A Nuclear Magnetic Resonance Investigation of Complex Formation between Imipramine and Related Psychotropic Drugs with Benzyl Alcohol and Other Aromatic Solutes

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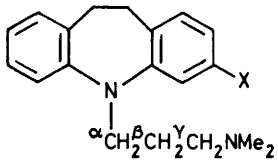
The interaction of imipramine, chlorimipramine, promazine, chlorpromazine, and protriptyline hydrochlorides with benzyl alcohol in $CDCl_3$ solution has been followed by n.m.r. spectroscopy. A specific complex is formed in which the aromatic ring of the benzyl alcohol interacts with the positively charged ammonium ion of the side-chain and in addition the hydroxy of the benzyl alcohol forms a hydrogen bond with the $\bar{C}l$ counter-ion of the hydrochloride ion-pair. Comparative studies with dibenzazepines and substituted dimethylpropylammonium chlorides and different aromatic groups show that this interaction is a general one provided certain steric and electrostatic requirements are satisfied. Thus phenol (and aniline) complex as strongly as benzyl alcohol but 2-phenylethanol much less so. The requirement of the counter-ion is demonstrated by the behaviour of the quaternary salt and the tetraphenylborate neither of which show strong association. The equilibrium constants and complex shifts have been evaluated and the complex shifts shown to agree with those calculated for a specific geometry. The effect of solvent on the complex has also been evaluated.

CLINICALLY active compounds with the tricyclic structure fall into two main classes: [1,2] (*a*) the antidepressants or thymoleptics, including imipramine (1) and numerous closely related analogues, and (*b*) the anti-psychotics or neuroleptics, including promazine (2), chlorpromazine



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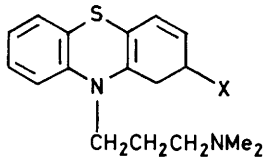
(1A) X = Cl



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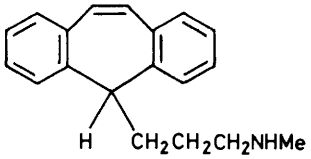
(3) X = Cl



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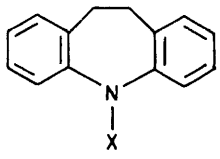

(5) X = H
(6) X = Me

$XCH_2CH_2CH_2NMe_2$

(7) X = Cl
(8) X = NH_2

$ClCH_2CH_2CH_2R$

(9) R = $\overset{+}{N}Me_3\bar{I}$
(10) R = $\overset{+}{N}HMe_2\bar{B}Ph_4$

(3), and many other phenothiazines of this type. Some of these drugs have been in use for more than 20 years, and the structural requirements for activity exhaustively covered.[3,4]

Despite the ready availability of these compounds in recent years, relatively few investigations of the importance of conformation have been reported. However, Sarges *et al.*[5] showed from the effects on the uptake of exogenous norepinephrine *in vivo* that the active conformation of the aminoalkyl side-chain is folded towards the aromatic ring. It is of some interest to note that although this conformation is neither of the two forms present in the crystal [6,7] n.m.r. studies showed that this is the predominant conformer of imipramine hydrochloride in solution.[8] A conformational study was thus initiated in which a variety of tricyclic compounds was examined in a range of solvents (both aqueous and non-aqueous).

In doing so, however, we observed a remarkable effect of benzyl alcohol on the chemical shifts of imipramine hydrochloride and we report here the results of this investigation into the nature of the complexes formed between imipramine (1) and chlorimipramine (1A) hydrochloride, promazine (2) hydrochloride, chlorpromazine (3) hydrochloride, and protriptyline (4) hydrochloride and the model compounds dibenzazepine (5), *N*-methyldibenzazepine (6), 3-chloro- (7) and 3-amino-*NN*-dimethylpropylamine (8) hydrochloride, 3-chloropropyl-*NNN*-trimethylammonium iodide (9), and 3-chloropropyl-*NN*-dimethylammonium tetraphenylborate (10) with benzyl alcohol and other aromatic solutes.

We shall show that these effects are connected with the presence of ion-pairs in solution of the drug molecules. From the extensive conductimetric investigations of ion-pairing [9,10] we may safely assume that imipramine hydrochloride (1),HCl exists very largely as free (solvated) ions in the polar protic solvents (D_2O, MeOD)

[1] C. L. Zirkle and C. Kaiser, 'Medicinal Chemistry,' ed. A. Bruger, Wiley–Interscience, New York 1970, Part II, p. 1410.
[2] W. O. Foye, 'Principles of Medicinal Chemistry,' Lea and Febiger, Philadelphia, 1974, chs. 10 and 13.
[3] J. H. Biel and B. Bopp, 'Medicinal Chemistry, Vol. 4–III, Psychopharmacological Agents,' ed. M. Gordon, Academic Press, New York, 1974, ch. 7, p. 283.
[4] C. L. Zirkle and C. Kaiser in ref. 3, ch. 2, p. 39.
[5] R. Sarges, B. K. Koe, A. Weissmann, and J. P. Schaefer, *J. Pharm. Experimental Therapeutics*, 1974, **191**, 393.
[6] A. S. Horn, M. L. Post, and O. Kennard, *J. Pharm. Pharmacology*, 1975, **27**, 553.
[7] M. L. Post, O. Kennard, and A. S. Horn, *Nature*, 1974, **252**, 493.
[8] R. J. Abraham, L. J. Kricka, and A. Ledwith, *J.C.S. Perkin* II, 1974, 1648.
[9] G. J. Janz and R. P. T. Tomkins, 'Nonaqueous Electrolytes Handbook,' Academic Press, New York, 1972, vol. 1.
[10] J. E. Gordon, 'The Organic Chemistry of Electrolyte Solutions,' Wiley, London, 1975.

whereas in non-polar solvents ($CDCl_3$, CD_2Cl_2) only ion-pairs, or higher aggregates are present. In the dipolar aprotic solvents (CD_3CN, DMSO) which are particularly poor solvators of anions, more balanced equilibria may be found. Furthermore, the dissociation constants for the salts (9) and (10), in both of which the strong NH · · · X bond cannot occur, will be much greater than in (1),HCl. For example the dissociation constants for R_4NX (R = Bu or pentyl; X = Br, I or picrate) are *ca.* 10^{-17} in benzene, 10^{-5} in CH_3CHCl_2, 10^{-3} in pyridine, and 2×10^{-2} in acetone, whilst for Et_3NHX (X = Br or picrate) in nitrobenzene they are 6×10^{-6} and 2×10^{-4} respectively.

Previous n.m.r. investigations of complexation involving ion-pairs are limited. Fraenkel and Kim studied the ^1H n.m.r. of anilinium salts in various solvents,[11] but were handicapped by the absence of any large changes in the proton chemical shifts which could be attributable to ion-pairs as distinct from the free (solvated) ions. For example the aromatic proton chemical shifts of *p*-toluidine hydrochloride in D_2O, MeOH, and DMSO are virtually identical and not very different from those of *p*-n-butylanilinium hydrochloride in $CDCl_3$. Larger variations in the proton chemical shifts of the quaternary salts $Bu^n_4\overset{+}{N}\bar{X}$ (X = Cl, Br, I, ClO_4 or picrate) were observed by Buckson and Smith [12] on dilution in nitrobenzene and were interpreted as due to dissociation of the ion-pairs. The use of aromatic ligands (*i.e.* solvents) to follow ionic dissociation was successfully exploited by Taylor and Kuntz for a variety of quaternary onium salts.[13] They determined qualitatively the various factors such as ion size and shape and the nature of the counter-ion influenced these solvent shifts and we shall show that their results are entirely consistent with ours on the more strongly associated drugs.

RESULTS

The proton chemical shifts (δ) of the compounds investigated are given in Table 1. Inspection of the data for imipramine hydrochloride shows the small variation in chemical shifts in changing from the solvated ion to the ion-pair. However, there is a systematic effect, though a small one. The *N*-methyl signal shows the largest effect, varying from δ 2.54—2.58 in the chlorinated solvents in which ion-pairs are present in overwhelming excess to δ 2.70—2.74 in the hydroxylic solvents in which solvated ions are largely present.* In the dipolar aprotic solvents, intermediate values are found as expected. A similar pattern is observed for the side-chain methylenes but the effects, as expected, are much smaller (γ-methylene, ion-pair δ 2.93—3.01, solvated ion δ 3.06—3.11; β-methylene, ion-pair δ 2.05—2.14, solvated ion δ 1.96—2.04; α-methylene no change). Interestingly in acetonitrile solvent, the shifts are similar to those in the less polar solvents, suggesting predominant ion-pairing, which would not be surprising at

TABLE 1

Proton chemical shifts (δ) of some psychotropic drugs and model compounds [a]

Compound	Solvent	N–Me	Ethano-bridge	α-CH_2	β-CH_2	γ-CH_2
(1)	$CDCl_3$	2.12	3.13	3.75	1.70	2.29
(1),HCl	$CDCl_3$	2.58	3.12	3.84	2.14	3.01
	$C_2D_2Cl_4$	2.54	3.13	3.82	2.12	2.93
	CH_2Cl_2	2.55	3.13	3.84	2.05	2.98
	Bu^tOD	2.71	3.08	3.80	1.99	3.10
	Pyridine	2.63	3.00	3.82	2.16	3.11
	$PhCH_2OH$	1.79	2.91	3.36	1.46	2.29
	CD_3OD	2.70	3.13	3.83	1.96	3.11
	CD_3CN	2.54	3.13	3.81	1.95	2.90
	$[^2H_6]$DMSO	2.62	3.11	3.86	1.91	3.06
	D_2O [b]	2.74	3.16	3.86	2.04	3.06
(1A),HCl	$CDCl_3$	2.64	3.10	3.82	2.09	2.95
(2),HCl	$CDCl_3$	2.59		4.02	2.29	3.09
	$PhCH_2OH$	1.79		3.52	1.69	2.38
	CD_3OD	2.71		4.02	2.15	3.17
(3),HCl	$CDCl_3$	2.66		4.04	2.35	3.13
(4),HCl [c]	$CDCl_3$	2.33	6.85	1.77	1.49	2.57
(7)	$CDCl_3$	2.21		3.58	1.92	2.41
(7),HCl	$CDCl_3$	2.89		3.72	2.42	3.27
	CH_2Cl_2	2.82		3.75	2.38	3.12
	CD_3OD	2.91		3.71	2.31	3.22
	CD_3CN	2.71		3.73	2.25	3.05
	$[^2H_6]$DMSO	2.73		3.76	2.25	3.06
	D_2O	2.91		3.70	2.24	3.24
(8) [d]	$CDCl_3$	2.21		2.74	1.60	2.31
(9)	CD_3CN	3.16		3.71	2.34	3.46
	D_2O	3.16		3.72	2.35	3.45
(10)	$CDCl_3$ [e]	2.40		3.57	2.14	2.59
	CD_3CN	2.61		3.53	2.07	2.93

[a] Compounds (5) and (6) in $CDCl_3$; ethano-bridge δ 3.06 and 3.14, NH δ 5.93, NMe δ 3.33. [b] 0.01M. [c] CH δ 3.94. [d] NH δ 1.23. [e] 0.05M.

* No dilution effect on the chemical shifts was observed down to 0.01M in $CDCl_3$, but there was a dilution shift in D_2O, in consequence the values given in Table 1 are for 0.01M solution.

[11] G. Fraenkel and J. P. Kim, *J. Amer. Chem. Soc.*, 1966, **88**, 4203.

[12] R. L. Buckson and S. G. Smith, *J. Phys. Chem.*, 1964, **68**, 1875.

[13] R. P. Taylor and I. D. Kuntz, *J. Amer. Chem. Soc.*, 1970, **92**, 4813.

these concentrations. Thus the change in chemical shifts on going from solvated ions to an ion-pair ($\overset{+}{N}H\overset{-}{Cl}$) is for the $CH_2CH_2CH_2\overset{+}{N}HMe_2$ fragment *ca.* 0.00, +0.10, −0.15, and −0.20 p.p.m. The change in sign on going from $CH\overset{+}{N}$ to $CHC\overset{+}{N}$ may be contrasted with the regular decrease in Δδ on protonation, which may be defined conveniently as the chemical shifts of the hydrochloride in D_2O minus those of the free base in $CDCl_3$. These are 0.11, 0.34, 0.77, and 0.62 p.p.m. for the α-, β-, γ-, and *N*-methyl protons respectively. The alternation effect is reminiscent of that found in the ^{13}C chemical shifts of amines on protonation.[14]

This general pattern is also followed by compound (7); in particular the analogous protonation shifts are 0.12, 0.32, 0.83, and 0.70 p.p.m. practically identical with those of (1). Also the solvents follow a similar grouping into non-polar ($CDCl_3$), dipolar aprotic (CD_3CN,DMSO), and protic ($MeOD,D_2O$) solvents. In this case, however, the differences between the solvents are much less than in (1), probably due to the effects of the polar C–Cl group which could both competitively solvate the cation of another molecule and also give rise to solvent effects *per se*.

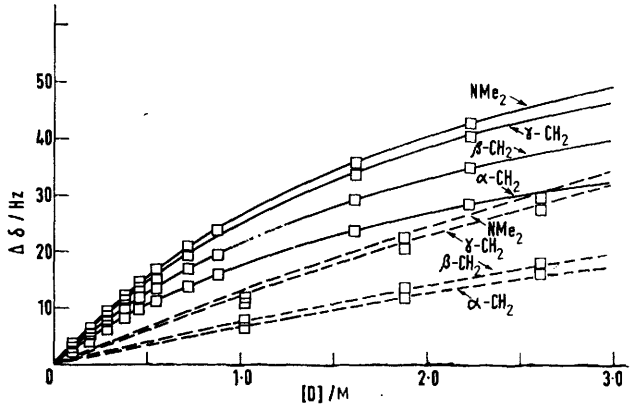

FIGURE 1 High-field shifts (Δδ, Hz) of imipramine hydrochloride protons in 0.23M $CDCl_3$ solution on the addition of benzyl alcohol (—) and benzene (· · ·)

However, the important point to note is the *small* change which occurs in going from the solvated ion to an ion-pair in these systems. This is entirely in accord with the results of Fraenkel and Kim on anilinium halides [11] and demonstrates that the major problem in n.m.r. studies of ion-pairing is the similarity between the chemical shifts of the ion-pair and the solvated ion. The ^{13}C chemical shifts of imipramine hydrochloride in $CDCl_3$ and D_2O are also virtually identical,[8] suggesting that it is the wave functions of the species which are similar rather than the lack of sensitivity of the nuclei to electron changes in the molecule, and it would be of interest to check this with ^{15}N n.m.r. measurements.

The Association Constants.—The major exception to this regular pattern occurs with benzyl alcohol as solvent, in which high-field shifts of almost 1 p.p.m. are observed (Table 1), which must be due to the anisotropic effect of the solvent. (Note that pyridine which is also an anisotropic solvent does not show these effects.) It is these shifts we wish to investigate further, and in such cases it is necessary to obtain the shifts produced by the addition of ligand to the solute in an inert solvent. Figure 1 shows the chemical shift changes (Δδ) observed on adding benzyl alcohol and benzene to a solution of (1),HCl in $CDCl_3$.

If we assume complex formation between (1),HCl and the ligands according to the Scheme then the shift of any proton in (1),HCl follows the formulation given therein, which is taken directly from that derived by Foster for charge-transfer interactions.[15] On the basis of the two

	A +	D ⇌	AD
Initial conc.	α	β	
Equilibrium conc.	α − *x*	β − *x*	*x*

$$\therefore \quad K = x/(\alpha - x)(\beta - x)$$

$$\delta_{obs}{}^A = (1 - x/\alpha)\delta_o{}^A + x/\alpha\delta_{AD}{}^A$$

$$\Delta\delta_{obs}{}^A = (\delta_{obs}{}^A - \delta_o{}^A) = x/\alpha(\delta_{AD}{}^A - \delta_o{}^A)$$

$$= x/\alpha\Delta\delta_{AD}{}^A$$

If $\beta \gg \alpha$, then $\beta - x \rightleftharpoons \beta$ and

$$\Delta\delta_{obs}{}^A = K\beta/(1 + K\beta)\Delta\delta_{AD}{}^A$$

i.e. $$1/\Delta\delta_{obs}{}^A = 1/K\beta\Delta\delta_{AD}{}^A + 1/\Delta\delta_{AD}{}^A$$

i.e. $$\Delta\delta_{obs}{}^A/\beta = -K\Delta\delta_{obs}{}^A + K\Delta\delta_{AD}{}^A$$

SCHEME

central assumptions of a 1 : 1 complex and an excess of added ligand a simple plot of the observed shift change $\Delta\delta_{obs}{}^A/\beta$ where β is the concentration of ligand, against $\Delta\delta_{obs}{}^A$ gives a straight line of slope *K* and intercept $K\delta_{AD}{}^A$. This analysis was performed for imipramine, chlorpromazine, and protriptyline hydrochlorides for the addition of benzyl alcohol and the values of the association constants *K* and complexation shifts $\Delta\delta_{AD}{}^A$ obtained are given in Table 2.

TABLE 2

Association constants (*K*) and complex shifts ($\Delta\delta_{AB}{}^A$) for some psychotropic drugs with benzyl alcohol in deuteriochloroform

Compound	*K* (l mol^{-1}) *	$\Delta\delta_{AB}{}^A$ † (Hz) NMe	γ-CH_2	β-CH_2	α-CH_2	Bridge protons
(1),HCl	0.43	87.0	82.5	70.2	57.5	19.1
(3),HCl	0.71	83.0	78.4	68.8	64.9	
(4),HCl	0.57	67.0	62.6	55.5	40.0	11.6

* Probable error ±0.01 l mol^{-1}. † Probable errors ±0.1 (Hz).

In Figure 1 the calculated curves for $\Delta\delta_{obs}{}^A$ are based on the complete equation (1), *i.e.* without assuming $\beta \gg \alpha$ and the good agreement with the observed shifts demonstrates the general validity of the procedure for this case. Furthermore, the analysis leads to reasonable values of both *K* and $\Delta\delta_{AD}{}^A$ (see later). This must be contrasted with the results of the same analysis of the benzene addition. This leads for imipramine hydrochloride to values of *K* and $\Delta\delta_{AD}{}^A$ for the *N*-methyl protons of 0.08 l mol^{-1} and 173.4 Hz, respectively. The value of the complexation shift $\Delta\delta_{AD}{}^A$ is manifestly unreal and this is obviously due to the breakdown of the central assumptions in the treatment; in particular that there is a specific 1 : 1 complex. The general problem of ASIS is too well known to need further discussion here,[16] but the probability that more than one benzene molecule preferentially solvates the cation in a less specific manner appears likely and this would account for

[14] J. G. Batchelor, J. Feeney, and G. C. K. Roberts, *J. Magnetic Resonance*, 1975, **20**, 19.

[15] R. Foster and C. A. Fyfe, *Progr. N.M.R. Spectroscopy*, 1968, **4**, 1.

[16] P. Laszlo, *Progr. N.M.R. Spectroscopy*, 1967, **3**, 231.

the failure of the method in this case. This result, however, is of importance in as much as it demonstrates that the benzyl alcohol–imipramine complex is *not* merely another manifestation of the general ASIS, but a more specific interaction.

TABLE 3

Complexation shifts ($\Delta\delta$) [a] for psychotropic drugs and model compounds with benzene (B) and benzyl alcohol (BA)

Compound	Solute	NMe	γ-CH_2	β-CH_2	α-CH_2	Ethano-bridge
(1)	B	−6.5	−7.2	−4.7	−6.5	−5.1
	BA	−23.7	−17.4	−12.6	−15.8	−5.5
(1),HCl	B	−29.3	−27.3	−18.0	−16.2	−6.9
	BA	−42.0	−38.8	−34.6	−26.9	−9.2
(1A),HCl	B	−26.4	−24.5	−16.8	−17.3	−7.4
	BA	−41.9	−39.3	−33.0	−31.5	−9.5
(3),HCl	B	−29.4	−27.8	−19.3	−21.7	
	BA	−51.3	−48.4	−43.1	−40.8	
(4),HCl [b]	B	−15.3	−14.4	−4.9	−5.1	−5.8
	BA	−36.4	−34.0	−30.5	−23.2	−6.3
(6)	B	−10.5				−6.1
	BA	−8.0				−6.3
(7)	B	−8.6	−9.5	−10.3	−10.6	
	BA	−22.0	−16.8	−18.5	−21.1	
(7),HCl	B	−32.1	−30.1	−21.6	−18.3	
	BA	−55.2	−51.3	−48.1	−38.7	
(8) [c]	B	−5.8	−8.7	−9.3	−10.3	
	BA	−25.5	−30.1	−30.3	−41.9	

[a] $\Delta\delta$ = the shift observed (Hz) on adding 1.5×10^{-3} mole ligand to a 0.23M solution of the compound in $CDCl_3$ (see text). [b] CH $\Delta\delta$ −3.9 (B); −13.7 (BA). [c] NH $\Delta\delta$ −17.3 (B). [d] Compound (5); ethano-bridge $\Delta\delta$ −7.6 (B), −7.2 (BA).

Model Compounds.—Having ascertained that there is a well defined complex formed between the drug hydrochlorides and benzyl alcohol, we wish to isolate the interactions responsible for this complex formation. The simplest technique in such cases is to use analogues and to vary in turn both the drug and the ligand moiety. In so doing it is more convenient to adapt a standard set of conditions and observe directly the shifts ($\Delta\delta$) produced by added ligand, rather than perform in each case the full analysis given previously. We have chosen standard conditions of 0.23M solutions of the compound in $CDCl_3$ (0.5 ml) to which is added 0.0015 mole (*ca.* 0.15 ml) of ligand, to give a 2.3M solution of ligand, *i.e.* a ten-fold excess. Table 3 gives the complexation shifts ($\Delta\delta$) observed for a range of model compounds for the addition of benzene and benzyl alcohol. For comparison the results for (1),HCl, (3),HCl, and (4),HCl are also given, although these shifts are directly related to the true complexation shifts $\Delta\delta_{AD}^{A}$ of Table 2.

We note that the shifts are largest for protons near the protonated nitrogen (NMe and γ-CH_2) and decrease steadily on going away from this centre and this implies that the interactions occurs near $\overset{+}{N}$. The charged nitrogen atom is essential for this interaction as is shown by the results for the free base (1), in which the benzene shifts are very small (5—7 Hz), and those of benzyl alcohol, though appreciable, are much less than for the hydrochloride. Note that for the free base–benzyl alcohol system a simple N · · · H–O hydrogen bond would account for these shifts, though this interaction is not possible in the salt.

The tricyclic part of imipramine, *i.e.* dibenzazepine (5) and the *N*-methyl derivative (6), were also measured to test for any π–π interactions. The shifts are again very small (<10 Hz) and in addition there is no difference between benzene and benzyl alcohol. This proves unambiguously that the aromatic part of the drugs does not interact appreciably with benzyl alcohol in $CDCl_3$ solution.

Indeed, we regard the $\Delta\delta$ values observed in these cases [and those of (1) with benzene] of *ca.* 0—10 Hz as being due to a non-specific averaging of the benzene ring current over the solute molecule (see later).

Positive support for the importance of the side-chain comes with the observation of even larger $\Delta\delta$ values for compound (7),HCl than for (1),HCl. Again in this case the free base shows much smaller shifts, as expected, but it is noteworthy that in both (7) and (7),HCl the $\Delta\delta$ values do not decrease so markedly on going from γ- to β- to α-methylene and this is very likely due to O–H · · · Cl interaction with the side-chain chlorine; indeed in (8) the α-methylene shift is larger than the *N*-methyl shift and again this can be readily explained on the basis that N–H · · · O is stronger than N · · · H–O bonding.

TABLE 4

Complexation shifts ($\Delta\delta$) [a] for imipramine hydrochloride and dimethylaminopropyl chloride hydrochloride with aromatic solutes in $CDCl_3$

Solute	Compound	NMe	γ-CH_2	β-CH_2	α-CH_2	Ethano-bridge
Benzene	(1),HCl	−29.3	−27.3	−18.0	−16.2	−6.9
	(7),HCl	−32.1	−30.1	−21.6	−18.3	
$PhCH_2OH$	(1),HCl	−42.0	−38.8	−34.6	−26.9	−9.2
	(7),HCl	−55.2	−51.3	−48.1	−38.7	
PhOH	(1),HCl	−37.3	−38.1	−38.2	−38.9	−13.1
	(7),HCl	−49.0	−49.7	−48.0	−51.7	
$PhCH_2OMe$	(1),HCl	−18.1	−17.0	−12.1	−9.6	−4.4
	(7),HCl	−26.6	−26.0	−18.6	−15.1	
$PhCH_2CH_2OH$	(1),HCl	−29.9	*b*	*b*	*b*	−5.9
	(7),HCl	−39.6	−34.0	*b*	−26.0	
$PhNH_2$	(1),HCl	−36.1	−37.8	−25.4	−25.9	−8.9
	(7),HCl	−50.6	−56.6	−39.0	−36.6	
Methanol [c] + benzene	(1),HCl	−18.0	−17.4	−19.2	−12.3	−5.2

[a] $\Delta\delta$ = the shift (Hz) on adding 1.5×10^{-3} mole ligand to a 0.23M solution of the compound. [b] Obscured by solute signals. [c] Addition of 2.5×10^{-3} mole methanol and 1.5×10^{-3} mole benzene.

Ligand Variations.—We now wish to isolate those factors in the ligand molecule responsible for the interaction and Table 4 gives the $\Delta\delta$ values observed for (1),HCl and (7),HCl in $CDCl_3$ solution for a variety of ligands, for the same conditions as given previously. The most significant result is obtained by comparison of the $\Delta\delta$ values for benzene, benzyl alcohol, and benzyl methyl ether. It can be seen that both for (1),HCl and (7),HCl, benzyl

methyl ether gives smaller $\Delta\delta$ values than benzene, which in turn are much less than benzyl alcohol. This demonstrates clearly that there is no specific interaction with benzyl methyl ether involving the oxygen as a donor and the effect of benzyl methyl ether is essentially a slightly diminished (due to steric factors) benzene effect. This is of fundamental importance as it rules out what at first sight may have been considered to be the strongest interaction, the $\overset{+}{N}$–H · · · O hydrogen bond. Clearly in the solutions considered here, this interaction does not occur without an associated effect (see later).

The specific interaction of the benzyl alcohol is therefore *via* the hydroxy-group, and it is of interest to consider the $\Delta\delta$ values of the series $Ph[CH_2]_nOH$ (n = 0—2) in which the separation of the phenyl and hydroxy-groups varies. Phenol gives essentially identical $\Delta\delta$ values to benzyl alcohol but for α-phenylethanol the effect is much reduced (for those protons which could be observed), and this suggests that the spatial configuration of the phenyl and hydroxy-groups is of importance. Also Table 4 shows that aniline gives very similar $\Delta\delta$ values, confirming the suggestion that the essential requirement is for a hydrogen bond acceptor in the ligand.

Finally Table 4 shows the effect of adding both benzene and methanol in 10- and 15-fold excess to (1),HCl. The observed high-field shifts are strikingly *less* than those obtained by benzene alone. Clearly in the systems and conditions considered in this investigation the effect of benzyl alcohol is a specific difunctional effect, not just an additive function of an aromatic and hydroxylic ligand. This is in contrast to Taylor and Kuntz's results (see Discussion section).

In conclusion these studies with model compounds show clearly that the essential requirements for this interaction are a charged nitrogen atom and a ligand with a hydrogen bond acceptor in proximity to an aromatic group. It is pertinent to note here that the quaternary nitrogen atom cannot function as a hydrogen-bond donor; thus we are led to the suggestion that the specific interaction of the drug–benzyl alcohol complex must invoke the $\bar{Cl}$ counter-ion of the ion-pair which of course can act as a hydrogen-bond donor. In this case we now have both an aromatic–protonated nitrogen and also a much stronger O–H · · · $\bar{Cl}$ interaction. This would explain the specific effect of benzyl alcohol and also the spatial relationship of the phenyl and hydroxy-groups mentioned above, and it is this proposal we test further as follows.

TABLE 5

Complexation shifts ($\Delta\delta$) [a] of imipramine hydrochloride and model compounds with benzene (B) and benzyl alcohol (BA) in various solvents

Solvent	ε	Solute	NMe	γ-CH_2	β-CH_2	α-CH_2	Ethano-bridge
(1),HCl							
$CDCl_3$	4.6	B	−29.3	−27.3	−18.0	−16.2	−6.9
		BA	−42.0	−38.8	−34.6	−26.9	−9.2
$(CDCl_2)_2$	8.2	B	−31.1	−26.3	−17.0	−15.8	−6.8
		BA	−34.5	−30.3	−28.5	−23.5	−7.5
CH_2Cl_2	8.9	B	−24.0	−22.3	−13.9	−13.2	−5.6
		BA	−35.5	−32.5	−29.8	−24.8	−8.7
CD_3OD	31.7	B	−17.3	−17.9	−10.0	−9.8	−4.2
		BA	−18.0	−18.2	−12.2	−11.0	−4.5
CD_3CN	35.9	B	−11.8	−13.3	−5.0	−7.6	−3.5
		BA	−15.5	−16.4	−14.7	−15.2	−5.6
DMSO	46.6	B	−4.5	−3.8	+2.8	−1.5	−0.5
		BA	−3.3	−5.0	−2.4	−4.9	−1.3
(7),HCl							
$CDCl_3$	4.6	B	−32.1	−30.1	−21.6	−18.3	
		BA	−55.2	−51.3	−48.1	−38.7	
CH_2Cl_2	8.9	B	−29.2	−27.0	−19.4	−17.7	
		BA	−43.6	−40.2	−40.8	−34.8	
CD_3OD	31.7	B	−16.1	−14.7	−11.1	−10.4	
		BA	−18.3	−17.1	−14.3	−12.4	
CD_3CN	35.9	B	−10.8	−11.2	−6.1	−8.0	
		BA	−15.6	−15.9	−18.6	−18.5	
DMSO	46.6	B	−1.0	+0.6	+4.0	−1.2	
		BA	−3.0	−2.9	−4.3	−6.9	
(9)							
CD_3CN	35.9	B	−9.3	−7.0	−9.9	−6.7	
		BA	−21.2	−21.3	−16.8	−12.6	
(10)							
CD_3CN	35.9	B	−16.5	−15.4	−12.8	−9.8	
		BA	−19.4	−17.9	−15.8	−11.5	

[a] $\Delta\delta$ = the shift (Hz) on adding 1.5×10^{-3} mole B(BA) to a 0.23M solution of the compound.

Solvent Effect on Complexation Shifts.—If the benzyl alcohol–imipramine hydrochloride complex is an ion-pair–molecular association then any dissociation of the ion-pair will result in a decrease in the complexation shift. The obvious method of dissociating the ion-pair is by varying the solvent, and the effect of changing the solvent on the $\Delta\delta$ values for benzene and benzyl alcohol is shown in Table 5. Increasing the dielectric constant of the solvent ($CDCl_3$, CD_2Cl_2, CD_3CN, DMSO) results in a monotonic decrease of the $\Delta\delta$ values, until with DMSO the values are very small (<5 Hz). This is to be expected on the basis of increasing dissociation, but the polar aprotic solvents CD_3CN and DMSO also form hydrogen bonds strongly with benzyl alcohol, thus competing effectively with the ion-pair. Interestingly, the benzene values, which are simply due to association of the benzene with the cationic

part of the ion-pair, also decrease to essentially zero in DMSO, presumably due to the preferential solvation of the cation by DMSO.

The effect of the protic solvent CD_3OD is also of interest. In this case the $\Delta\delta$ values are less than for $CDCl_3$, as expected, but significantly the values for benzyl alcohol and benzene are essentially identical. This demonstrates that the specific effect of the benzyl alcohol hydroxy-group has been completely removed, probably because in this solvent, which can solvate both the cations and anions, the ion-pair is largely dissociated. However, it is conceivable that the effect of methanol is also a competitive one, as the methanol could also form a hydrogen bond strongly to the ion-pair. (We note that the addition of a two-fold excess of methanol to a $CDCl_3$ solution of imipramine and benzyl alcohol did not produce any changes in the $\Delta\delta$ values, which supports the dissociation hypothesis.)

These experiments were checked with the side-chain (7),HCl (Table 5) and very similar results obtained in this case also, supporting the general explanations given above.

Another method of testing the central hypothesis is to vary the cation and counter-ion independently and the results of these experiments are also given in Table 5, though solubility limitations precluded more detailed studies. The quaternary alkylammonium iodide (9) in CD_3CN gives benzene $\Delta\delta$ values very similar to those of (7),HCl in this solvent, which is as expected, but more surprisingly shows similar effects to (7),HCl with benzyl alcohol also. It would be expected that (9) should be more dissociated than (7),HCl in CD_3CN, but it is possible that at the high concentrations used (9) is still considerably associated even in CD_3CN solution. There is a change in the pattern of the δ values; in (9) there is a pronounced decrease going from γ- ⟶ β- ⟶ α-methylene whereas in (7),HCl there is an opposite tendency. This could be due to steric factors as the $\overset{+}{N}Me_3$ group in (9) is much bulkier than the $\overset{+}{N}HMe_2$ group of (7),HCl and this is indeed reflected in the virtually complete preference for the *trans*-orientation of the $CCH_2CH_2\overset{+}{N}Me_3$ part in (9).[17]

A more illustrative example is the tetraphenylborate salt (10) and here the $\Delta\delta$ values in CD_3CN are more in accord with predictions. In this case the interaction of the benzyl alcohol hydroxy-group with the anion will be removed as the BPh_4 anion cannot form hydrogen bonds, leading to $\Delta\delta$ values for benzyl alcohol of the same magnitude as those for benzene. This is precisely what is observed and this provides considerable support for our proposed model.

The Geometry of the Complex.—It is of interest to consider whether the proposed model can account even semi-quantitatively, for the observed complexation shifts (Table 2). The basic assumptions of such calculations are that there is a 1 : 1 complex of well defined geometry and that the complexation shifts ($\Delta\delta_{AD}{}^{A}$) are entirely due to the ring current effect of the benzyl alcohol ligand.

The first assumption is supported by the well defined values of K and $\Delta\delta_{AD}{}^{A}$ obtained previously. However, it is pertinent to note that there is always the possibility of a small amount of 1 : 2 (or higher) aggregate occurring, as the ligand is in large excess and these would not be detected by the analysis. It is not meaningful to include any additional complexation in the analysis but the effect of higher aggregates would be to increase the values of $\Delta\delta_{AD}{}^{A}$ obtained (which was of course observed in the case of benzene as ligand). Thus the values in Table 2 will be if anything too large. An additional factor arises when we consider the quantitative interpretation of these shifts. There is (*cf.* Table 3) a general ASIS of *ca.* 5—10 Hz even in those cases where no specific interaction is envisaged, due to the non-zero averaging of the benzene anisotropy over the solute. This effect is included in all the complexation shifts of Table 3 and therefore has been extrapolated, along with the specific contribution in the $\Delta\delta_{AD}{}^{A}$ values of Table 2. Extrapolating this non-specific effect to the same extent as for the $\Delta\delta_{AD}{}^{A}$ values suggests that *ca.* 10—20 Hz of the shifts of Table 2 will be due to this non-specific effect. Considerable support for this comes immediately from the calculations (see later), as for any reasonable geometry of the molecular complex the ring current shift of the benzyl alcohol is almost zero at the ethano-bridge protons, which have $\Delta\delta_{AD}{}^{A}$ values of 12—19 Hz (Table 2).

Ring current shifts are perhaps the only really well defined part of n.m.r. chemical shifts, and it is reasonable to assume that the effect of the benzyl alcohol is very largely due to the ring current (particularly in view of the very small shift changes occurring in going from the ion-pair to the solvated ion). The calculations were performed by varying the position of the aromatic ring, calculating the ring current shifts at the different protons in the molecule using the equivalent dipole approximation and then averaging the different sets of protons. The value of the equivalent dipole used was standardised against the Johnson and Bovey current-loop model [18] to give the final equation: shift $= 27.0(3\cos^2\theta - 1)/r^3$ p.p.m.[19] This procedure has the great advantage over the direct use of the current-loop expressions in that the expression used is exactly the same equation as that for the calculation of lanthanide shifts. Thus merely by inserting the appropriate value of the equivalent dipole the LIS program may be used unchanged. (In our case this is not an iterative program but exactly the same comment holds for the sophisticated search LIS programs which may be used unchanged for the calculation of aromatic molecular complexation.) Also for the distances considered ($\geqslant$4—5 Å), the equivalent dipole is an excellent approximation.[19] We compared the calculated and observed shifts for linearity and approach to the origin, bearing in mind the considerations outlined above. The calculated *versus* observed shifts in Figure 2 are those for the molecular configuration shown in Figure 3. Figure 2 shows that the observed *versus* calculated shifts are linearly related with, however, an intercept of *ca.* 40 Hz on the abscissa, *i.e.* the observed $\Delta\delta_{AD}{}^{A}$ values of Table 2 equal the calculated values plus 42 Hz. The above considerations suggest that at least half of this intercept is due to non-specific averaging (which affects each proton equally). The remainder may be due to the presence of higher complexes. In particular some of the 1 : 2 complex could well be present, as there are two ' sides ' of the aminoalkyl side-chain and thus the attachment of one benzyl alcohol molecule would not hinder the approach of a second ligand (Figure 3).

However, in this case although the linearity of Figure 2 would remain, the slope of the observed *versus* calculated shifts would increase from unity, which is not observed.

Figure 3 shows that the benzene plane of the ligand is

[17] R. J. Abraham, K. Lewtas, and W. A. Thomas, unpublished results.

[18] C. E. Johnson and F. A. Bovey, *J. Chem. Phys.*, 1958, **29**, 1012.

[19] R. J. Abraham, S. Fell, and K. M. Smith, *Org. Magnetic Resonance*, 1977, **9**, 367.

positioned away from the tricyclic ring but in reasonable proximity to the Cl counter-ion, and the agreement is very reasonable considering all the factors involved in such an attempt. It should be emphasised at this point that the calculations do not uniquely define the geometry, as there is an area of general agreement with the observed shifts.

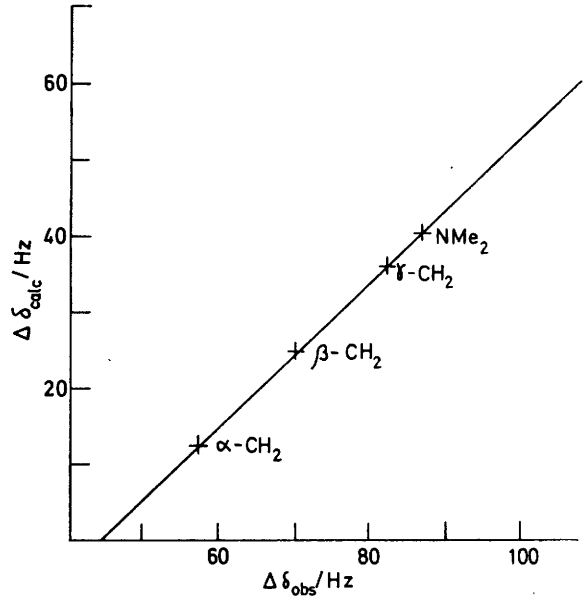

FIGURE 2 Observed *versus* calculated complexation shifts ($\Delta_{AD}{}^{A}$ Hz at 100 MHz) of imipramine hydrochloride–benzyl alcohol

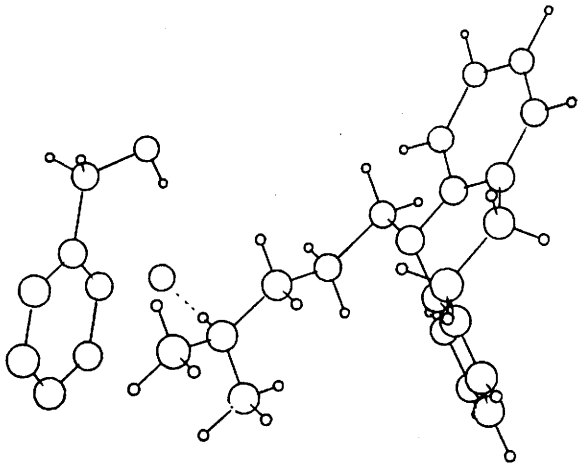

FIGURE 3 The imipramine hydrochloride–benzyl alcohol complex

What the calculations do demonstrate is that a model of a specific complex does give calculated shifts in broad agreement with those observed, thus supporting considerably the proposed model.

DISCUSSION

Although there have been only few n.m.r. investigations of ion-pairs the concept of an aromatic ligand acting as a template for an ion-pair was suggested some time ago by Hyne.[20] Further investigations of the example considered ($Bu_4\overset{+}{N}\overset{-}{Br}$ in nitrobenzene) by Buckson and Smith [12] showed that the ion-pair dissociation constant was not abnormal and also the infinite dilution chemical shift of the α-methylene protons of δ 3.47, presumably the free ion value, was to *high* field of the value in the ion-pair (δ 3.87), in contrast to our investigations, suggesting that there is preferential association of the solvent with the free ion rather than the ion-pair. This is supported by the results of Taylor and Kuntz,[13] on the effect of aromatic solvents on the proton chemical shifts of a number of quaternary onium salts and it is of interest to consider their results in detail. For example the chemical shift of the methyl protons of $Me\overset{+}{P}Ph_3\overset{-}{Cl}$ shows analogous solvent shifts to the systems investigated here.

The shift in $CDCl_3$ (δ 3.42) of presumably the ion-pair, is to low field of that in methanol (δ 2.98) of the solvated ion, in contrast to the imipramine hydrochloride where a high-field shift is observed. This could well be due to the very different position of the counter-ion in the two cases, which is along the N–H bond in imipramine hydrochloride but near the N–Me in $Me\overset{+}{P}Ph_3\overset{-}{Cl}$. The solvent effect of nitrobenzene is, however, very similar in $Me\overset{+}{P}Ph_3\overset{-}{Cl}$ and in $Bu_4\overset{+}{N}\overset{-}{Br}$, the P–Me shift of δ 3.15 for the lowest concentration (0.004M) studied changing to δ 3.48 at 0.05M, again a down-field shift on increasing the concentration. Note that the shift of the same species will be very different in aromatic compared with non-aromatic solvents; indeed a very large ASIS was obtained for $Me\overset{+}{P}Ph_3\overset{-}{Cl}$ and similar salts when dissolved in moderately polar aromatic solvents (the authors used 1-bromonaphthalene as a standard), which were interpreted on the basis of a cation–aromatic solvent interaction in which the effect of the counter-ion was merely to reduce in some cases these high-field shifts. This was clearly demonstrated by the addition of methanol to these solutions which enhanced the high-field shift by dissociating the ion-pair and thus allowing an increased ligand–cation interaction.

This is exactly the opposite of our observations (Tables 4 and 5), where the complexation shifts are substantially decreased both for methanol addition and in methanol as solvent as expected if the complex dissociates. Taylor and Kuntz obtained similar results with benzyl alcohol as solvent, in that the high-field shifts of $Me\overset{+}{P}Ph_3\overset{-}{X}$ are independent of the anion, which is not the case with 1-bromonaphthalene as solvent, showing that the effect of benzyl alcohol is to dissociate the ion-pair, allowing greater cation–ligand interaction. The differences observed with benzyl alcohol in our case are very probably due to the much stronger ion-pair association in the case of the $R_3\overset{+}{N}H\overset{-}{X}$ compounds studied here, when compared with the $R_4\overset{+}{M}\overset{-}{X}$ salts studied by Taylor and Kuntz [13] (K_d for $Et_2\overset{+}{N}H_2\overset{-}{Cl}$ is 3.8×10^{-7},[21] *cf.* $Bu_4\overset{+}{N}\overset{-}{Cl}$ of 2.5×10^{-2},[12] both in nitro-

[20] J. B. Hyne, *J. Amer. Chem. Soc.*, 1963, **85**, 304.
[21] M. C. Haulait and P. L. Huyskens, *J. Phys. Chem.*, 1975, **79**, 1812.

benzene). However, it should be noted that although our results are consistent with a specific 1 : 1 complex they do not in any way rule out the possibility of a separated ion-pair as the actual complex. The stoicheiometry and therefore analysis of the dilution curves (Figure 1) are identical for a ligand-separated or ligand-attached complex and indeed the molecular geometry given previously is also compatible with either, in as much as in both cases the benzyl alcohol will be close to the positive nitrogen with the hydroxy-group bonding to the $\bar{C}l$ (Figure 4). In the solvent separated ion-pair

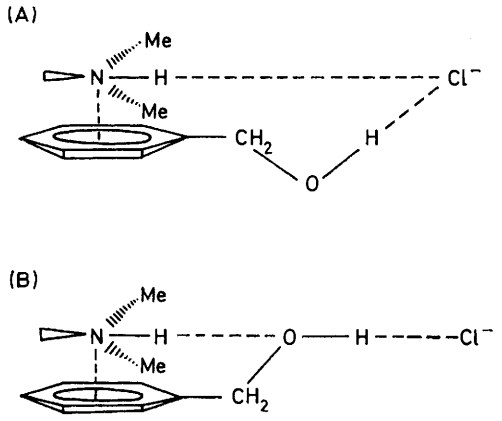

FIGURE 4 The ligand-attached (A) and ligand-separated (B) model of the imipramine hydrochloride–benzyl alcohol complex

there is a $\overset{+}{N}$–H · · · O bond whereas in the ligand attached model there is a N–H · · · Cl bond.

Rulinda and Huyskens' investigations of the association of phenols with ion-pairs XNR_4 (X = Cl, Br or I; R = Bu or heptyl) gave enthalpies of formation of 4—7 kcal mol^{-1}.[22] In these cases, however, the quaternary ammonium cation cannot act as a hydrogen-bond acceptor, and therefore only the ligand attached model is appropriate.

EXPERIMENTAL

Chemicals.—The patented drugs used in this initial study were obtained from the following sources: imipramine hydrochloride from Geigy Pharmaceuticals, promazine hydrochloride from John Wyeth and Bro., chlorpromazine hydrochloride from May and Baker, protriptyline hydrochloride from Merck, Sharp, and Dhome. Analogues (7) and (8) were obtained commercially (Aldrich Chemical Co.) and (5) and (6) were samples supplied by Professor A. Ledwith. The synthesis of the remaining tricycles and analogues are well documented.[3,23]

$CDCl_3$ used throughout these experiments was dried over molecular sieve (sodium aluminosilicate) grade 4A (8—12 mesh beads) stored over silver foil and passed through an alumina column to remove acid before use.

The trimethyl derivatives of imipramine (1) and dimethylaminopropyl chloride (7) were obtained from the free bases by reaction with methyl iodide in benzene. The tetraphenylborate of (7) was prepared with sodium tetraphenylborate in a 1 : 1 solution of methanol–water and recrystallised from absolute ethanol. 3-Chloropropyl-*NNN*-trimethylammonium iodide had m.p. 227 °C (lit.,[24] 225—226 °C) and the tetraphenylborate had m.p. 129 °C. The n.m.r. spectrum was entirely consistent with the proposed structure and no evidence of any impurities was observed.

Computing.—The COSMODEL program calculates the molecular co-ordinates from the input of bond lengths and angles, after the MODELBUILDER program,[25] and also incorporates the calculation of $(3\cos^2\theta - 1)/r^3$ from any given atom (usually the lanthanide atom). Specifying this as the centre of the benzene ring gives immediately the ring current shift on the equivalent dipole approximation. The program can handle up to 100 atoms and vary up to three dihedral angles simultaneously.

The COSMODEL program was adapted to produce an interactive graphical facility on a P.D.P.11 computer with visual display unit accessory. Additional information indicating the attached atoms enables the positioning and rotation of the three-dimensional model to be made and displayed as a two-dimensional image, as shown in Figure 3.

N.m.r. Spectra.—Two n.m.r. spectrometers were used in this investigation: a Varian HA-100, and a Varian XL-100-15 with internal deuterium lock. All spectra were recorded at 35 °C unless stated in the text. All concentrations were 0.23M unless stated otherwise. Chemical shifts are measured in p.p.m. downfield from tetramethylsilane (δ values) and are quoted to within 1 Hz, although the signals were measured to an accuracy of at least $\pm$0.1 Hz in all cases by taking spectra at expanded spectral width and averaging at least two recorded spectra. Differences in chemical shifts ($\Delta\delta$ values) are given to within $\pm$0.1 Hz and are equal to (δ values in solvent − δ value in solvent with shift reagent). Spectra were checked with a secondary standard where necessary (*e.g.* t-butyl alcohol and DSS in D_2O solutions).

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[7/704 *Received*, 26*th April*, 1977]

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[25] M. S. Gordon and J. A. Pople, MODELBUILDER, QCPE Programme No. 135, Indiana University, Bloomington.