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Conformational analysis. Part 16* Conformational free energies in substituted piperidines and piperidinium salts

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SUMMARY

The conformational free energies ($-\Delta G°$) of a number of 4-substituted piperidines and piperidinium salts have been determined by the J-value method. For the 4-substituted piperidines (R = Me, Phenyl, CO_2Et, Br, OH, F) the relative conformer energies are almost identical to those of the analogous cyclohexanes.

The methyl and phenyl compounds showed no change in the couplings on protonation, implying no change in the conformer energies. In contrast, in the remaining compounds with polar 4-substituents an almost constant stabilisation of the axial conformer of ca. 0.7 – 0.8 kcal mol^{-1} was observed on protonation. In three cases (R = F, OH and Br) the conformational preference is reversed on protonation and the axial form is favoured.

The conformer energies of both the free bases and the piperidinium salts can be quantitatively predicted by molecular mechanics calculations using the COSMIC force-field, in which the electrostatic interactions are calculated by a simple Coulombic model with the partial atomic charges in the molecules given by the CHARGE2 routine, and an effective dielectric constant of five. The precise agreement obtained demonstrates conclusively that the electrostatic interactions between the substituents and the protonated nitrogen are the cause of the conformational changes on protonation, and that these can be modelled successfully using existing force-fields.

INTRODUCTION

The prediction of the conformational energies of charged molecules is currently one of the most

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pressing problems in theoretical organic chemistry [2]. Quantum mechanics, even at the ab initio level, cannot by itself reproduce the very considerable effects of solvation on molecular conformational energies. A recent illustration of this was the disparity between the calculated (STO-3G) and observed (D_2O solution) *gauche-trans* energy difference in β-alanine [3] (calculated 31.3 kcal mol^{-1} in favour of the *gauche* form, observed 0.1 kcal mol^{-1}).

Thus, recent advances in the prediction of molecular conformation energies in solution have utilised Monte-Carlo-type calculations within a molecular mechanics approach [4]. These have given some encouraging results, but cannot yet be said to provide definitive calculations for charge molecules. Still the most widely applied methods are those based on the continuum model, with an effective dielectric constant [5]. A major problem for both methods is the accurate reproduction of the molecular electrostatic energy, and, in consequence, a knowledge of the partial atomic charges in these systems. The development of the CHARGE2 programme [6] does provide a chemically reasonable set of partial atomic charges designed to be used with such molecular mechanics methods.

Another problem in this area has been the lack of accurate conformational energies of theoretically amenable molecules in solution. In a recent study of 1,2-disubstituted ethanes in solution, in both their uncharged and charged forms, Abraham et al. [3], utilised the NMR couplings to obtain the conformational preferences in solution and this still represents one of the most direct methods of obtaining this data for aqueous solutions.

In many respects substituted cyclohexanes (and analogues) are better models to use than substituted ethanes, as the rigidity and stability of the chair conformation gives a more well defined system which allows more subtle effects to be observed. For example, the conformational transmission of the electrostatic effect of polar substituents (Cl, Br) from the C_1 to the C_4 substituent has been well documented [7], resulting in non-additive A values [8] for 1,4-dihalocyclohexanes.

The largest effects of this type would be expected to be observed with charged molecules such as piperidine salts. Recently, some of us have demonstrated that cobalt(III) porphyrins can serve as conformational probes for substituted piperidines [9]. Complexation to the cobalt atom slows the ring conformational inversion so that it is slow on the NMR timescale, giving separate NMR spectra for the axial and equatorial conformers from which free energy differences can be accurately measured. These conformer energies were not always the same as those reported for the corresponding free bases, and it was speculated that complexation with the cobalt may result in a partially positively charged nitrogen atom which could affect the conformational preference of the substituent. If this was the case, then the effect of protonating the piperidine nitrogen atom should be even more pronounced.

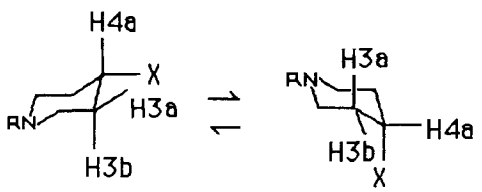
We present here a detailed NMR investigation of the conformer free energies of a number of 4-substituted piperidines as the free bases and also as the salts, together with a theoretical calculation of the conformer energies. The large effects observed can indeed be quantified as primarily electrostatic in nature.

There have been few previous systematic studies of these systems. Booth et al. [10] have obtained by low-temperature NMR the conformer preferences in 4-bromo- and 4-methoxypiperidine and Eliel et al. [11] have obtained the corresponding value for 4-methyl-piperidine. Terui and Tori [12] used the coupling-constant approach to obtain the conformer energies of both the 3- and 4-substituted hydroxy and acetoxypiperidines and the corresponding piperidinium salts. They also showed that differences in the free energies due to protonation could be at least rationalised on the basis of a simple electrostatic model with a dielectric constant of 4.

THE DETERMINATION OF CONFORMER FREE ENERGIES ($-\Delta G°$)

The principles of the J-value method of determining conformer energies are well established [13], however, it is important to document them as the errors which can occur in these determinations mainly arise from incorrect assumptions in the treatment.

We consider here the conformational equilibrium in 4-substituted piperidines and piperidinium salts, which can be conveniently written as in Eq. 1, due to fast inversion of the nitrogen atom in the free bases and the rigid conformation of the quaternary nitrogen atom in the salts. The two observed proton coupling constants of the H4 proton are the weighted averages of the couplings in the equatorial and axial conformers. However, we note immediately that only the *trans* coupling (J_{3b-4a}) will show any large change between the two conformers, the *cis* coupling being virtually unchanged. Thus the common practice of combining these couplings in order to obtain conformational energies merely introduces an unnecessary loss of definition, and we shall concentrate henceforth on the *trans* coupling (fortunately, there is no ambiguity about the assignment of these couplings, see later).



(1)

$$J_{3b-4a}\,(\text{obs.}) = n_e\,J_{ax-ax} + (1-n_e)\,J_{eq-eq}$$
$$J_{3a-4a}\,(\text{obs.}) = n_e\,J_{ax-eq} + (1-n_e)\,J_{eq-ax}$$
$$n_e = [J_{3b-4a}\,(\text{obs.}) - J_{eq-eq}]/[J_{ax-ax} - J_{eq-eq}]$$
$$-\Delta G° = RT \ln [n_e/(1-n_e)]$$

It is then only necessary, apart from measuring the observed coupling, to obtain good values for the limiting couplings J_{ax-ax} and J_{eq-eq} for the particular fragment considered, as these couplings may change appreciably with the substituent X. One possible approach is that these limiting values for the fragment under consideration can be taken from the appropriate cyclohexane derivatives for which there is reliable data, and Table 1 gives these couplings in locked or frozen cyclohexane derivatives. Interestingly, there is an excellent linear relationship (Eq. 2) between J_{ax-ax} and the Huggins electronegativity [18] of the substituent and this predicts a value of 10.8 Hz for the fluoro-derivative. The equatorial–equatorial coupling is essentially invariant to the substituent electronegativity (Table 1); we shall use the value of 3.0 Hz for all substituents except OH and F for which a value of 2.7 Hz will be used.

$$J_{ax-ax} = 16.45 - 1.44\,Ex \tag{2}$$

An alternative procedure is to use the analogous couplings in the conformationally locked cobalt(III) porphyrin piperidine complexes reported previously. Due to the increased line width of these spectra only the axial–axial couplings could be resolved and these are given in parentheses in Table 1. These are in good agreement with the more accurate values of the cyclohexane analo-

TABLE 1
$^3J_{HH}$ COUPLINGS (Hz) IN CYCLOHEXANE AND (PIPERIDINE)[a] DERIVATIVES

Substituent	Equatorial conformer		Axial conformer		Ref.
	J_{ax-ax}	J_{ax-eq}	J_{eq-ax}	J_{eq-eq}	
H	13.3 (12.9)	3.6	3.6	3.0	14
CN	12.7 (12.1[b], 12.2[c])	3.5	4.3	2.7	15
Br	12.2 (11.7)	4.0	3.0	3.0	15
Cl	11.9 –	4.1	3.0	3.0	15
$N^+Me_3Cl^-$	11.9 –	3.3	–	–	16
OAc	11.4 (10.9)[d]	4.2	2.7	2.7	17
F	10.8[e] (11.0)[f]	–	–	–	

[a] J_{ax-ax} in parentheses from cobalt (III) porphyrin piperidine derivatives (see text).
[b] Phenyl derivative.
[c] CO_2Et derivative.
[d] OH.
[e] From Eq. 2.
[f] This work.

gues, with an almost constant decrease of ca. 0.4 – 0.5 Hz in J_{ax-ax}, which could be due to small changes in the ring conformation in the piperidine complexes.

The data in Table 1 can be used, together with the analogous observed couplings in the piperidines and piperidine salts, to obtain from Eq. 1 the required ΔG° values.

EXPERIMENTAL

The piperidines used in the study were obtained either commercially or from methods available in the literature. Samples of 4-methyl, 4-phenyl, 4-carbethoxy and 4-hydroxypiperidine were obtained commercially as the free bases and used without further purification. A literature method [10] was used to prepare 4-bromo-piperidine HBr and a sample of 4-fluoropiperidine HCl was generously donated by Dr. J. Kollonitsch (Merck, Sharp and Dohme, Rahway, NJ).

NMR spectra were obtained using a Bruker WM250 spectrometer. Typical conditions included a probe temperature of 298 K, spectral window 1000 Hz, 8 K data points and a 45° pulse. The data was resolution enhanced using a Gaussian multiplication (typically LB = −0.5 and GB = 0.2) and zero-filled to 32 K to give a digital resolution of 0.06 Hz/point. For the free base piperidines, 50-mM solutions of the amine were prepared in $CDCl_3$ and the residual chloroform peak was used as a reference (δ 7.25). Where the amine was obtained as a salt, the free base was prepared by dissolving the salt in D_2O, neutralising with sodium carbonate and extracting into $CDCl_3$. Solutions of the piperidinium salts were also prepared in $CDCl_3$, either by dissolving the salt (F) or by adding one drop of TFA to a solution of the free base (Br, OH, CO_2Et, Me, Ph). For some samples (Br, F, OH) one or two drops of d_6-DMSO were added to completely dissolve the salt.

Assignments for all of the free base piperidines except for 4-fluoropiperidine have been reported previously [9]. The proton spectra of the piperidinium salts used in this study were not rigorously analysed and the assignments given below are provisional. However, in each case the coupling constants for H4 could be unambiguously assigned (c = *cis* to substituent, t = *trans*) 4-fluoropiperidine free base H4 4.68; H3 2.01 – 1.61; H2 2.68t; 3.08c J_{H-F} = 48.7 Hz. 4-Fluoropiperidinium

salt H4 4.84; H3 1.99c, 2.16t; H2 3.21 – 3.04 J_{H-F} = 47.5 Hz (gem), 36.4 Hz (*trans*), 9.8 Hz (*cis*). 4-Bromopiperidinium salt H4 4.50; H3 2.18c, 2.40t; H2 3.21t, 3.41c. 4-Hydroxypiperidinium salt H4 3.61; H3 1.43c, 1.64t; H2 2.67t, 2.97c. 4-Carbethoxy-piperidinium salt H4 2.67; H3 1.60c, 1.88t; H2 2.64t, 3.09c. 4-Methyl-piperidinium salt H4 1.70; H3 1.43c, 1.90t; H2 2.98t, 3.47c. 4-Phenylpiperidinium salt H4 2.87; H3 2.09c, 2.18t; H2 3.21t, 3.68c.

RESULTS

The required J_{34} coupling constants in 4-fluoropiperidine (free base and salt), and the salts of the other 4-substituted piperidines measured are given in Table 2, together with the couplings in the corresponding free bases taken from Ref. 9.

The assignment of these couplings to the *cis* and *trans* coupling given in Table 2 is straightforward. From Eq. 1 and Table 1, the value of the *cis* coupling (J_{3a-4a}) is always <4.3 Hz, which unequivocally assigns all the couplings.

The values of the *trans* coupling (J_{3b-4a}) given in Table 2, together with the appropriate values of J_{ax-ax} and J_{eq-eq} from Table 1 give immediately from Eq. 1, the required $-\Delta G°$ values.

However, for the methyl and particularly phenyl substituents the conformational equilibrium is too heavily biased towards the equatorial conformer to be able to be calculated by this method, and this is confirmed by the absence of any appreciable change in the couplings in going from the free base to the salt. The value of $-\Delta G°$ of 1.9 kcal mol^{-1} for 4-methyl piperidine was obtained by different methods [11].

Conversely, for the electronegative substituents of interest (F, OH, Br) the conformational equilibrium is not heavily biased and the $-\Delta G°$ values obtained are thus not very dependent on the precise values of J_{ax-ax} and J_{eq-eq} used. We have used J_{ax-ax} values from the cyclohexane derivatives in these cases (Table 1, first column). Only for the more heavily biased equilibrium of the CO_2Et group does the value of J_{ax-ax} become more critical and we use the value of 12.2 Hz from the corresponding cobalt(III) porphyrin complex.

Before considering these free energy differences further, it is important to stress the errors and assumptions made in this analysis. We have assumed that the intrinsic values of the couplings do

TABLE 2
$^3J_{HH}$ COUPLINGS (Hz) IN 4-SUBSTITUTED PIPERIDINES AND THE CORRESPONDING SALTS

Substituent	Free base [a]		Salt	
	J_{3a-4a} (J *cis*)	J_{3b-4a} (J *trans*)	J_{3a-4a}	J_{3b-4a}
CH_3	3.8	10.7	3.6	11.4
Ph	3.8	12.0	3.9	11.9
CO_2Et	3.9	11.3	4.2	9.6
Br	4.1	9.0	3.3	6.2
OH	4.2	9.6	3.2	6.5
F	3.9	7.7	2.3	4.6

[a] From Ref. 9 except F substituent.

not change on protonating the piperidine ring. There is no evidence that they do change. Indeed, in 4-phenyl-piperidine (which is essentially in one conformation) the couplings do not change on protonation, supporting this assumption. Also, the errors involved in the determination of the free energy differences are very dependent on the actual value of ΔG°. If the compound is predominantly in one conformation, the errors in both the observed and the limiting couplings add to give larger uncertainties in the ΔG° values. Thus the ΔG° values are estimated to be accurate to 0.1 kcal mol^{-1} for values < 1 kcal mol^{-1} but only to 0.3 kcal mol^{-1} for $\Delta G^\circ > 1$ kcal mol^{-1}.

The conformer free energy differences in the piperidines and their salts obtained here are given in Table 3, together with those recorded by other workers. There is complete agreement, and this is particularly pleasing in those cases for which other methods have been used to deduce the free energies. Thus Booth et al.'s value for the 4-bromo derivative from direct integration at low temperature [10] is in complete agreement with our value, and so is the energy difference for the 4-hydroxy compound obtained by Chen and LeFevre [19]. The values obtained by Terui and Tori [12] in contrast, utilise the same approach as the present one. The small differences observed (e.g., in the 4-hydroxy compound) can easily be attributed to different assumptions in the treatment.

These values of the conformer free energy differences are of some interest. The values for the piperidine free bases are, as may have been anticipated, very similar to the well-known values recorded for substituted cyclohexanes. The A values for the substituents of Table 3 are (in kcal mol^{-1}): 0.5 (Br), 0.25 (F), 0.5 – 0.9 (OH), 1.1 (CO_2R) and 1.8 (CH_3) [8]. All the values are the same within the experimental error as those in Table 3. Note that the A value for the OH group depends on the solvent due to hydrogen bonding interactions in the axial and equatorial conformers.

TABLE 3
OBSERVED AND CALCULATED CONFORMER ENERGIES (kcal mol^{-1}) FOR 4-SUBSTITUTED PIPERIDINES AND PIPERIDINIUM SALTS

Substituent		Calculated energy[a]		Conformer energy			
				Free base		Piperidinium salt	
		NH_{eq}	NH_{ax}	Calc.	Obs.	Calc.	Obs.
Br	eq	0.00	0.01	0.5	0.4(0.3)[b]	−0.4	−0.4
	ax	0.46	0.59				
F	eq	0.00	0.02	0.2	0.2	−0.5	−0.8
	ax	0.21	0.36				
OH[c]	eq	0.04	0.00	0.7	0.8(0.6)[d] (0.8)[e]	−0.1	−0.1(−0.2)[d]
	ax	0.72	0.80				
CO_2Et[f]	eq	0.00	0.01	1.2	1.3	0.7	0.6
	ax	1.13	1.29				
CH_3	eq	0.03	0.00	1.8	1.9[g]	1.7	(1.9)[h]
	ax	1.81	1.82				

[a] Relative to the most stable conformer.
[b] Ref. 10.
[c] *Gauche* conformation of C–H–O–H bond.
[d] See Ref. 12.
[e] See Ref. 13.
[f] *Gauche* conformation of H–C–C=O bond.
[g] See Ref. 11.
[h] No change in observed coupling.

In complete contrast the conformer stabilities *reverse* in the salts with electronegative substituents, whilst remaining unaffected for the non-polar substituents. Thus in the 4-bromo, fluoro and hydroxyl piperidinium salts the axial conformer is preferred, and there is an almost constant difference in the conformer energies on protonation, of ca. 0.8 kcal mol^{-1}. The difference is also observed for the 4-carboxyethyl compound, but here the conformational equilibrium in the free base is more biased towards the equatorial conformer ($-\Delta G^{\circ}$, 1.3 kcal mol^{-1}) and thus the extra stabilisation of the axial conformer is not sufficient to reverse the conformer stabilities on protonation.

Note, however, that the 4-methyl and 4-phenyl piperidines show no observable changes in the couplings on salt formation, and thus no changes in the conformer energies.

These effects strongly suggest an electrostatic interaction between the protonated nitrogen and the C_4 substituent to be the cause of these remarkable changes, and it was therefore of some interest to see whether the conformer energies in both the free bases and the salts could be accounted for by molecular mechanics calculations. The calculations used the COSMIC force-field of Vinter et al., which is completely described in Ref. 20. The only significant amendment made to this force-field is the inclusion of a more refined HH non-bonded potential obtained by Abraham and Haworth [21] by fitting ab initio calculations. The partial atomic charges in the molecules were given by the CHARGE2 routine, of which full details are given elsewhere [6]. Full relaxation of the molecules was performed in all cases, and the dielectric constant of the medium was taken as that appropriate to a chloroform solution (4.8), i.e., the Coulombic electrostatic interactions were divided by 4.8.

In the free bases the conformations with NH axial and equatorial were treated separately. The overall effective conformational free energy difference can easily be obtained by combining the populations of the NH axial and NH equatorial conformations. For the asymmetric OH and CO_2Et substituents, the most stable conformations were those with the H–C–O–H and H–C–C–O dihedrals in the *gauche* form, and these energies are given in Table 3. Including the other rotamers does not affect the overall conformational energy.

Inspection of Table 3 shows the excellent agreement between the observed and calculated free energy differences for both the free bases and the piperidinium salts*. The agreement for the free bases is noteworthy, in that the conformer energies are often not well reproduced by many force-fields. The inclusion of the polar 4-substituents, in an already polar molecule, is handled automatically and easily. No extra terms are needed in the force-field and the polar interactions are accounted for by the straightforward Coulombic term, together with the CHARGE2 partial atomic charges.

The extra stabilisation of the axial conformer in all the substituted piperidines (except the 4-methyl and 4-phenyl) on protonation is extremely well reproduced, and demonstrates conclusively that this effect originates in the electrostatic interaction between the protonated nitrogen atom and the polar substituents. Indeed, as the conformations of the molecules do not change appreciably on protonation there is little change in the other terms in the force-field, as the torsional and

* It should be noted that the comparison in Table 3 is between calculated enthalpy differences and observed free energy differences. Thus we assume that entropy differences between the conformers and entropy solvation differences may be ignored.

steric interactions are almost unaffected. The use of a dielectric constant of five for these calculations would appear reasonable as these measurements were all performed in $CDCl_3$ solution. However, it should be emphasised that this is an effective dielectric constant. Terui and Tori [12] used a value of four for ammonium ions in aqueous solution, and their experimental conformer energies for the 4-hydroxypiperidinium salt in the more polar CD_3OD and D_2O solutions were not significantly different from our result in $CDCl_3$.

However, it is extremely encouraging that a conceptually simple force-field with the inclusion of an electrostatic term calculated from already defined partial atomic charges should give such excellent agreement with the experimental results. This lends much support to the use of this model in predicting the conformations of more complex, charged molecules of biological and pharmacological interest.

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