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LARGE TEMPERATURE AND SOLVENT EFFECTS IN THE CONFORMATIONAL EQUILIBRIUM OF PHENCYCLIDINE [1-PHENYL-1-(N-PIPERIDYL)CYCLOHEXANE]

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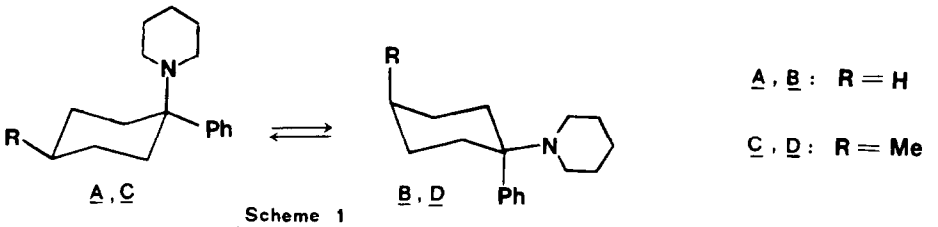
Abstract. The conformational equilibrium of phencyclidine [1-phenyl-1-(N-piperidyl)cyclohexane or 1-(1-phenylcyclohexyl)piperidine, PCP] is strongly dependent on solvent and in the hydrogen-bonding solvent methanol also on temperature.

Phencyclidine (PCP) was developed in the late 1950's as a general anesthetic, but because of psychotomimetic effects was withdrawn from human use. In the past few years, PCP has become a major drug of abuse and has been the subject of renewed chemical and pharmacological interest.[1] Kamenka and Geneste[2] have suggested that the drug "is likely to take on two profiles" both in its physical and its biological properties, corresponding to the two conformations shown in Scheme 1 (R=H). Evidence was adduced that the less abundant conformer A was the more lipophilic one, in as much as the hydrophilic nitrogen atom of the piperidine moiety is "buried" in this conformation.



Scheme 1

We show here that the equilibrium (Scheme 1 B/A) is strongly influenced by solvent, being considerably more on the right in a hydrogen-bonding (CD_3OD/CD_2Cl_2) than in a non-polar (CD_2Cl_2) solvent. In as much as both polar, hydrogen-bonding and non-polar media are of importance in living organisms, the former inside the cells, the latter in the cell membranes, this observation may be of interest. However, the equilibrium in CD_3OD/CD_2Cl_2 is shifted toward the left when the temperature is raised; moreover in a polar but not hydrogen-donor solvent mixture (acetone-d_6/acetonitrile-d_3), it is actually more on the left than in CD_2Cl_2.

PCP hydrochloride has been found by X-ray diffraction,[3] by NMR study in solution[4,5] and by pK_a measurement[6] to exist almost entirely with the phenyl group in the axial position. The preference for this conformation is much larger than for 1-methyl-1-phenylcyclohexane[7] presumably not only because of the larger size of the piperidinium compared to the methyl moiety, but also

because solvation of the salt is much more favorable when the ammonium group is equatorial.[8,9] The conformation equilibrium of PCP (base) has also been determined[6] by the pK_a method[10,11] in solvent methyl cellosolve; since the equilibrium of PCP was too one-sided, that of the 4-methyl homolog, 4-MePCP (Scheme 1, D/C) was determined instead, giving the $\Delta G°$ value of +0.7 kcal/mol. From this value, assuming $\Delta G°_{Me}$ = -1.7 kcal/mol, a value of -1.0 kcal/mol was computed for $\Delta G°$ for PCP itself (B/A).

We felt it desirable to determine this value independently by low-temperature C-13 NMR study. To this end, solutions of PCP and 4-MePCP in various solvents were cooled to -70° or -80°C and their spectra recorded with the results shown in Table 1. The relative areas of well-resolved signals for the two conformers were then measured and their ratio taken as the equilibrium contant (Tables 2,3). This method has been discussed in detail elsewhere.[12]

The free-energy difference for 4-MePCP (Scheme 1, D/C and Table 3) is 0.045±0.015 kcal/mol in CD_3OD/CD_2Cl_2 and 1.28±0.04 kcal/mol in CD_2Cl_2. For the equilibrium of PCP itself (Scheme 1 B/A) $\Delta G°$ in CD_2Cl_2 is -0.45±0.03 kcal/mol; this value is in excellent agreement with that for 4-MePCP if one takes into account that $\Delta G°_{Me}$ = 1.74 kcal/mol;[13] the value calculated thus for PCP from 4-MePCP would be 1.28-1.74 = -0.46 kcal/mol. The corresponding value in CD_3OD/CD_2Cl_2 is too large to be determined directly, but can be calculated from the 4-MePCP value in like manner; it is 0.05-1.74 = -1.69 kcal/mol. Thus the equilibrium of Scheme 1 is displaced toward the right in methanol-$\underline{d}_4$/methylene-$\underline{d}_2$ chloride relative to pure methylene-$\underline{d}_2$ chloride by 1.24 kcal/mol in $\Delta G°$. Presumably this large difference reflects the stabilization of the conformation with the piperidine ring in the equatorial position by hydrogen bonding to methanol; similar stabilization of the axial piperidine ring is sterically inhibited. The polarity of the solvent as such is not responsible; on the contrary, it appears that the conformational equilibrium for PCP (Scheme 1, R=H) is actually shifted <u>to the left</u> when the more polar solvent mixture acetone/acetonitrile is substituted for methylene chloride ($\Delta G°$%0).

The value for $\Delta G°$ found for 4-MePCP in CD_3OD/CD_2Cl_2, 0.045 kcal/mol, deviates considerably from the value determined by Geneste and Kamenka (0.7 kcal/mol) in methyl cellosolve by the pK_a method.[6] Neither the slight difference in solvents nor the difference in methodology and attendant error limits would appear to account for such a large difference. We therefore checked the experimental chemical shifts at 25°C against those calculated by the equation $\delta = n_C\delta_C + n_D\delta_D$.[14] Whereas in the case of CD_2Cl_2 and CD_3COCD_3/CD_3CN as solvents, reasonable agreement was found (save for the ipso carbon); the agreement in the case of CD_3OD/CD_2Cl_2 was very poor. For example, in the case of C(1) (whose assignment cannot be in doubt), the calculated shift at room temperature for n_C = 0.52, n_D = 0.48 is 61.46 ppm whereas the experimental value is 60.30. It is unlikely that such a large discrepancy would be due only to temperature dependence of the chemical shift as such, especially since nearly <u>all</u> room temperature shifts in CD_3OD/CD_2Cl_2 are much closer to the shift of $\underset{\sim}{C}$ than a calculation of the above type would lead one to expect. If one assumes - as the other extreme - that the shifts as such are temperature invariant, one can use the above equation to calculate n_C and n_D ($n_C + n_D = 1$); using the shifts for C(1) this gives, at 25°C, K = 3.26, $\Delta G°$ = 0.7 kcal/mol, which, in turn, leads to a value of 0.7-1.74 or -1.04 kcal/mol for the PCP equilibrium (Scheme 1, B/A) in methanol-$\underline{d}_4$/methylene-$\underline{d}_2$ chloride, in excellent agreement with the -1 kcal/mol value determined earlier.[6] Presumably hydrogen bonding

Table 1

C-13 NMR Spectra of PCP and 4-MePCP (Scheme 1)
in Various Solvents (Shifts in ppm from TMS at 62.89 MHz)

Cpd.	Solv.	t°C	Me	C(1)	C(2)	C(3)	C(4)	C(2')[a]	C(3')[a]	C(4')[a]	C(i)[b]	C(m)[c]	C(o)[c]	C(p)
PCP,	CD_2Cl_2,	25	-	61.05	34.02	22.75	26.92	46.92	27.63	25.52	141.23	127.69	127.47	126.23
	B,	-80	-	62.11	33.66	23.09	26.32	46.30	26.88	25.07	136.21	128.44	127.92	126.41
	A,	-80	-	59.06	33.37	21.45	26.67	46.30	27.23	25.07	141.64	127.55	126.41	126.41
PCP,	Mix[d],	25	-	61.33	34.35	23.02	27.25	47.35	28.01	25.95	141.83	128.29	127.80	126.82
	B,	-70	-	62.50	33.83	23.45	26.92	46.76	27.49	25.62	137.00	128.84	128.20	126.98
	A,	-70	-	59.59	33.83	21.86	26.92	46.76	27.49	25.62	141.60	128.50	126.98	126.98
PCP	CD_3OD[e],	25	-	63.06	34.13	23.57	27.41	47.51	27.30	25.73	139.17	128.88	128.45	127.26
4-MePCP,	CD_2Cl_2,	25	22.48	59.38	33.70	30.39	32.99	46.81	27.57	25.46	142.70	127.53	126.61	126.17
	D,	-80	18.14	62.44	f	28.30	f	46.24	f	f	135.57	128.38	f	f
	C,	-80	22.90	58.68	33.25	29.94	33.05	46.24	27.18	25.14	141.71	127.53	126.54	126.34
4-MePCP,	CD_3OD[e],	25	22.21	60.30	33.37	30.66	32.78	47.24	27.79	25.73	142.21	127.96	127.26	126.71
	D,	-80	18.13	63.92	27.65	28.69	27.65	46.70	26.20	24.93	134.44	129.41	128.44	127.50
	C,	-80	23.11	59.19	33.75	30.46	33.75	46.70	27.05	25.60	142.02	127.95	126.93	126.78

[a]Primed positions are in piperidine ring. [b]C-ipso. [c]The signals for C-ortho and C-meta may, in some instances, have to be interchanged. [d]CD_3COCD_3:CD_3CN (4:1 v/v). [e]Actually CD_3OD:CD_2Cl_2 (2:1 v/v). [f]Not clearly identified.

Table 2

Conformational Equilibrium for PCP (Scheme 1 B/A)
at -80°C in CD_2Cl_2 and CD_3COCD_3/CD_3CN

Carbon	B/A Ratio[a]	K[a]	B/A Ratio[b]	K[b]	B/A Ratio[c]
1	142:44	3.23	127:38	3.34	0.75:1
2	45:15	3.00	68:22	3.09	n.d.[d]
3	47:14.5	3.24	68:20	3.40	1.15
ipso	107:32	3.34	129:37.5	3.44	ca.1[e]
(Average)		3.20±0.14		3.32±0.15	0.97±0.2

[a]In CD_2Cl_2 without gating or pulse delay. [b]In CD_2Cl_2 with gating and 10-sec. pulse delay. [c]In CD_3COCD_3/CD_3CN by computer integration. [d]Not resolved. [e]Estimated from peak height.

Table 3

Conformational Equilibrium for 4-MePCP (Scheme 1 C/D)
at -80°C in CD_2Cl_2 and CD_3OD/CD_2Cl_2

Carbon	C/D Ratio[a]	K[a]	C/D Ratio[b]	K[b]
1	122/110	1.11	c	
2 + 4	63/55	1.15	c	
3	46/40	1.15	c	
6	40/34	1.18	528/20	26.4
7	18/16	1.13	c	
Me	22/21	1.05	272/9	30.2
ipso	90/84.5	1.07	c	
(Average)		1.12±0.05		28.3±2.7

[a]In CD_3OD/CD_2Cl_2 (2:1 v/v). [b]In CD_2Cl_2. [c]Not determined.

to PCP by methanol is a process involving a large negative free entropy, $\Delta S°$, since it requires a "freezing" of the methanol molecules about the piperidine moiety of PCP, and therefore becomes less important as the temperature is increased. Hence the difference in the PCP conformational equilibrium (Scheme 1) as between CD_3OD/CD_2Cl_2 and pure CD_2Cl_2 is reduced from about 1.25 kcal/mol at -80°C to 0.55 kcal/mol at room temperature. (The results in CD_3CN/CD_3COCD_3 would seem to exclude the possibility that the large shift to the left in the D/C equilibrium in CD_3OD/CD_2Cl_2 at low temperature is due to the increase in dielectric constant of methanol under these conditions.)

In summary, we find that the PCP equilibrium (Scheme 1) is strongly solvent dependent at -80°C, $\Delta G°$ being -0.45 kcal/mol in CD_2Cl_2, (non-polar), nearly zero in CD_3COCD_3/CD_3CN (polar) and -1.7 kcal/mol in CD_3OD/CD_2Cl_2 (hydrogen-bonding). However, as the temperature is increased to 25°C, the CD_3OD/CD_2Cl_2 value diminishes to -1.0 kcal/mol, presumably because hydrogen bonding to methanol of conformer B becomes entropically less attractive at higher temperatures. The ratio of B/A (Scheme 1) thus varies from 99:1 in methanol-methylene chloride at -80°C to 1:1 in acetone/acetonitrile at room temperature.

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References and Footnotes

1. cf. "PCP (Phencyclidine) : Historical and Current Perspectives", ed. E.F. Domino, NPP Books, Ann Arbor, Michigan (1981).
2. J.M. Kamenka and P. Geneste, "Synthesis, Conformation and Physical Properties of Phencyclidine and Its Derivatives", chapter 6 in ref. 1.
3. P. Argos, R.E. Barr and A.H. Weber, Acta Cryst., 26, 53 (1970). Although it is claimed in the abstract and text of this paper that the phenyl is equatorial, the diagram clearly shows it to be axial, which is the correct information: P. Argos, personal communication, August 24, 1982.
4. P. Geneste and J.M. Kamenka, Org.Magn.Reson., 7, 579 (1975).
5. G.A. Brine, E.E. Williams, K.G. Boldt and F.I. Carroll, J.Heterocyclic Chem., 16, 1425 (1979).
6. P. Geneste, J.M. Kamenka, S.N. Ung, P. Herrmann, R. Goudal and G. Trouiller, Eur.J.Med.Chem.-Chimica Therapeutica, 14, 301 (1979).
7. E.L. Eliel and M. Manoharan, J.Org.Chem., 46, 1959 (1981).
8. E.L. Eliel, E.W. Della and T.H. Williams, Tetrahedron Lett., 831 (1963).
9. J. Sicher, J. Jonas and M. Tichy, Tetrahedron Lett., 825 (1963).
10. M. Tichy, J. Jonas and J. Sicher, Coll.Czech.Chem.Commun., 24, 3434 (1959).
11. R.D. Stolow, J.Am.Chem.Soc., 81, 5806 (1959).
12. e.g. E.L. Eliel, D. Kandasamy, C.-y. Yen and K.D. Hargrave, J.Am.Chem.Soc., 102, 3698 (1980).
13. H. Booth and J.R. Everett, JCS Chem.Commun., 278 (1976).
14. Method of E.L. Eliel, Chemistry and Industry (London), 568 (1959).

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