution, acquiring proton spectra from temperatures of 323 to 193 K every 20 K. In both cases the axial and equatorial conformations could be observed separately at low temperatures. A selection of these results is given in Table 1 with the full assignment of the spectra. More complete data are given in ref. 20. The spectrum of the zwitterion in MeOD solution showed that H^{2a}/H^{2e} gave a very closely coupled multiplet and the ABX system of H^{2a}/H^{2e} and H^3 was analysed using the LAOCOON programme.[21] At 40 °C the H^{2a}/H^{2e} separation was increased sufficiently that the analysis was first order. Both these analyses are given in Table 1. For the D_2O, DCl and NaOD solutions the corresponding coupling data from ref. 14 are given in parentheses. There is generally good agreement between the two sets of results, but some differences in the acid and alkaline solutions, possibly due to differences in the solution pH.

1-Methylnipecotic acid was also analysed in neutral, acidic and basic media. In the anion only one averaged spectrum is observed, but in both the zwitterion and the cation there is slow exchange at room temperature between the *cis* and *trans* configurations of the *N*-Me and carboxy group as these isomers can only interconvert *via* deprotonation of the nitrogen atom. The separate ^{1}H NMR spectra have been assigned and are given in Table 2. The assignment of the isomers was based on the splitting patterns. *E.g.* H^{4a} is a large 1 : 3 : 3 : 1 quartet in the *cis* conformer but a 1 : 2 : 1 triplet in the *trans* form.

Ethyl nipecotate was studied as a free base and as the hydrochloride salt. As the proton spectrum was very clearly resolved at room temperature (Fig. 5) this compound was examined in a number of solvents both as the free base and the cation to study the effect of solvent on the conformational equilibrium. Variable temperature experiments were performed on the free base in a 3 : 1 mixture of $CFCl_3$–CD_2Cl_2 and methanol, acquiring proton spectra from room temperature to 190 K every 20 K. In both solutions, axial and equatorial conformations could be observed separately at low temperatures. Again a selection of these results is given in Table 3.

Ethyl 1-methylnipecotate was also studied as the free base and cation. The spectrum of ethyl 1-methylnipecotate cation

Table 1 Proton chemical shifts and couplings of nipecotic acid[a]

Chemical shifts (δ) (ppm)									
Solvent	2a	2e	3	4a	4e	5a	5e	6a	6e
MeOD	3.15	3.23	2.55	1.91	2.02	1.79	1.91	3.16	3.16
MeOD (Conf. E)[b]	2.90	3.45	2.49	1.54	2.18	1.73	1.98	2.90	3.30
MeOD (Conf. A)[b]	2.98	3.49	2.68	1.79	2.16	—	—	2.97	3.32
MeOD–D_2O (1:1)	3.17	3.31	2.61	1.8	2.02	1.8	1.92	3.10	3.21
D_2O	3.18	3.41	2.68	1.8	2.08	1.8	1.95	3.11	3.31
MeOD–DCl	3.24	3.46	2.85	1.85	2.17	1.85	1.96	3.08	3.29
MeOD–DCl (Conf. E)[b]	3.01	3.56	2.76	1.61	2.27	1.77	2.01	2.91	3.37
MeOD–DCl (Conf. A)[b]	3.11	3.65	—	—	2.25	—	—	3.00	3.26
DCl	3.27	3.47	2.94	1.8	2.11	1.8	1.92	3.09	3.29
NaOD	2.53	3.05	2.28	1.48	1.95	1.43	1.67	2.47	2.90

Coupling constants/Hz[c]					
Solvent	$^2J_{2a-2e}$	$^3J_{2a-3}$	$^3J_{3-4a}$	$^3J_{2e-3}$	$^3J_{3-4e}$
MeOD	12.54	7.55	7.15	3.55	4.04
MeOD (40 °C)	12.48	6.59	⟨6.40⟩	3.65	3.65
MeOD (Conf. E)[b]	11.5	⟨12.2⟩	⟨12.2⟩		
MeOD–D_2O (1:1)	12.75	8.34	—	3.72	—
D_2O[d]	12.65 (12.62)	9.17 (9.15)	8.99 (9.15)	3.75 (3.84)	4.20 (4.29)
MeOD–DCl	12.82	9.4	8.7	3.81	4.59
MeOD (Conf. E)[b]	11.2	—	10.6	—	—
MeOD (Conf. A)[b]	12.2	—	—	—	—
DCl[d]	12.93 (12.91)	8.64 (8.71)	8.87 (7.73)	3.81 (4.19)	4.90 (5.06)
NaOD[d]	12.25 (12.25)	10.97 (10.76)	11.27 (9.22)	⟨3.75⟩ (3.41)	⟨3.75⟩ (4.42)

[a] At 295 K unless stated otherwise. [b] 195 K. [c] ±0.1 Hz unless stated otherwise. [d] Ref. 14. — Not observed. ⟨ ⟩ Averages of two couplings.

Table 2 Proton chemical shifts and couplings of 1-methylnipecotic acid[a]

Chemical shifts (δ) (ppm)												
Solvent		2a	2e	3a	3e	4a	4e	5a	5e	6a	6e	CH_3
MeOD[b]	*cis*	3.03	3.70	2.82		1.58	2.23	1.82	2.05	2.93	3.50	2.91
	trans	3.14	3.73		3.06	1.79	2.19	1.85	1.93	3.00	3.40	2.88
MeOD–DCl[b]	*cis*	3.03	3.68	2.85		1.57	2.21	1.84	2.03	2.93	3.49	2.90
	trans	3.15	3.72		3.06	1.79	2.17	1.87	1.91	3.01	3.40	2.88
D_2O–DCl	*cis*	3.05	3.70	2.87		1.58	2.20	1.8	2.06	2.93	3.51	2.90
	trans	3.14	3.73		3.12	1.8	2.16	1.8	1.92	3.00	3.44	2.87
NaOD		1.99	2.93	2.35		1.27	1.90	1.50	1.73	1.94	2.79	2.21

Coupling constants/Hz[c]								
Solvent		$^2J_{2a-2e}$	$^3J_{2a-3}$	$^3J_{3-4a}$	$^3J_{2e-3}$	$^3J_{3-4e}$	$^2J_{6a-6e}$	
MeOD[b]	*cis*	⟨12.46⟩		⟨12.46⟩		⟨3.89⟩	12.3	
	trans	12.66	3.69		—	—	12.2	
MeOD–DCl[b]	*cis*	⟨12.38⟩		⟨12.38⟩		⟨3.85⟩	12.41	
	trans	12.77	3.74		—	—	—	
D_2O–DCl	*cis*	⟨12.40⟩		⟨12.39⟩		⟨3.83⟩	12.51	
	trans	—	3.84		—	—	—	
NaOD		11.23	11.49	12.19		⟨3.77⟩		

[a] At 295 K unless stated otherwise. [b] 273 K. [c] ±0.1 Hz unless stated otherwise. — Not observed. ⟨ ⟩ Averages of two couplings.

was examined in methanol solution and the *cis* and *trans* isomers assigned as for the 1-methylnipecotic acid. These results are given in Table 4.

Ethyl 1,1-dimethylnipecotate was also studied in a variety of solvents as the chloride salt and the results are given in Table 5. The chemical shifts of the protons alpha to the nitrogen atom (H^2,H^6 and Me) show an intriguing solvent dependence in that they move to high field on going from less polar to more polar solvents, which is the opposite of the usual change. This may be due to ion pairing in the nonpolar solvents.

The spectra of nipecotamide, 1-methylnipecotamide and *N*,*N*-diethylnipecotamide were analysed in a number of solvents at room temperature and in neutral and acidic solutions and these results are given in Tables 6, 7 and 8. Variable temperature experiments were performed on nipecotamide free base in CD_2Cl_2 and acetone solutions, acquiring proton spectra from room temperature to 200 K every 20 K. Nipecotamide is only slightly soluble in these solvents at 200 K giving a poor signal to noise ratio for the spectra acquired at this temperature. In CD_2Cl_2 solution, small impurity peaks at room temperature appear much bigger at low temperature as compared to the nipecotamide peaks but both conformers could be observed. In acetone the impurity peaks eclipsed the peaks corresponding to the axial conformation of nipecotamide, making the calculation of the conformer populations by direct integration impractical. However, the conformer chemical shifts obtained from the low temperature experiments are given in Table 6.

Table 3 Proton chemical shifts and couplings of ethyl nipecotate in different solvents[a]

Chemical shifts (ppm)

Solvent	2a	2e	3	4a	4e	5a	5e	6a	6e	NH/NH_2^+	
$CFCl_3$–CD_2Cl_2	2.75	3.08	2.35	1.62	1.93	1.42	1.64	2.60	2.87	1.45	
$CDCl_3$	2.81	3.16	2.43	1.65	1.99	1.46	1.68	2.64	2.94	1.69	
CD_2Cl_2	2.73	3.10	2.38	1.60	1.94	1.41	1.64	2.58	2.88	1.76	
Acetone	2.66	3.08	2.37	1.56	1.92	1.40	1.60	2.52	2.85	2.63	
MeOD	2.70	3.10	2.47	1.60	2.00	1.49	1.67	2.57	2.90	—	
MeOD(Conf. E)[b]	2.54	3.16	2.44	1.48	2.04	1.48	1.73	2.47	2.96	—	
MeOD (Conf. A)[b]	2.70	3.37	2.6	1.50	2.20	1.50	1.7	2.5	2.96		
D_2O	2.76	3.15	2.59	1.7	2.00	1.50	1.7	2.61	2.93	—	
$CDCl_3$–TFA	3.3	3.48	2.90	1.90	2.13	1.80	1.90	3.08	3.3	8.30	8.89
DCl	3.26	3.49	2.93	1.8	2.10	1.8	1.90	3.07	3.30	—	—

Coupling constants/Hz[c]

Solvent	$^2J_{2e-2a}$	$^3J_{2a-3}$	$^3J_{3-4a}$	$^3J_{2e-3}$	$^3J_{3-4e}$	$^2J_{6a-6e}$	$^3J_{6a-5a}$
$CFCl_3$–CD_2Cl_2	12.31	9.10	9.77	3.69	4.21[s]	12.39	10.21
$CFCl_3$–CD_2Cl_2 (Conf. E)[b]	11.60	11.60	11.24	—	—	12.36	11.63
$CFCl_3$–CD_2Cl_2 (Conf. A)[b]	13.1	3.2	—	—	—	—	—
$CDCl_3$	12.39	9.29	9.93	3.81	4.1[s]	12.44	10.37
CD_2Cl_2	12.33	9.37	9.73	3.86	4.0[s]	12.42	10.30
Acetone	12.15	9.48	10.15	4.14	3.7[s]	12.30	10.37
MeOD	12.57	9.84	10.24[s]	3.50	4.30[s]	12.68	10.60
D_2O	12.45	9.85	9.99[s]	3.74	3.76[s]	—	—
$CDCl_3$–TFA	—	⟨8.71⟩		⟨4.0⟩		—	—
DCl	12.87	9.03	9.1[s]	4.04	—	—	—

[a] At 295 K. [b] 190 K. [c] ±0.1 Hz. — Not observed. ⟨ ⟩ Averages of two couplings.

Table 4 Proton chemical shifts and couplings of ethyl 1-methylnipecotate in different solvents[a]

Chemical shifts (ppm)

Solvent		2a	2e	3	4a	4e	5a	5e	6a	6e	NCH_3
$CFCl_3$–CD_2Cl_2		2.07	2.84	2.50	1.40	1.86	1.55	1.69	1.93	2.62	2.21
CCl_4		2.02	2.80	2.44	1.35	1.84	1.54	1.67	1.89	2.58	2.18
$CDCl_3$		2.10	2.95	2.57	1.40	1.94	1.59	1.73	1.97	2.72	2.29
Acetone		2.04	2.82	2.49	1.36	1.83	1.51	1.67	1.90	2.60	2.18
MeOD		2.14	2.94	2.56	1.41	1.92	1.58	1.75	2.02	2.74	2.28
DMSO		2.02	2.76	2.78	1.32	1.77	1.46	1.62	1.89	2.55	2.14
D_2O		2.23	2.95	2.62	1.43	1.93	1.55	1.74	2.08	2.73	2.24
MeOD–DCl	*cis*	3.05	3.69	2.90	1.57	2.19	1.86	2.03	2.90	3.50	2.90
	trans	3.19	3.74	3.10	—	2.15	—	—	2.97	3.41	2.89

Coupling constants/Hz[b]

Solvent		$^2J_{2e-2a}$	$^3J_{2a-3}$	$^3J_{3-4a}$	$^3J_{2e-3}$	$^3J_{3-4e}$	$^3J_{4a-5a}$	$^2J_{5a-5e}$
$CFCl_3$–CD_2Cl_2		11.3	9.99	10.77	⟨3.88⟩		11.53	13.23
CCl_4		11.10	10.04	10.92	⟨3.88⟩		11.63	13.14
$CDCl_3$		11.1	10.34	11.14	⟨3.88⟩		11.86	13.38
Acetone		—	9.98	10.62	⟨3.91⟩		11.42	11.42
MeOD		11.31	10.44	11.08	⟨3.89⟩		11.83	13.56
DMSO		—	9.89	10.44	⟨3.84⟩		11.20	13.09
D_2O		—	⟨10.59⟩		⟨3.89⟩		—	——
MeOD–DCl	*cis*	12.18	12.30	12.37	3.81	3.81	—	—
	trans	12.80	3.80	—	2.83	—	—	—

[a] 295 K. [b] ±0.1 Hz unless stated otherwise. — Not observed. ⟨ ⟩ Averages of two couplings.

1-Methylnipecotamide free base was also analysed at various temperatures in CD_2Cl_2 solution. At low temperature both conformations could be observed separately.

The spectrum of 1-methyl-*N*,*N*-diethylnipecotamide was analysed in a few solvents of different polarity and a VT experiment was performed in methanol solution in which spectra were acquired from room temperature to 193 K every 20 K. As in the diethylnipecotamide only the equatorial conformer could be observed at 193 K. Again a selection of these results is given in Table 9.

Conformational analysis

The results in Tables 1–9 together with the direct integrations of the separate conformers at low temperature allow the deduction of the conformer populations and energies and hence any intramolecular hydrogen bonding energy. As there are a number of possible conformers and intramolecular hydrogen bonds it is convenient to consider each system in turn.

Nipecotic acid exists as the zwitterion, cation and anion in neutral, acidic and basic media. Each presents a different

Table 5 Proton chemical shifts and couplings of ethyl 1,1-dimethylnipecotate in different solvents[a]

Chemical shifts (ppm)											
Solvent	2a	2e	3	4a	4e	5a	5e	6a	6e	NCH_3	
$CDCl_3$	3.61	4.05	3.02	1.80	2.31	2.1	2.1	3.58	3.99	3.49	3.64
Acetone	3.67	3.95	3.32	1.71	2.2	2.2	2.2	3.65	3.83	3.45	3.53
MeOD	3.42	3.73	3.17	1.62	2.21	2.08	1.96	3.33	3.52	3.17	3.24
D_2O	3.41	3.73	3.17	1.63	2.23	2.04	2.02	3.29	3.50	3.13	3.22

Coupling constants/Hz[b]						
Solvent	$^2J_{2e-2a}$	$^3J_{2a-3}$	$^3J_{3-4a}$	$^3J_{2e-3}$	$^3J_{3-4e}$	$^2J_{6a-6e}$
$CDCl_3$	12.61	⟨11.64⟩		⟨4.17⟩		12.96
Acetone	12.78	⟨12.37⟩		⟨3.97⟩		12.65
MeOD	12.76	⟨12.32⟩		⟨4.00⟩		12.70
D_2O	12.90	⟨12.30⟩		⟨4.04⟩		12.5

[a] At 295 K unless stated otherwise. [b] ±0.1 Hz unless stated otherwise. — Not observed. ⟨ ⟩ Averages of two couplings.

Table 6 Proton chemical shifts and couplings of nipecotamide in different solvents[a]

Chemical shifts (ppm)												
Solvent	2a	2e	3	4a	4e	5a	5e	6a	6e	NH	NH_2	
$CDCl_3$	2.98	3.10	2.39	1.8	1.8	1.52	1.7	2.8	2.8	2.00	6.00	7.37
CD_2Cl_2	2.93	2.95	2.32	1.8	1.8	1.46	1.69	2.8	2.8	1.86	5.57	7.72
CD_2Cl_2 (Conf. E)[b]	2.63	3.16	2.3	1.6	1.93	1.43	1.6	2.52	2.98	—	6.15	6.30
CD_2Cl_2 (Conf. A)[b]	2.75	3.22	3.0	2.38	1.93	1.51	1.7	2.58	3.03	1.75	6.07	8.99
Acetone	2.74	2.97	2.27	1.6	1.81	1.40	1.6	2.60	2.81	2.70	6.10	7.02
Acetone (Conf. E)[b]	2.56	3.04	2.33	—	—	—	—	2.43	2.92	—	—	—
MeOD	2.69	3.04	2.38	1.63	1.93	1.50	1.71	2.57	2.93	—	—	—
DMSO	2.48	2.89	2.17	1.45	1.76	1.32	1.54	2.39	2.79	—	6.73	7.31
D_2O	2.61	3.09	2.46	1.56	1.95	1.47	1.73	2.52	2.94	—	—	—
DCl	3.17	3.40	2.86	1.8	2.06	1.8	1.96	3.07	3.31	—	—	—

Coupling constants/Hz[c]								
Solvent	$^2J_{2e-2a}$	$^3J_{2e-3e/2a-3a}$	$^3J_{3e-4e/3a-4a}$	$^3J_{2a-3e/2e-3a}$		$^3J_{3a-4e/3e-4a}$	$^2J_{6a-6e}$	$^3J_{5a-6a}$
$CDCl_3$	12.0	5.60	6.16	3.69		4.69	—	—
CD_2Cl_2	12.08	5.97	—	3.52		—	—	—
Acetone	12.14	8.42	9.02	3.82		4.38	12.08	9.59
MeOD	12.41	10.43	10.79	3.63			12.62	11.39
DMSO	11.94	10.49	10.3		⟨3.81⟩		12.3	—
D_2O	12.17	10.91	11.37		⟨3.66⟩		12.5	11.6
DCl	12.74	9.46	9.70	3.78		4.1	12.6	—

[a] At 295 K unless stated otherwise. [b] 200 K. [c] ±0.1 Hz unless stated otherwise. — Not observed. ⟨ ⟩ Averages of two couplings.

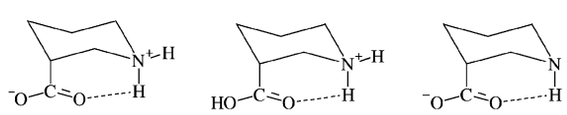


Fig. 6 Nipecotic acid zwitterion (left), cation (middle) and anion (right).

intramolecular interaction in that in the zwitterion the hydrogen bonding is between two charged species whereas in the cation and anion the interaction is between positive and neutral ions and negative and neutral ions respectively (Fig. 6).

The conformer populations and value of ΔG_{A-E} for the equilibrium of Fig. 2 were calculated from eqns. (1), (4), (5) by inserting the value of the coupling $^3J_{2a-3}$ (Table 1) and the ΔG_{A-E} values are shown in Table 10. There is a pronounced solvent dependence of ΔG_{A-E} in the zwitterion, the equatorial form being more favoured in the more polar D_2O solvent. ΔG_{A-E} was also obtained at 195 K in methanol solution by direct integration to give a value of 0.31 ± 0.07 kcal mol^{-1}. Interestingly this value is comparable to the value in D_2O at room temperature and this supports the suggestion that the polarity of the solvent is a major factor (the relative permittivity of methanol at 195 K is 52.0,[22] similar to that of D_2O at room temperature). ΔG_{A-E} was also obtained for the cation at 195 K in methanol solution by direct integration to give 0.38 ± 0.02 kcal mol^{-1}, again agreeing with the room temperature measurements.

In this equilibrium the hydrogen bond energy can be deduced from the value of ΔG_{A-E} if the axial–equatorial free energy difference of the substituent is known (Fig. 3). ΔG_{A-E} for the carboxylate anion CO_2^- in cyclohexanecarboxylate is quoted by Eliel[23] as 2.0 kcal mol^{-1} and the corresponding value for the CO_2H group in cyclohexanecarboxylic acid as 1.4 kcal mol^{-1}. For the anion the energy difference of 0.5 kcal mol^{-1} of the N–H in the axial *vs.* equatorial conformer (Fig. 4) has to be included. Inserting these values into eqn. (6) gives the hydrogen bond energies for the conformers of Fig. 6 in Table 10. These figures show clearly that the hydrogen bond energy in the zwitterion (1.7–2.0 kcal mol^{-1}) is much larger than that in the cation or anion (*ca.* 1.0 kcal mol^{-1}). Thus the introduction of one charged species has little effect on the hydrogen bond energy but when both the donor and acceptor groups are charged the hydrogen bond energy almost doubles in this

Table 7 Proton chemical shifts and couplings of 1-methylnipecotamide in different solvents[a]

Chemical shifts (ppm)

Solvent		2a	2e	3	4a	4e	5a	5e	6a	6e	CH_3	NH_2	
$CDCl_3$		2.32	2.72	2.50	1.6	1.8	1.6	1.8	2.17	2.59	2.25	5.48	—
CD_2Cl_2		2.32	2.65	2.43	1.55	1.75	1.55	1.75	2.15	2.54	2.22	5.44	7.5
CD_2Cl_2 (Conf. E)[b]		1.93	2.96	2.47	1.47	1.9	1.55	1.72	1.9	2.80	—	6.31	6.31
CD_2Cl_2 (Conf. A)[b]		2.04	2.98	2.43	1.49	1.9	1.54	1.73	1.9	2.85	—	6.56	8.71
Acetone		2.2	2.63	2.39	1.47	1.71	1.50	1.67	2.0	2.49	2.18	6.16	7.02
MeOD		2.13	2.86	2.47	1.43	1.85	1.60	1.75	2.01	2.77	2.28	—	—
D_2O		2.11	2.94	2.53	1.39	1.90	1.55	1.77	2.03	2.81	2.24	—	—
CD_2Cl_2–TFA	*cis*	3.01	3.66	3.21	1.71	2.09	1.97	2.09	2.79	3.64	2.90	7.01	7.16
	trans	3.05	3.71	3.16	1.97	2.09	1.97	2.09	3.05	3.58	2.94	6.81	7.08
MeOD–TFA	*cis*	3.03	3.55	2.76	1.61	2.0	1.9	2.0	2.93	3.49	2.89	—	—
	trans	3.06	3.61	3.0	—	—	—	—	—	3.41	2.84	—	—
D_2O–TFA	*cis*	3.01	3.60	2.82	1.60	2.1	1.8	2.1	2.94	3.51	2.89	—	—
	trans	3.08	3.63	3.08	—	—	—	—	—	2.86	2.86	—	—

Coupling constants/Hz[c]

Solvent		$^2J_{2e–2a}$	$^3J_{2e–3e/2a–3a}$	$^3J_{3e–4e/3a–4a}$	$^3J_{2e–3a/2a–3e}$	$^3J_{3a–4e/3e–4a}$	$^2J_{5a–5e}$	$^3J_{5a–6a}$
$CDCl_3$		—	⟨4.18⟩		⟨4.72⟩		—	—
CD_2Cl_2		—	—	—	⟨4.82⟩		—	—
CD_2Cl_2 (Conf. E)[b]		⟨11.3⟩	⟨11.3⟩					
CD_2Cl_2 (Conf. A)[b]		11.9	3.1					
Acetone		—	⟨8.96⟩		⟨3.93⟩		—	—
MeOD		11.3	10.69	11.31	⟨3.82⟩		13.50	11.56
D_2O		11.30	11.40	11.62	⟨3.77⟩		13.6	11.76
CD_2Cl_2–TFA	*cis*	⟨12.1⟩	⟨12.1⟩		⟨3.69⟩		—	—
MeOD–TFA	*cis*	12.38	12.3	12.3	⟨3.8⟩		—	—
	trans	12.58	3.39	—	—		—	—
D_2O–TFA	*cis*	—	⟨12.3⟩	⟨12.3⟩	—		—	—

[a] At 295 K unless stated otherwise. [b] 213 K. [c] ±0.1 Hz unless stated otherwise. — Not observed. ⟨ ⟩ Averages of two couplings.

Table 8 Proton chemical shifts and couplings of *N*,*N*-diethylnipecotamide in different solvents[a]

Chemical shifts (ppm)

Solvent	2a	2e	3	4a	4e	5a	5e	6a	6e	NH
$CFCl_3$	2.74	2.88	2.48	1.7	1.7	1.44	1.64	2.62	2.86	1.38
$CDCl_3$	2.86	3.0	2.60	1.7	1.81	1.51	1.7	2.66	3.0	1.65
CD_2Cl_2	2.74	2.9	2.56	1.65	1.78	1.45	1.67	2.60	2.9	1.93
MeOD	2.70	2.96	2.72	1.65	1.82	1.53	1.70	2.56	2.93	—
MeOD (Conf. E)[b]	2.62	2.97	2.71	1.59	1.82	1.49	1.71	2.51	2.92	
DMSO	2.47	2.8	2.53	1.50	1.68	1.37	1.54	2.38	2.8	—
D_2O	2.66	3.0	2.81	1.59	1.88	1.52	1.74	2.56	3.0	—
DCl	3.26	3.3	3.1	1.8	2.0	1.8	2.0	3.1	3.3	—
NaOD	2.60	3.0	2.78	1.57	1.84	1.49	1.72	2.51	3.0	—

Coupling constants/Hz[c]

Solvent	$2J_{2e–2a}$	$^3J_{2a–3}$	$^3J_{3–4a}$	$^3J_{2e–3}$	$^3J_{3–4e}$	$^2J_{6a–6e}$	$^3J_{5a–6a}$	$^3J_{5e–6a}$
$CFCl_3$	12.15	9.48	—	—		11.98	11.09	2.85
$CDCl_3$	12.19	10.02	10.32	⟨3.85⟩		⟨11.84⟩		2.81
CD_2Cl_2	12.29	9.90	10.44	⟨3.72⟩		⟨12.0⟩		2.81
MeOD	—	10.37	—	—		12.52	11.63	2.88
MeOD (Conf. E)[b]	⟨11.4⟩	—	—	—		—	—	—
DMSO	11.69	10.29	10.4	⟨3.3⟩		⟨12.14⟩		2.77
D_2O	12.30	10.72	10.88	⟨3.52⟩		⟨12.25⟩		3.1
DCl	13.69	7.24	—	—		—	—	—
NaOD	12.31	10.89	11.2	⟨3.48⟩		⟨12.3⟩		2.95

[a] At 295 K unless stated otherwise. [b] 193 K. [c] ±0.1 Hz unless stated otherwise. — Not observed. ⟨ ⟩ Averages of two couplings.

system. The obvious explanation is direct electrostatic attraction even in these polar solvents.

1-Methylnipecotic acid was also analysed in neutral and acidic media. In the cation the conformer populations were obtained by direct integration of the room temperature spectra as there is slow interconversion between the *cis* and *trans* forms (*cf*. Figs. 7, 8) and the conformer energies and hydrogen bond energies obtained as for nipecotic acid are also given in Table 10. The hydrogen bond energies closely follow those for nipecotic acid as would be expected.

Ethyl nipecotate derivatives

Ethyl nipecotate was studied as a free base and as the hydrochloride salt. In ethyl 1-methylnipecotate only the cation can form an intramolecular hydrogen bond (Fig. 9).

Table 9 Proton chemical shifts and couplings of *N*,*N*-diethyl-1-methylnipecotamide[a]

Chemical shifts (δ) (ppm)

Solvent	2a	2e	3	4a	4e	5a	5e	6a	6e	NCH_3
CCl_4	2.00	2.61	2.58	1.49	1.6	1.6	1.6	1.86	2.71	2.17
$CDCl_3$	2.16	2.8	2.74	1.53	1.76	1.62	1.76	1.93	2.8	2.29
MeOD	2.12	2.81	2.81	1.45	1.76	1.64	1.76	1.97	2.88	2.29
MeOD (Conf. E)[b]	2.08	2.83	2.74	1.37	1.76	1.58	1.76	1.95	2.89	2.29
D_2O	2.13	2.85	2.85	1.41	1.80	1.58	1.80	2.03	2.85	2.25

Coupling constants/Hz[c]

Solvent	$^2J_{2e-2a}$	$^3J_{2a-3}$	$^3J_{3-4a}$	$^3J_{2e-3}$	$^3J_{3-4e}$	$^2J_{6a-6e}$	$^3J_{5a-6a}$	$^3J_{5e-6a}$
CCl_4	10.66	11.31	10.53		⟨3.54⟩	10.93	11.78	2.85
$CDCl_3$	⟨11.14⟩		⟨11.14⟩		⟨3.36⟩	⟨11.74⟩	⟨11.74⟩	2.51
MeOD	⟨12.11⟩		⟨11.69⟩		⟨3.50⟩	11.48	12.37	2.76
MeOD (Conf. E)[b]	⟨11.20⟩		⟨11.48⟩					
D_2O	⟨12.03⟩		—		—	—	—	2.83

[a] At 295 K unless stated otherwise, NEt group CH_2 3.3 δ, CH_3 1.2 δ, $^3J_{HH}$ 7.1 Hz in all solvents. [b] 193 K. [c] ±0.1 Hz unless stated otherwise. — Not observed. ⟨ ⟩ Averages of two couplings.

Table 10 Conformer free energy differences ΔG_{A-E}[a] and intramolecular hydrogen bonding energy ΔG_{HB} (kcal mol^{-1}) in nipecotic acid and 1-methylnipecotic acid

	Zwitterion		Cation		Anion	
Solvent	ΔG_{A-E}	ΔG_{HB}	ΔG_{A-E}	ΔG_{HB}	ΔG_{A-E}	ΔG_{HB}
Nipecotic acid						
MeOD	0.0	−2.0	0.48	−0.90	—	—
MeOD–D_2O (1:1)	0.19	−1.8	—	—	—	—
D_2O	0.41	−1.6	0.27	−1.1	1.46	−1.0
1-Methylnipecotic acid						
MeOD	0.33	−1.7	0.38	−1.0	—	—
D_2O	—	—	0.26	—1.1	—	—

[a] ±0.1 kcal mol^{-1} unless stated otherwise.

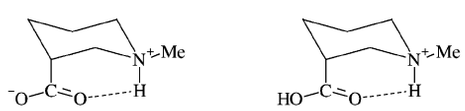


Fig. 7 1-Methylnipecotic acid zwitterion (left) and cation salt (right).

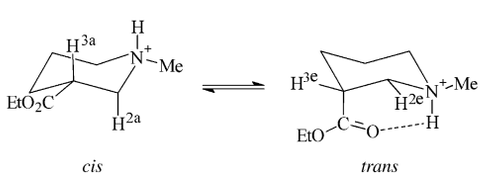


Fig. 8 Diastereomeric equilibrium of ethyl 1-methylnipecotate salt.

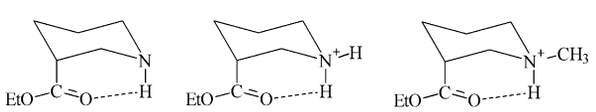


Fig. 9 Ethyl nipecotate free base and cation and ethyl 1-methylnipecotate cation (right).

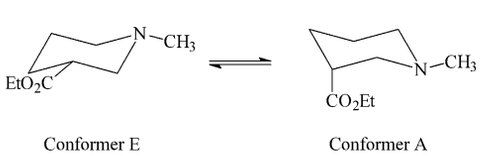


Fig. 10 Conformational equilibrium of ethyl 1-methylnipecotate.

The axial/equatorial free energy difference of the CO_2Et group in the piperidine ring (ΔG_{CO_2Et}) was obtained from the analysis of the ethyl 1-methylnipecotate free base (*cf*. Fig. 10). J_{2a-3} (Table 4) is almost independent of solvent with an average value of 10.1 (±0.1) Hz. This when inserted into eqn. (4) gives $n_E = 0.82$ and $\Delta G_{CO_2Et} = 0.89 \pm 0.1$ kcal mol^{-1}. This figure is very comparable to the *A* value quoted for the CO_2Et group in ethyl cyclohexanecarboxylate (1.1–1.2 kcal mol^{-1}).[23] These values would be expected to be very similar. One axial–axial interaction in axial cyclohexanecarboxylate has been replaced by the less demanding substituent–lone pair interaction in piperidine, but this is counterbalanced by the smaller C–N *vs*. C–C bonds giving a larger axial–axial repulsion for any given axial substituent–axial hydrogen interaction.

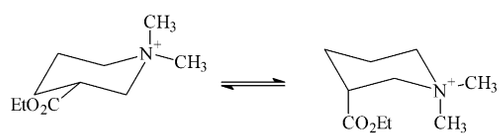
The conformer free energy differences in ethyl nipecotate were obtained from the $^3J_{2a-3}$ coupling at room temperature for the free base and cation (Table 3) using eqns. (4) and (5) and by direct integration at room temperature of the ethyl 1-methylnipecotate (E1MN) cation spectrum. In the free base the value of $^3J_{2a-3}$ increases significantly with the polarity of the solvent from 9.10 to 9.85 Hz. (Table 3) resulting in an increase in the value of ΔG_{A-E} (Table 11). The conformer energy differences were also calculated at 190 K by direct integration in both $CFCl_3$–CD_2Cl_2 and MeOD solvents to give values of 0.57 and 0.73 ± 0.10 kcal mol^{-1} in excellent agreement with the room temperature measurements.

Using eqn. (6) and the value of ΔG_{CO_2Et} of 0.89 kcal mol^{-1} for the piperidine ring obtained above gives the H-bond energy in this system (Table 11). For ethyl nipecotate and

Table 11 Conformer energy difference ΔG_{A-E}[a] and intramolecular hydrogen-bonding energy ΔG_{HB} (kcal mol^{-1}) of ethyl nipecotate and nipecotamide derivatives in different solvents at room temperature

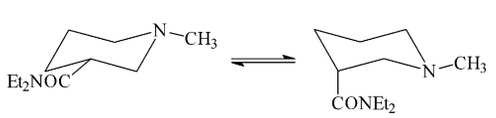
	Ethyl nipecotate		Diethylnipecotamide		Nipecotamide		1-Methylnipecotamide	
Solvent	ΔG_{A-E}	ΔG_{HB}	ΔG_{A-E}	ΔG_{HB}	ΔG_{A-E}	ΔG_{HB}[c]	ΔG_{A-E}	ΔG_{HB}
Free base								
$CFCl_3$–CD_2Cl_2	0.50	−0.89	0.63	−1.8	—	—	—	—
$CDCl_3$	0.56	−0.83	0.84	−1.6	−0.46	−2.4	—	—
CD_2Cl_2	0.59	−0.80	0.79	−1.6	−0.41	−2.3	−0.39	−2.3
Acetone	0.63	−0.76	—	—	0.30	−1.6	0.48	−1.4
MeOD	0.77	−0.62	1.0	−1.4	1.06	−0.8	1.30	−0.6
DMSO	—	—	1.0	−1.4	1.10	−0.8	—	—
D_2O	0.78	−0.61	1.2	−1.2	1.39	−0.5	1.93	0.0
Cation								
$CDCl_3$	0.29	−1.11					0.70[d]	−1.2
MeOD	—	—	—	—	—	—	0.15	−1.7
D_2O–DCl	0.37	−1.03	−0.08	0.49	−2.4	−1.4	0.47	−1.4
E1MN[b]/MeOD	0.48	−0.92	—				—	

[a] ±0.1 kcal mol^{-1} unless stated otherwise. [b] Ethyl 1-methylnipecotate cation. [c] Type *b* H-bonding (Fig. 15). [d] CD_2Cl_2 solvent.



Conformer E Conformer A

Fig. 11 Conformational equilibrium of ethyl 1,1-dimethylnipecotate.



Conformer E Conformer A

Fig. 12 Conformational equilibrium of *N*,*N*-diethyl-1-methylnipecotamide.

E1MN cations the value of the ax–eq conformer energy of the CO_2Et group in cyclohexane (1.40 kcal mol^{-1})[23] was used in eqn. (6) as this more resembles the protonated piperidine ring.

The hydrogen bond energies in ethyl nipecotate free base in nonpolar solvents are very similar to those in the cation and to the corresponding nipecotic acid species, again showing that the introduction of one charged group does not affect the hydrogen bond energy in this system. There is however a large solvent effect on the hydrogen bonding energies in the free base, the value in D_2O being almost half that in $CFCl_3$.

Ethyl 1,1-dimethylnipecotate was examined as the chloride salt. There is a large repulsive 1,3-diaxial interaction in the axial conformation with no possible intramolecular hydrogen bonding in this compound. Thus this molecule would be expected to exist entirely as conformer E (Fig. 11).

Accurate measurement of the $^3J_{2a-3}$ coupling was not possible due to unresolved fine structure but the average value of the coupling of *ca*. 12.3 Hz (Table 5) is the same as that for *cis*-1-methylnipecotate in acid solution (Table 4). This again implies that there is no significant amount of conformer A in this molecule.

Nipecotamide derivatives

N,*N*-Diethyl-1-methylnipecotamide in neutral solution cannot form an intramolecular hydrogen bond and therefore, ΔG_{A-E} is the free energy difference of the $CONEt_2$ group between the axial and equatorial positions (Fig. 12). There is no systematic variation of the coupling constants with solvent (Table 9) as expected and the conformer energy was calculated from the $^3J_{2a-3}$ coupling in CCl_4 solution (11.31 Hz) *via* eqn. (4)

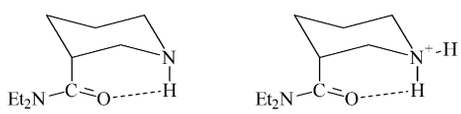


Fig. 13 *N*,*N*-Diethylnipecotamide free base (left) and cation (right).

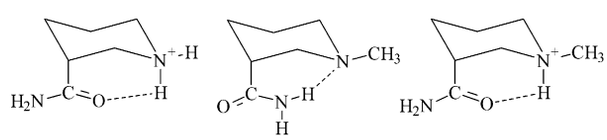


Fig. 14 Nipecotamide cation (left), 1-methylnipecotamide free base (middle) and cation (right).

to give ΔG_{A-E} 1.9 ± 0.2 kcal mol^{-1}. In the other solvents, this coupling could not be measured accurately as it was not resolved from the geminal coupling $^2J_{2a-2e}$.

N,*N*-Diethylnipecotamide was studied in neutral and acidic solutions, *i.e.* as the free base and cation respectively (Fig. 13). On going from the nonpolar $CFCl_3$ solvent to water the $^3J_{2a-3}$ coupling increases from 9.48 to 10.72 Hz corresponding to an increase in the equatorial conformer, *i.e.* increasing ΔG_{A-E} (Table 11). For the free base the hydrogen bond energy was obtained as usual *via* eqn. (6) using the above value of 1.9 kcal mol^{-1} for the substituent free energy difference. For the cation a more appropriate value is for the corresponding cyclohexane derivative. The value of ΔG_{A-E} used was that for the CONHMe group in *N*-methylcyclohexanecarboxamide of 2.3 ± 0.2 kcal mol^{-1} obtained by VT NMR in our laboratory.[20]

Nipecotamide and 1-methylnipecotamide (Fig. 14) were analysed in a large range of solvents of different polarity. In both the free bases $^3J_{2e-3}$ increases dramatically with solvent polarity: in nipecotamide from 5.6 Hz in chloroform to 10.9 Hz in water (Table 6) and in 1-methylnipecotamide from 4.2 to 11.4 Hz (Table 7). In both compounds the $^3J_{2e-3}$ coupling in the nonpolar solvents (CD_2Cl_2 and $CDCl_3$) is now so small that the H^3 peak is no longer a triplet of triplets but a 1:4:6:4:1 quintet from which only the average coupling of H^3 with $H^{2a/2e}$ and $H^{4a/4e}$ is obtained. In nipecotamide the $^3J^{2e-3}$ coupling was obtained from the $H^{2e/2a}$ peaks, but in 1-methylnipecotamide the α proton resonances of $H^{2e/2a}$ and $H^{6e/6a}$ in both solvents were broad unresolved humps at room temperature. The conformer energies for both compounds were obtained from the low temperature spectra in CD_2Cl_2 to give values of ΔG_{A-E} of −0.26 kcal mol^{-1} for nipecotamide and −0.39 kcal mol^{-1} for the 1-methylnipecotamide. The value for nipecotamide is in reasonable agreement with that obtained from the room

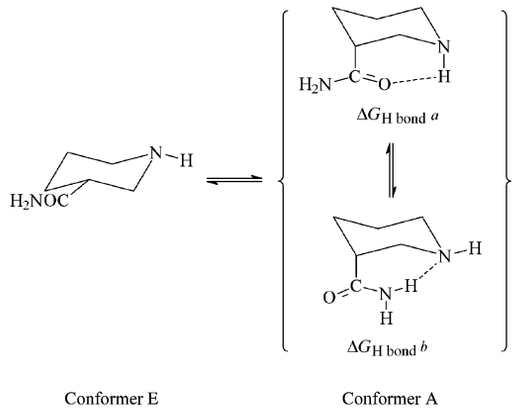


Fig. 15 The conformational equilibrium and hydrogen bonding in nipecotamide free base. Top, type *a*, amine to carbonyl; bottom, type *b*, amide to amine

temperature coupling (−0.41, Table 11) and the value for 1-methylnipecotamide is given in Table 11. The low temperature spectrum of nipecotamide was also obtained in acetone solution, but the low solubility at this temperature resulted in a poorly resolved spectrum from which only the major E conformer could be identified.

Incorporating the measured values of $^3J_{2e-3}$ given in Tables 6 and 7 into eqn. (4) gives the values of ΔG_{A-E} in the two compounds shown in Table 11. The large change in ΔG_{A-E} with solvent is particularly noteworthy. Conformer A is the *major form* in both compounds in the nonpolar solvents (CD_2Cl_2 and $CDCl_3$) but the variation in ΔG_{A-E} with solvent is so large that Conformer E is predominant in the polar solvents.

In nipecotamide free base there are two possible modes of hydrogen bonding in the axial conformation, C=O···HN (type *a*) and CONH···N (type *b*) (see Fig. 15). If the only hydrogen bond in conformer A is the amine to carbonyl one (type *a*) the free energy of the equilibrium may be analysed as previously (eqn. (6)). If, however, there is an amide to amine hydrogen bond (type *b*) the free energy is analysed following eqn. (7).

$$\Delta G_{A-E} = \Delta G_{CONH_2} + \Delta G_{HB}{}^{b} \qquad (7)$$

ΔG_{CONH_2} is the conformer energy difference of the amide substituent which is assumed to be equal to 1.9 kcal mol^{-1}, the value found earlier for the $CONEt_2$ group. Table 11 gives the values of the hydrogen bonding energy assuming type *b* interaction. This has been shown to be the preferred interaction for these groups from intermolecular hydrogen bonding studies.[24] For the type *a* interaction all the values are increased by 0.5 kcal mol^{-1}, the NH ax/eq energy difference. It is possible that both modes of hydrogen bonding are occurring (see later) in which case the above simple analysis is not exact. However the general conclusions will still be valid.

In 1-methylnipecotamide free base only type *b* hydrogen bonding is possible and thus eqn. (7) was used to obtain the hydrogen bonding energies from the ΔG_{A-E} values. These are given in Table 11.

The results of Table 11 show the dramatic effect of the solvent polarity on the hydrogen bonding energies for both nipecotamide and 1-methylnipecotamide. The effect of the solvent polarity is so great that the hydrogen bond energies decrease from *ca.* 2.4 kcal mol^{-1} in chloroform to almost zero for water solution. In all the solvents the hydrogen bond energies for the two compounds are similar which supports the view that type *b* hydrogen bonding is occurring in both molecules.

The $^3J_{2a-3}$ coupling in nipecotamide changes significantly with the temperature. The coupling changed from 8.87 to 8.21 Hz in going from 0 to 50 °C in acetone solution which corresponds to a change in ΔG_{A-E} from 0.38 to 0.25 kcal mol^{-1}. The enthalpy and entropy of the system can be calculated from these data to give $\Delta H_{A-E} = 1.11$ kcal mol^{-1} and $\Delta S_{A-E} = 2.7\ 10^{-3}$ kcal mol^{-1} K^{-1}.

The values of ΔG_{A-E} in the corresponding cations were obtained from the $^3J_{2e-3}$ coupling *via* eqn. (5) in nipecotamide and by direct integration of the spectra at room temperature in the diastereomeric equilibria of 1-methylnipecotamide. The data for nipecotamide were obtained in D_2O–DCl solution but for the more basic 1-methylnipecotamide trifluoroacetic acid (TFA) was added to the solutions. In both the cations only type *a* hydrogen bonding is possible (Fig. 14) and the identical value of ΔG_{A-E} for water solution (0.5 kcal mol^{-1}, Table 11) supports a similar interaction in both cases.

ΔG_{A-E} of the 1-methylnipecotamide cation in CD_2Cl_2 solution (0.70 kcal mol^{-1}) is much higher than that of the free base in the same solvent (−0.39 kcal mol^{-1}) and also higher than that of the salt in methanol and water solutions. Thus the axial conformation is not very favoured for the cation in this solvent. This may be due to the formation of ion pairs between the TFA anions and the 1-methylnipecotamide cations. The ion pair formation competes for the interaction with the amine proton with the intramolecular hydrogen bonding, shifting the diasteromeric equilibrium towards the formation of the *cis* isomer. In methanol and water solutions the TFA anions are efficiently solvated and do not intervene in the equilibrium.

Conclusions

The data of Tables 10 and 11 are of some interest in that they provide a quantitative measure of both the hydrogen bonding interaction in these systems and the effects of solvation.

As may have been expected the hydrogen bond energies in polar solvents are largest when two oppositely charged species are donor and acceptor as in the nipecotic acid zwitterions (Table 10). Interestingly this interaction is significant (*ca.* 1.7 kcal mol^{-1}) even in the polar protic solvents of methanol and water. Unfortunately it was not possible to obtain a measure of the hydrogen bond strength in nonpolar solvents due to the lack of solubility.

The cation (C=O···H–N$^+$) and anion (CO_2^-···HN) hydrogen bond energies in nipecotic acid are roughly comparable (*ca.* 1 kcal mol^{-1}, Table 10) and again are fairly constant in the small range of solvents used. This is also the case for the analogous ethyl nipecotate cation in which the H-bond energy (C=O···H–N$^+$) is almost constant in $CDCl_3$ and D_2O (Table 11).

In complete contrast to the above is the large solvent dependence of the H-bonding between neutral donor and acceptor groups. The most extreme case is 1-methylnipecotamide in which the NH···N H-bonding interaction is *ca.* 2.3 kcal mol^{-1} in CD_2Cl_2 and decreases to zero in D_2O. This behaviour is almost identical to that of the analogous OH···O interaction in *cis*-cyclohexane-1,3-diol in which the H-bonding interaction decreases from *ca.* 2 kcal mol^{-1} in nonpolar solvents to zero in D_2O.[3] It would appear from these studies that NH···N and OH···O intramolecular hydrogen bonding is essentially zero in aqueous solution.

The hydrogen bonding in nipecotamide is similar to that of the 1-methyl compound though in this case there is the possibility of both NH···N and C=O···HN hydrogen bonding occurring in polar solvents. The C=O···HN interaction in diethylnipecotamide and ethyl nipecotate is also affected by solvation but to a much lesser extent and in these compounds the hydrogen bonding is still significant (*ca.* 0.6 and 1.2 kcal mol^{-1} respectively) in D_2O solution.

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