SOLVENT EFFECTS IN CONFORMATIONAL EQUILIBRIA OF ONIUM SALTS[+]

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Abstract - The equilibria of the S-methyl group in cis- and trans-S-methyl-4-t-butylthianium salts and of the N-methyl groups in corresponding N-methyl-4-t-butylpiperidinium and N-cis-2,6-trimethylpiperidinium salts have been studied as a function of solvent, concentration and gegenion. The effects of these factors are appreciable, causing variations of up to 0.2 kcal/mol in ΔG° in the thianium and 0.4 kcal/mol in the piperidinium salts. Rationalizations for these effects are provided.

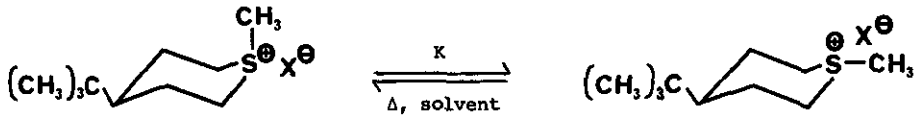
INTRODUCTION

The effect of solvent variation on conformational equilibria in molecules with dipolar substituents has been well studied experimentally[1] as well as predicted[1b,2] on the basis of electrostatic models. Solvent effects on conformational equilibria involving hydrogen bonding are also well understood.[3] However, little is known about the effects of solvents on conformational equilibria involving charged (monopolar) species. We had previously studied conformational equilibria in S-methylthianium[4] and N-methylpiperidinium[5] salts; we have now explored the effect of solvent and related changes in these equilibria.

RESULTS AND DISCUSSION

The effect of solvent changes on the methylthianium equilibrium (Scheme 1) is summarized in Table 1. Equilibria were established in the solvent and at the temperatures indicated and were measured by means of proton or C-13 NMR spectroscopy or both, as previously described,[4] with t-butyl serving as the conformation-holding group. The precision is judged to be ±0.05 in K. The bulk of the data refers to perchlorate but some data relating to hexafluorophosphate and p-toluenesulfonate are included.

[+] Dedicated to Herbert C. Brown on the occasion of his 70th birthday.



Scheme 1

Table 1

Equilibria of cis- and trans-1-Methyl-4-t-butylthianium Salts[a]

Solvent	E[b]	DN[c]	K (-ΔG, kcal/mol) 77.8°C		85.9°C	99.1°C	109.5°C
D_2O	80.4	~33[6b]	1.33	(0.20)	1.27	1.20	1.16
				(0.18)[d]	1.25[d]	1.19[d]	1.16[d]
						1.27[e]	
DMSO-d_6	46.4	29.8	1.44	(0.25)	1.29	f	
			1.44	(0.25)[d]	d,f		
THF	7.6	20.0	1.49	(0.28)	1.37	f	
acetone-d_6	20.7	17.0	1.52	(0.29)	1.43	f	
CD_3CN	37.5	14.1	1.58	(0.32)	1.44	1.34	1.28
					1.44[d]	1.35[d]	1.27[d]
					1.50[e]	1.43[e]	
$C_6H_5NO_2$	34.8	4.4	1.69	(0.36)	1.66[e]	1.59	1.56
						1.59[d]	1.56[d]
					1.78[e]	1.67[e]	
$ClCH_2CH_2Cl$	10.7	0	1.79	(0.40)	1.72	1.68	1.59
						1.82[e]	

[a] Perchlorates unless noted otherwise. [b] Dielectric constant for protiated solvents in the 20-25°C range.[6a] [c] Donicity (donor number) for protiated solvent.[6] [d] Hexafluorophosphate. [e] p-Toluenesulfonate. [f] Not stable at this temperature.

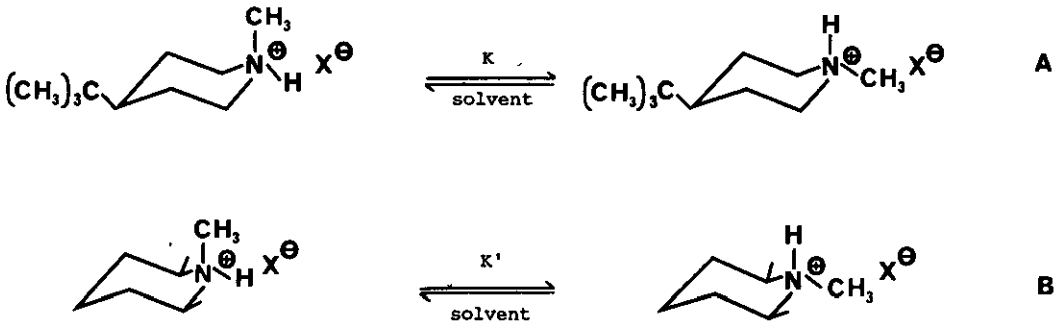
It is evident from Table 1 that the S-methyl equilibrium is palpably affected by solvent, although the effect is not large (range of K 1.33 in water to 1.79 in 1,2-dichloroethylene at 77.8°C). Of considerable interest is the fact that K correlates well with donicity[6] (donor number) *and not* at all well with dielectric constant. Thus at 77.8°C, there is a considerable difference in K between

tetrahydrofuran (THF) (1.49) and 1,2-dichloroethane (1.79) even though the dielectric constants of the two solvents (7.6, 10.7) are similar. On the other hand, K in DMSO (1.44) is similar to that in THF (1.49) even though the dielectric constants of these solvents are quite different (46.4 vs. 7.6). On the other hand, DMSO and THF have comparable donicity (29.8 vs. 20.0) and, indeed, an increase in K as one goes down Table 1 corresponds to a decrease in donor number throughout. The simplest explanation is that the better donor solvents prefer to associate with the sulfonium ion from the equatorial side and thus favor the configuration with axial methyl, diminishing K.

The effect of changing gegenion is small, there being no significant difference between perchlorate and hexafluorophosphate and only a slight increase in K with p-toluenesulfonate. This suggests that effects of ion pairing are not large or that there is little ion pairing altogether between the large sulfonium cation and the equally large and poorly nucleophilic anions employed. (The sulfonium salts are not stable to heating in the presence of nucleophilic gegenions.)

K diminishes with temperature, as would be expected, but the extent of change differs for different solvents, suggesting subtle influences of solvent on enthalpy and entropy differences between stereoisomers. Our data do not span a large enough temperature range to make calculation of $\Delta S°$ and $\Delta H°$ meaningful; unfortunately equilibrium is established too slowly below 75°C and decomposition tends to set in, at least in some solvents, above 90°C.

The N-methylpiperidinium salt equilibria studied by ^{13}C NMR[5] are shown in Scheme 2 and pertinent data are summarized in Table 2. Since, in solvents other than D_2O, it was not possible to effect the pH control previously prescribed,[5] the salts (chlorides, perchlorates) were prepared dry and dissolved in appropriate solvent, it being assumed that, at the autogenous pH of the salt, equilibrium between diastereomers (with equatorial and axial NMe) would be rapidly established.



Scheme 2

Table 2

Equilibria of cis- and trans-1-Methyl-4-t-butyl- and

1,cis-2,6-Trimethylpiperidinium Salts

Compound	Gegenion	Solvent	Concentration (M)	K	$-\Delta G^{\circ}$[a] kcal/mol
A	Cl^-	D_2O	1.5	18.5	1.79
			1.0	19.3	1.81
			0.5	21.4	1.88
			0.3	24.4	1.96
A	Cl^-	$CDCl_3$	1.0	25.2	1.98
			0.5	21.4	1.88
			0.3	20.5[b]	1.85
A	ClO_4^-	CD_3CN (14.1)[c]	1.0	18.1	1.77
		$C_6D_5NO_2$ (4.4)[c]	1.3	27.5	2.03
			1.0	28.9	2.06
		$CDCl_3$ (~0)[c]	1.3	30.9	2.10
			1.0	34.8	2.17
B	Cl^-	D_2O	1.0	2.77	0.62
			0.5	2.38	0.53
	Cl^-	$CDCl_3$	1.5	1.81	0.36
			1.0	1.71	0.33
			0.5	1.39	0.20
B	ClO_4^-	D_2O (33)[c]	1.0	1.72	0.33
			0.5	1.84	0.37
		$C_6D_5NO_2$ (4.4)[c]	1.0	2.30	0.53
		$CDCl_3$ (~0)[c]	1.0	2.96	0.66
			0.5	3.06	0.68

[a] At 35±1°C. [b] Approximate value; the spectrum was excessively noisy.

[c] Donicity of protiated solvent.[6]

With respect to the variation of solvent, when the gegenion is perchlorate (which has little tendency to ion pairing), we see the same effect as in the thianium salts (vide supra): as the donicity of the solvent decreases, the amount of axial isomer at equilibrium decreases (i.e. K increases). Thus here, also, it appears that the stereoisomeric salt with axial methyl is favored by donor solvents. It is known[7] that solvation of a tertiary amine salt is mainly from the side of the proton (rather than the alkyl groups) and it is also known[8] that solvation is easier from

the equatorial than from the axial side. Thus the isomer with the equatorial proton (axial methyl) is favored by donor solvents through solvation of that proton.

The situation becomes much more complicated when the gegenion is chloride. With salt A, it is still true that K is smaller in the high-donicity solvent water than in the low-donicity solvent chloroform at concentrations above 0.5M. However, whereas in chloroform K decreases with dilution, in water it increases. This is not easy to understand, for if ion pairing occurs (which is likely with an ion as small and nucleophilic as chloride) it should increase with concentration and presumably favor the axial isomer. However, the contrary is true in chloroform where one might expect ion pairing to be more important than in water. An additional factor - perhaps ion aggregation - must be at work, but further study is required to eludidate this point. Interestingly, with the chloride B, the equilibrium constant K diminishes in both water and chloroform as the solutions are diluted. This would appear sensible for solvent water (vide supra) but not for solvent chloroform where one might have expected ion pairing to favor the axial isomer and to increase with concentration. The contrary is the case. The data could be explained better if ion pairing favored equatorial N-Me, in which case one could simply say that ion pairing is dominant with B (in which the nitrogen is shielded by the 2,6-methyl groups) in both $CDCl_3$ and D_2O whereas the more open A, ion pairing dominates in $CDCl_3$ and solvation in D_2O. However, the hypothesis that ion pairing favors equatorial N-Me seems inherently far-fetched.

In any case it is of interest the $-\Delta G°$ for piperidinium salt A (Scheme 2) varies between 1.77 and 2.17 kcal/mol, depending on conditions. This may explain why the value previously determined by us for the cis-3,5-dimethyl analog in D_2O (2.1 kcal/mol[5]) was so much larger than that determined by Booth[9] in CF_3CO_2H (~1.7 kcal/mol).

METHODOLOGY

1-Methyl-4-t-butylthianium perchlorate[4] was prepared from the thiane,[10] methanol and perchloric acid.[11] The hexafluorophosphate[4] was made from the parent thiane and trimethyloxonium hexafluorophosphate[4] and the p-toluenesulfonate from the thiane and methyl p-toluenesulfonate; the latter two salts had correct C/H analyses. Equilibrations were carried out in a vaporstat in sealed NMR tubes and analyses were effected by proton and/or C-13 NMR spectroscopy.[4] The hydroperchlorates and hydrochlorides of amines A and B (Scheme 2) were prepared by treating the corresponding amines[5] with the appropriate acids; the hydroperchlorates had correct elemental (C/H) analyses. The salts were dissolved in the appropriate solvents and the solutions analyzed by C-13 NMR spectroscopy.[5]

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