The Nuclear Magnetic Resonance Spectra and Conformations of Cyclic Compounds. Part X.† Conformational Equilibria in 5-Substituted 10,11-Dihydrodibenz[*b,f*]azepines

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The conformational equilibria in 5-substituted 10,11-dihydrodibenz[*b,f*]azepines have been studied by variable temperature ^1H and ^{13}C n.m.r. spectroscopy. For the parent compound and its *N*-alkyl-substituted derivatives, including imipramine, the conformational inversion of the seven-membered ring is too fast to be observed by these techniques. However for the *N*-acyl derivatives hindered rotation about the *N*-acyl bond produces a concomitant decrease in the rate of ring inversion due to the buttressing effect of the dibenzo-groups. The ring conformation of the *N*-acetyl derivative is deduced from the observed $^3J_{HH}$ couplings of the ethano-bridge to be *ca.* 50° buckled. Ring inversion barriers for the *N*-acetyl, *N*-chloroacetyl, and *N*-ethoxycarbonyl derivatives are estimated and discussed. The conformation of the dimethylaminopropyl side chain of imipramine and its hydrochloride has also been deduced. Remarkably the side chain appears to exist in one predominant conformation with a *gauche*-C_α–C_β and *trans*-C_α–C_β orientation in the hydrochloride in $CDCl_3$ solution. In D_2O solution this conformation in the hydrochloride is less favoured (though still preferred), but the free base in $CDCl_3$ solution shows little conformational preference.

DERIVATIVES of the 10,11-dihydrodibenz[*b,f*]azepine ring system (iminobibenzyl) (1), especially those bearing γ-dimethylaminopropyl and carbamoyl substituents at the 5-position, are of importance as pharmacological agents;[1,2] imipramine and its hydrochloride (6), and similar compounds are classified as thymoleptic drugs and are widely used in treatment of depression. Surprisingly the fundamental physical and chemical properties of this ring system have not been systematically investigated and in particular there does not appear to have been any attempt to correlate pharmacological activity with conformational effects of the ring system and its substituents. Studies of the ^1H n.m.r. spectra of iminobenzyls are confined to the tabulation of chemical shifts,[3] whilst for the related iminostilbene ring system (7) amide rotational barriers in *N*-acylated derivatives, *e.g.* (8),[4] and barriers

† Part IX, R. J. Abraham, C. M. Holden, P. Loftus, and D. Whittaker, *Org. Magnetic Resonance*, 1974, **6**, 184.

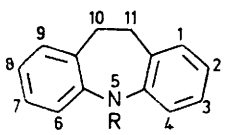
[1] F. Haefliger and V. Burckhardt in ' Psychopharmacological Agents,' Academic Press, New York, 1964, vol. 1, p. 35.

[2] L. J. Kricka and A. Ledwith, *Chem. Rev.*, 1974, **74**, 101.

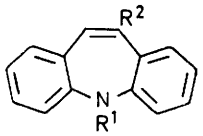
[3] L. J. Kricka and A. Ledwith, *J.C.S. Perkin I*, 1973, 859.

[4] E. Gipstein, W. A. Hewett, and O. U. Need, *J. Polymer Sci. A-1*, 1970, **8**, 3285.

to inversion of the central azepine ring of *N*-alkyliminostilbenes, *e.g.* (9), have been studied by variable temperature n.m.r. spectroscopy.[5]



(1) R = H
(2) R = Ac
(3) R = $COCH_2Cl$
(4) R = CO_2Et
(5) R = Me
(6) R = $CH_2CH_2CH_2\overset{+}{N}HMe_2Cl^-$



(7) $R^1 = R^2 = H$
(8) $R^1 = COCH_2CH_2Cl$, $R^2 = H$
(9) $R^1 = Et$, $R^2 = CMe_2OH$

Previously we have noted [3,6] differences between the ^1H n.m.r. spectra of 5-acyl- and 5-alkyl-iminobibenzyls and now present detailed analyses of their temperature-dependent ^1H and ^{13}C spectra.

RESULTS AND DISCUSSION

Temperature-dependent Spectra.—The ^1H n.m.r. spectrum of 5-acetyl-10,11-dihydrodibenz[*b*,*f*]azepine (5-acetyliminobibenzyl) (2) shows a remarkable variation with temperature (Figure 1). At −30° and below all the protons of the ethano-bridge are non-equivalent (Figure 1a) and form an ABCD spin system [7] which gives rise to two complex unsymmetrical groups of peaks centred at δ *ca.* 2·8 and 3·3. As the temperature is raised the ABCD spectrum is gradually transformed into that of an AA'BB' spin system (T_c *ca.* room temperature) which appears as two symmetrical groups of absorptions at δ 2·85 and 3·43 (Figure 1c) at 70°. A further increase in temperature leads to a broadening of the AA'BB' absorptions which eventually coalesce to a single absorption (T_c 112°).

The low temperature spectrum (Figure 1a) has so far defied all attempts at analysis, but the AA'BB' spectrum (Figure 1c) may be completely assigned, using the standard rules for such spin systems [7] and analysed. The analysis was completed with the iterative computer program LAOCOON III [7] and the results from this analysis, together with the probable errors are $W_{1,2}$ 343·18 (0·02), $W_{3,4}$ 286·48 (0·03), J_{12} 5·09 (0·04), $J_{13(24)}$ −15·84 (0·04), $J_{14(23)}$ 8·68 (0·03), and J_{34} 5·09 (0·04) Hz with an r.m.s. error (observed *versus* calculated) of 0·08 Hz. Note that in the iteration J_{13} and J_{24} are varied together as are J_{14} and J_{23}, and this is an essential requirement for this spin system, but J_{12} and J_{34} are iterated separately. The agreement between the observed and computer simulated spectrum confirms the correctness of the analysis and also the assignment of the protons.

Other *N*-acylated iminobibenzyl derivatives exhibit temperature-dependent n.m.r. spectra similar to those obtained for 5-acetyliminobibenzyl (see Table 1). The ethano-bridge protons of 5-chloroacetyliminobibenzyl (3) appear as a broad multiplet at room temperature, but as the temperature is raised the spectrum is resolved at *ca.* 62° into an AA'BB' type spectrum ($\delta\nu_{AB}$ 56 Hz).

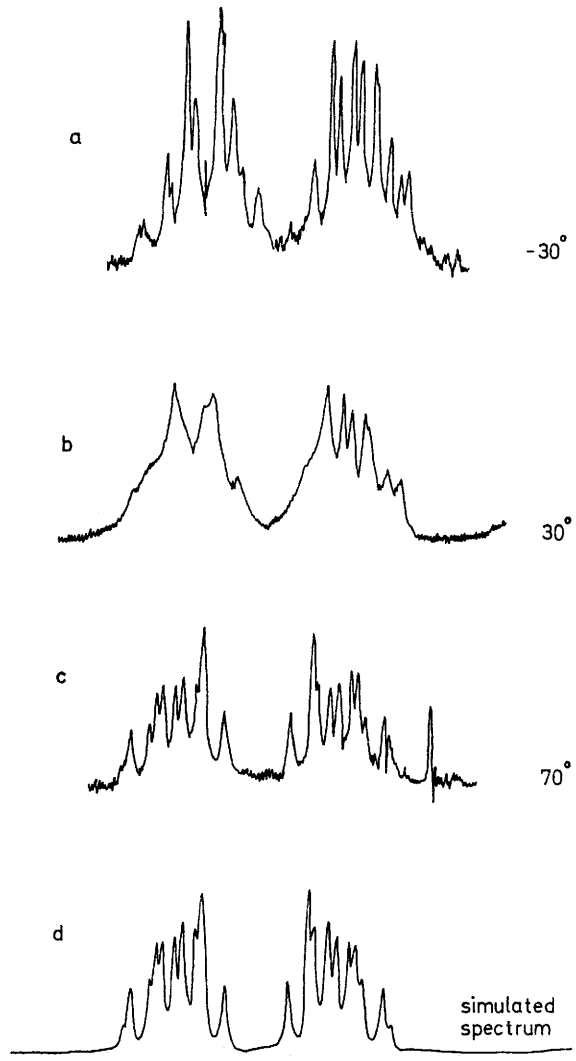


FIGURE 1 ^1H N.m.r. spectra of 5-acetyliminobibenzyl as a function of temperature

Likewise the ethano-protons of 5-ethoxycarbonyl- (4) and 3,5-diacetyl-iminobibenzyl (11) are non-equivalent at low temperatures and form successively an AA'BB' and an A_4 spin system, as the temperature is raised. The collapse of the AA'BB' to an A_4 spin system for (4) and (11) occurs at *ca.* 45 and 140°, respectively.

The methylene proton signals of the chloroacetyl and ethoxycarbonyl groups in (3) and (4) respectively, also exhibit a temperature dependence. For (3) the methylene protons appear as an AB quartet (J_{AB} 13·0, $\delta\nu_{AB}$ 8·6 Hz) at 6° but as the temperature is raised this collapses to give a single absorption (T_c *ca.* 30°). Similarly at low

[5] M. Nogradi, W. D. Ollis, and I. O. Sutherland, *Chem. Comm.*, 1970, 159.

[6] R. J. Abraham, L. J. Kricka, and A. Ledwith, *J.C.S. Chem. Comm.*, 1973, 282.

[7] R. J. Abraham, ' The Analysis of High Resolution N.M.R. Spectra,' Elsevier, Amsterdam, 1971.

temperatures the ethyl group of (4) forms an ABX_3 system over the temperature range −60 to −15° (J_{AB} 10·3, $J_{AX,BX}$ 6·8, $\delta\nu_{AB}$ 9·6 Hz) and at higher temperature (T_c *ca.* −5°) the methylene protons become equivalent and the ethyl group forms the usual A_2X_3 spin system.

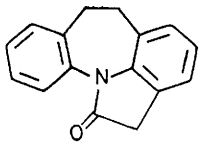
TABLE 1

Proton chemical shifts (δ) of iminobibenzyl derivatives [a]

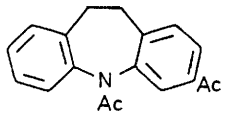
Compound	Solvent	Temp. (°C)	$[CH_2]_2$	ArH	Other
(2)	$CDCl_3$	30	*ca.* 2·8, 3·3 [b]	7·1—7·3	1·98 ($NCOCH_3$)
	$CDCl_3$	70	2·85, 3·43 [c]		
	$C_6H_3Cl_3$	160	2·93 [d]		
(3)	$CDCl_3$	62	2·8, 3·4 [e]	7·2	4·01 ($NCOCH_2Cl$)
(4)	$CDCl_3$	30	2·8, 3·4	8·0—8·3	5·13 (OCH_2), 1·17 (CH_3)
	$CDCl_3$	6	2·79, 3·38 [c]		
(5)	$CDCl_3$	30	3·12	6·9—7·2	3·29 (NCH_3)
(6) [e]	$CDCl_3$	30	3·08	6·7—7·1	$CH_2CH_2CH_2NMe_2$ 3·70, 1·67, 2·26, 2·07
(6) [f]	$CDCl_3$	30	3·10	6·8—7·1	3·82, 2·12, 2·95, 2·56
	D_2O	30	2·80	6·7—7·1	3·49, 1·67, 2·75, 2·47
(10)	$CDCl_3$	37	3·0	6·9—7·3 7·9 (1H)	3·7 ($COCH_2$)
(11)	$CDCl_3$	37	*ca.* 2·9, 3·3 [c]	7·3—7·7	2·00 ($COCH_3$), 2·52 ($NCOCH_3$)

[a] 100 MHz except where otherwise stated. [b] ABCD type spectrum. [c] AA'BB' type spectrum. [d] 60 MHz. [e] Free base. [f] Hydrochloride.

In direct contrast to these *N*-acyl derivatives all the *N*-alkyl derivatives studied and the parent compound show the ethano-bridge protons as a single line down to the lowest temperatures attained (−100°).



(10)



(11)

Similar effects are observed in the ^{13}C spectra of these compounds. For those molecules with no amide fragments (1) and (5), and imipramine hydrochloride (6), the ring carbon atoms exhibit only seven separate resonances, as the molecules may be considered to have an effective plane of symmetry caused by the rapid inversion. All these signals are sharp and their provisional assignments (obtained from the relative intensities of the quaternary and methine carbons and thence from consideration of steric effects and substituent group parameters [8]) are given in Table 2. For the ethoxycarbonyl compound (4) however, although there are still only seven separate ring carbon signals they are now all rather broad ($\delta\nu_{\frac{1}{2}}$ *ca.* 5 Hz) indicating the onset of restricted rotation.

This is confirmed for the $COCH_2Cl$ compound (3) in which the ethano-bridge carbons are almost at coalescence point ($\delta\nu_{\frac{1}{2}}$ *ca.* 15 Hz) whilst the spectrum of the remaining ring carbons is now clearly resolved into twelve overlapping signals. Finally in the *N*-acetyl compound (2) all fourteen ring carbons give separate sharp signals. Of particular note is the separation of the ethano-bridge carbons at this temperature (35°), which shows conclusively that the ring system does not have an effective plane of symmetry at this temperature (see later). These signals coalesce to a single line at *ca.* 50°. Similarly at −40° the carbons of (3) are a sharp doublet.

Estimation of Rate Parameters.—The coalescence process ABCD ⟶ AA'BB' is complex and ill defined and would require the complete analysis of the ABCD spectrum and a total line shape analysis to obtain any rate parameters.[9] However, the other coalescence processes may be used to obtain approximate rate data from the simple equations (1A—C). The rate constant for the equally populated two site exchange at the coalescence temperature (T_c) is given by equation (1A) where $\delta\nu$

$$k = \pi\delta\nu/\sqrt{2} \qquad (1A)$$

is the chemical shift separation in the absence of exchange. For the coupled system AB ⟶ A_2 this equation is modified to (1B).[9] Also for the simple two

$$k = \pi[(\delta\nu)^2 + 6J_{AB}^2]^{\frac{1}{2}}/2^{\frac{1}{2}} \qquad (1B)^*$$

site exchange the line width of the coalesced peak, from coalescence onwards is given by equation (1C) [10] where h is

$$k = \delta\pi\nu[(\delta\nu/h)^2 - (h/\delta\nu)^2 + 2]^{\frac{1}{2}}/2 \qquad (1C)$$

the half-height line width of the collapsed peak and the equation is valid for $h \gg$ the natural line width.

From the definition of k as equation (2) the free energy of activation of the process may be estimated.

$$k = [RT \exp(-\Delta G^{\ddagger}/RT)]/Nh \qquad (2)$$

Table 3 gives the results for the various coalescence

TABLE 2

^{13}C Chemical shifts (δ) of *N*-substituted dihydrodibenzazepines [a]

Compound	C-1, -9	C-2, -8	C-3, C-7	C-4, -6	C-10, -11	C-9a, -11a	C-4a, -5a
(1)	130·1	119·0	126·2	117·5	34·7	128·1	141·9
(5)	129·2	118·3	125·9	121·3	32·8	132·6	148·2
(4) [b]	129·3	126·9	126·1	127·9	30·6	135·5	140·3
(6) [c]	129·5	119·1	126·1	122·6	32·0	133·4	146·7
(6) [d]	129·5	119·7	126·5	122·6	31·8	133·5	14·73
e	129·2	119·6	125·8	122·0	32·2	133·7	147·8

[a] *ca.* 1M solutions in $CDCl_3$ unless stated otherwise. [b] $CO_2CH_2CH_3$ δ 154·5, 61·6, and 14·5 respectively. [c] $CH_2CH_2CH_2\overset{+}{N}HMe_2$, δ 47·2, 22·2, 55·6, and 42·3 respectively. [d] In D_2O solution $CH_2CH_2CH_2\overset{+}{N}HMe_2$, δ 46·8, 22·4, 55·4, and 42·5 respectively (standardised with $CDCl_3$ solution). [e] Free base of (b). $CH_2CH_2CH_2NMe_2$, δ 48·7, 26·1, 57·5, and 45·2 respectively.

* We are grateful to a referee for pointing this out.

[8] G. C. Levy and G. L. Nelson, ' Carbon-13 N.M.R. for Organic Chemists,' Wiley, New York, 1972.

[9] G. Binsch, *Topics Stereochem.*, 1968, **3**, 97.

[10] A. Allerhand, H. S. Gutowsky, J. Jones, and R. A. Meinzer, *J. Amer. Chem. Soc.*, 1966, **88**, 3185.

processes investigated by these approximate formulae. It must be stressed that *all* these formulae are approximations even in the simple two site to one site equilibrium. (For an authoritative discussion of this, see ref. 9.) Thus in our case, particularly in the coupled systems, the values of $\Delta G^{\ddagger}$ must be treated with care. Nevertheless they still provide some interesting information. We note from Table 3 that the use of equation (1B) rather than (1A) for the AA'BB' $\longrightarrow$ A_4 coalescence has little effect (due to the large value of $\delta\nu$) and this has only been recorded in one case [compound (2)]. However, for the AB $\longrightarrow$ A_2 equilibrium equation (1B) has a pronounced effect [*cf.* compound (3)] lowering $\Delta G^{\ddagger}$ by *ca.* 2 kcal mol^{-1}. Encouragingly the value of $\Delta G^{\ddagger}$ obtained in this way is in eclipsed or more generally if the fragment is equilibrating between two mirror-image conformations. Thus we interpret the spectrum as being due to a rapid interconversion between two enantiomers (Figure 2).

The ethano-fragment of (2) may also be visualised as in Figure 3, from which it can be seen that the observed vicinal couplings are given by equation (3) where the value of ϕ, the dihedral angle, may be calculated from the

$$J_{cis} = J_{12.34} = J\phi$$
$$J_{trans} = J_{14.23} = \tfrac{1}{2}[J(120 + \phi) + J(120 - \phi)] \quad (3)$$

observed couplings once the form of the coupling *versus* dihedral angle equation appropriate to the C·CH_2·CH_2·C fragment is established.

TABLE 3

Free energies of activation for inversion–rotation processes in dihydrodibenzazepines

Compound	Solvent	Nuclei	Coalescence process	$\delta\nu$ (Hz)	T_c (°C)	Equation used	$\Delta G^{\ddagger}$/kcal mol^{-1} (at T/K)
(2)	$C_6H_3Cl_3$	^1H [a]	AA'BB' $\longrightarrow$ A_4	32·4	112	(1A)	19·5 (385)
	[$^2H_6$]DMSO	^1H [a]	AA'B''B' $\longrightarrow$ A_4	46·6	115	(1A)	19·3 (388)
						(1B)	19·1 (388)
						(1C) [b]	19·5 (393)
	[$^2H_6$]DMSO	^{13}C	2A $\longrightarrow$ A_2	13	50	(1A)	16·8 (320)
						(1C) [b]	16·8 (330)
(3)	$C_6H_3Cl_3$	^1H	AA'BB' $\longrightarrow$ A_4	56·6	130	(1A)	20·0 (400)
						(1C) [b]	20·1 (410)
	C_6H_6Cl	^1H [a]	AB $\longrightarrow$ A_2	11·5	25	(1B)	14·9 (298)
	$CDCl_3$	^1H [a]	AB $\longrightarrow$ A_2	8·6	30	(1A)	17·4 (300)
						(1B)	15·4 (300)
	$CDCl_3$	^{13}C	2A $\longrightarrow$ A_2	22	35	(1C) [b]	15·5 (308)
(4)	$CDCl_3$	^1H	AA'BB' $\longrightarrow$ A_4	59·0	45	(1A)	15·6 (318)
	$CDCl_3$	^1H	AB $\longrightarrow$ A_2	9·6	−5	(1B)	13·5 (268)

[a] 60 MHz, all others 100 MHz. [b] h = 42, 4·5, 30, and 15·8 Hz respectively.

excellent agreement with that from the ^{13}C spectrum using equation (1C). These values will be discussed later.

Conformation of the Seven-membered Ring.—The results of the analysis of the AA'BB' spectrum of (2) may be used to provide information on the conformation of this CH_2·CH_2 fragment. Inspection of the couplings shows first that the chemically equivalent pairs of hydrogens must be situated on the same side of the seven-membered ring, *i.e.* in a *cis*-configuration. (For example J_{13} has the characteristic sign and value of a coupling between two geminal hydrogen atoms next to a phenyl ring [11]).

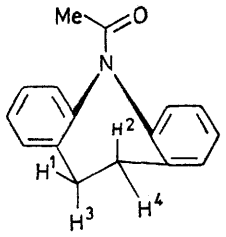


FIGURE 2

The symmetric AA'BB' spin system can only be produced from such a molecular fragment if the fragment is

[11] A. A. Bothner-By, 'Advances in Magnetic Resonance,' ed. J. S. Waugh, Academic Press, New York, 1965, ch. 1.

[12] E. W. Garbisch and M. C. Griffith, *J. Amer. Chem. Soc.*, 1968, **90**, 6543.

Garbisch and Griffith [12] have proposed the relationship as $J = 12{\cdot}95 \cos^2\phi$ from the observed low temperature couplings of [$^2H_4$]cyclohexane and St. Jacques and

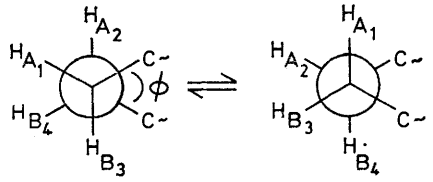


FIGURE 3

Vaziri [13] have used this equation to obtain the conformation of the seven-membered ring in benzocycloheptene from the low temperature couplings with some success; thus this should be a reasonable approximation for the very similar fragment considered here.

Solution of equation (3) with the modified $\cos^2\phi$ equation above gives ϕ 51°, J_{cis} calculated 5·1 (observed 5·1), J_{trans} calculated 7·2 (observed 8·7). The agreement is reasonable after consideration of all the approximations implicit in such calculations. In particular any increase of the C·C·C angles in the seven-membered ring from the tetrahedral will produce a concomitant decrease in the H·C·H angles and hence an increase in J_{trans} from that calculated by equation (3).

[13] M. St. Jacques and C. Vaziri, *Org. Magnetic Resonance*, 1972, **4**, 77.

Furthermore this value for the dihedral angle is entirely consistent with those of similar systems, *cf.* metacyclopentane [14] *ca.* 60° and 6,7,8,9-tetrahydro-5*H*-benzocycloheptene [13] 73°, *i.e.* essentially a completely staggered ethano-bridge.

Concerted Rotation–Inversion Process.—We interpret the temperature-dependent spectra in terms of restricted rotation about the amide C–N bond and an inversion of the central seven-membered azepine ring. Conjugation of the amide system with the nitrogen lone pair (even though the nitrogen may not be planar in these molecules) results in the amide group adopting a preferred conformation essentially parallel to the molecular long axis. This has the effect of ' freezing ' the conformation of the seven-membered ring, as ring flip would involve large steric interactions between the amide group and the aromatic protons at C-4 and C-6. As the temperature is raised so that amide rotation becomes detectable the steric restrictions imposed on the ring inversion are removed. Clearly in the limit of rapid amide rotation and ring flipping the ethano-bridge protons will collapse to an A_4 system.

When the amide group is held in a rigid planar conformation as in (10) the steric interactions of the amide group and the *ortho*-protons are much reduced, and in agreement with prediction, the ethano-bridge protons of (10) are a single line down to −60°. Similarly the seven-membered ring by itself has a very low barrier to inversion, as is evidenced by the spectra of the *N*-alkyl derivatives in which no change was observed even down to −100°.

Thus the general picture of a concerted amide rotation–ring inversion mechanism would appear to be well substantiated. However, the details of this process are still not clear, and in particular whether there is only one molecular rate process occurring which is responsible for all the coalescence phenomena or whether more than one process is involved. The only possible distinction between these alternatives is to be found in the values of the activation parameters obtained. Obviously if all the coalescence phenomena give the same value of the activation parameters, then only one molecular process (concerted or not) is involved.

The low temperature values of $\Delta G^{\ddagger}$ of Table 3 are consistent and in particular the values obtained from the proton AB ⟶ A_2 collapse in (3) are identical within the limits of error with those from the ^{13}C spectra obtained at the same temperature (*cf.* Table 3, 15·4 and 15·5 kcal mol^{-1} respectively). Thus we may safely assume that the same molecular process is responsible for these rate processes. This also makes sense on symmetry arguments. When the two carbon atoms of the ethano-bridge are equivalent (on the n.m.r. time-scale) then it follows that the ring has an effective plane of symmetry, *i.e.* that the two halves of the molecule are mirror images. Furthermore, the methylene protons on the side-chain will become isochronous and also the ethano-bridge protons will reduce to an AA'BB' system. (Note that in this AA'BB' system the protons on the same side of the ring are isochronous, thus the effective plane of symmetry is still maintained.)

The values of $\Delta G^{\ddagger}$ for this process for compounds (2)—(4) of 16·8, 15·4, and 13·5 kcal mol^{-1} are also in reasonable accord with the relative rotational barrier in similar fragments. For example in *NN*-dimethylacetamide, *NN*-dimethyl-2-chloroacetamide, and methyl *NN*-dimethylcarbamate E_a is given as 18·9, 17·5, and 14·8 kcal mol^{-1} respectively.[9] The barrier would be expected to be lower in the compounds studied here as the nitrogen could well be non-planar and there would be some steric interaction in the ground state. Thus this supports the view that the room temperature coalescence phenomena are all due to amide rotation and consequent ring flip to give an effective plane of symmetry of the molecule on the n.m.r. time-scale.

The problem occurs with the AA'BB' ⟶ A_4 coalescence. From Table 3 it is clear that the values of $\Delta G^{\ddagger}$ obtained for this coalescence are very different from those of the other rate processes.

Furthermore the various estimates of this activation energy in Table 3 are in reasonable agreement. Even considering the approximate nature of the treatment it is unlikely that the values of $\Delta G^{\ddagger}$ can be so far out as 20·0 and 15·4 kcal mol^{-1}.

There are two possible alternatives to this problem. These are two values of $\Delta G^{\ddagger}$ obtained at very different temperatures. There is no reason to suppose that the entropy of activation of this process should be zero. A substantial negative entropy of activation would provide consistent rate parameters. For example in (2) values of $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ of 10·5 kcal mol^{-1} and −20 cal mol^{-1} K^{-1} would give values of $\Delta G^{\ddagger}$ at 390 and 330 K of 18·3 and 17·1 kcal mol^{-1} which compare reasonably with the observed values of 19·3 and 16·8 (Table 3).

It is not clear why there should be such a large negative entropy of activation and an even larger value would be needed to explain the results for (3). However, this possibility cannot be definitely excluded at this stage.

The other possibility is that there is a different molecular process occurring in the AA'BB' ⟶ A_4 coalescence. It is indeed possible to conceive of such a process. The rotation of the amide group plus ring flexing which occurs at low temperatures does not produce full equivalence of the ethano-bridge protons even though the two halves of the molecule become equivalent on the n.m.r. time-scale. When we recall that the molecule is non-planar, that at low temperatures the aromatic rings are dissimilar, and that owing to this non-planarity the rotation of the amide group is asymmetric, a possible explanation is as follows.

The first coalescence process involves the lower energy rotation of the amide group and will involve the smallest atom, the carbonyl oxygen, by-passing the aromatic protons. When this occurs ring flexing (*not* inversion) also takes place and this equates the two halves of the molecule, but *not* the two sides of the molecule. Com-

[14] H. S. Gutowsky and C. Juan, *Discuss Faraday Soc.*, 1962, **34**, 52.

plete rotation of the amide group occurs at a higher temperature and when this happens ring inversion also occurs. Obviously this barrier will be higher than the previous one; the less energetic pathway will come first.

Support for this interpretation comes from the reversal in the barriers of (2) and (3) (Table 3). The less energetic pathway involves the carbonyl group by-passing the abutting aromatic protons and this activation energy merely reflects the double bond character of the N–COX bond for the differing X substituents, as found. However, the more energetic pathway involves the methyl group by-passing the aromatic protons in (2) and the CH_2Cl group in (3). Interestingly enough the barrier in (3) is significantly larger than in (2) which would be expected. The CO_2Et group which on this basis is nearly symmetric would give much more equal barriers on rotation, again as observed.

Although we prefer this latter explanation, we cannot at this stage entirely rule out entropy effects, especially as the higher energy barriers are subject to considerable errors. An investigation of a suitable model compound *e.g.* a 10,10-dimethyl derivative, may differentiate these alternatives.

Conformation of the Dimethylaminopropyl Side-chain.—The n.m.r. method may also be used to determine the preferred conformation of the side-chain in imipramine and its hydrochloride (6). Again the method utilises the vicinal coupling constants in each $CH_2{\cdot}CH_2$ fragment, though now we are concerned with an averaged coupling over the distinct rotamers, as there is rapid interconversion (on the n.m.r. time-scale) between them.

Abraham and Gatti [15] have developed equations for the calculation of these couplings for the individual rotamers of any $CH_2{\cdot}CH_2$ fragment, and the method has already been applied to the calculation of rotamer populations in histamine [16] and choline [17] analogues. In the case of the $-N{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2NMe_2$ side-chain in imipramine we may extend the method by simply utilising it for the calculation of the *trans–gauche* energy difference of each $CH_2{\cdot}CH_2$ fragment separately. Each fragment on this model will have one *trans-* and two equivalent *gauche-*conformations, exactly as any 1,2-disubstituted ethane, and the equations developed in ref. 15 may be used unchanged.

However, the spectra given by the side-chain $\geq N{\cdot}CH_2$ protons are merely the first-order 1 : 2 : 1 triplet, rather than the full AA'BB' spectrum and in this case only one 'averaged' coupling (J_{av}) can be obtained from the spectrum (see ref. 7 for a full discussion). It is more convenient in this case to formulate the basic equations [15] in terms of the parameter N ($J_{13} + J_{14}$; *cf.* Figure 3) which is simply defined as the separation between the outer lines of the triplet pattern (and equals of course $2J_{av}$ for a first-order spectrum).

Although the spectrum of the CH_2NMe_2 group was not a simple triplet pattern the separation of the outer transitions may easily be measured to give the required value of N for this fragment. The observed value of N is then simply obtained as the weighted average of the value in the *trans*-(N_t) and *gauche*-(N_g) conformations, *i.e.* equations (4), ΔE ($E_g - E_t$) being the excess of

$$\begin{aligned} N_{obs} &= n_g N_g + n_t N_t \\ n_g/n_t &= 2 \exp(-\Delta E/RT) \\ n_g + n_t &= 1 \end{aligned} \quad (4)$$

energy (strictly free energy) of the *gauche*-form. Simplifying equation (4) gives (5); thus all that is required to

$$\Delta E = E_g - E_t = RT \ln [2(N - N_g)/(N_t - N)] \quad (5)$$

calculate the rotamer energy is the value of N_t and N_g for the $N{\cdot}CH_2{\cdot}CH_2{\cdot}C$ fragment.

We note that protonating the nitrogen has no effect on the vicinal couplings (*cf.* $^3J_{HH}$ in Et_3N and $Et_4\overset{+}{N}$ both 7·4 Hz),[10] thus the same parameters may be used for the $C{\cdot}CH_2{\cdot}CH_2N$ and $C{\cdot}CH_2{\cdot}CH_2\overset{+}{N}$ fragments. The data in ref. 15 give N_t as the observed value in $Bu^tCH_2CH_2\overset{+}{N}Me_3\ I^-$, which is entirely in the *trans*-conformation, as 17·37 Hz and N_g as the observed value in piperidine in which of course the $CH_2{\cdot}CH_2$ fragment exists entirely in the *gauche*-conformation, as 11·67 Hz.

Incorporation of these values into equation (5) thus gives ΔE immediately from the observed value of N, for any such fragment. It is of interest to note that the value of N_{av} [$\frac{1}{3}(2N_g + N_t)$] corresponding to equally populated *trans-* and *gauche*-rotamers is 13·6 Hz and thus if the observed value of N is larger than this the *trans*-rotamer is preferred (up to 17·37 Hz) whereas smaller values than this indicate a preference for the *gauche*-orientation (to 11·67 Hz).

Imipramine in $CDCl_3$ solution gives an essentially first-order pattern for the side-chain protons, *i.e.* triplet J_{av} 6·9 Hz (N 13·8) for the C_α methylene, a distorted triplet N 14·64 for the C_γ protons, and a complex pattern, approximating to a 1 : 4 : 6 : 4 : 1 quintet (J 7·1 Hz) for for C_β protons.

Incorporation of the values of N in equation (5) gives immediately ΔE ($E_g - E_t$) values of 0·10 kcal mol^{-1} for the C_α–C_β fragment and 0·47 kcal mol^{-1} for the C_β–C_γ fragment.

In the case of imipramine hydrochloride in D_2O solution the side-chain proton resonances are broad and ill-resolved at probe temperature, but at 80° the spectrum is much sharper and easily analysed. (The broadening we ascribe to slow exchange of the $\overset{+}{N}H$ poton in these solutions.)

The α-methylene signal is the normal first-order triplet with N 13·1 Hz but the γ-methylene is overlapped by the ethano-bridge resonance. However, the value of N can still be obtained as 15·9 Hz. These values give ΔE values of −0·28 (C_α–C_β) and +0·74 (C_β–C_γ) kcal mol^{-1} respectively.

[15] R. J. Abraham and G. Gatti, *J. Chem. Soc.* (*B*), 1969, 961.
[16] C. R. Ganellin, E. S. Papper, G. N. J. Port, and W. G. Richards, *J. Medicinal Chem.*, 1973, **16**, 610.
[17] P. Partington, J. Feeney, and A. S. V. Burgen, *Molecular Pharmacology*, 1972, **8**, 269.

The hydrochloride is also soluble in $CDCl_3$ giving N values of 12·4 (α-methylene) and 16·5 Hz (γ-methylene). In this case the γ-methylene resonance is not first order but again the separation of the outermost transitions is easily measured. These values give corresponding ΔE values of −1·2 (C_α–C_β) and +1·0 (C_β–C_γ) kcal mol^{-1}.

The rotamer energy differences are of considerable interest. The free base in $CDCl_3$ shows, as may have been expected, no great preference for any conformation. The essentially zero energy difference for the C_α–C_β fragment demonstrates the small steric effect of the benzazepine nucleus due to the conformation of the ring system, bending away from the side-chain. The value of 0·5 kcal mol^{-1}, in favour of the *trans*-conformation of the C_β–C_γ fragment is entirely reasonable (*cf.* n-butane ΔE 0·8 kcal mol^{-1}).[18] Protonation of the amino-nitrogen further favours the *trans*-conformation, again as expected (*cf.* $-\Delta G°$ for axial to equatorial cyclohexanes *ca.* 1·5 for NH_2 and 1·9 kcal mol^{-1} for $\overset{+}{N}H_3$),[18] so that in $CDCl_3$ there is a very considerable preference (ΔE *ca.* 1·0 kcal mol^{-1}) for the *trans*-conformation. Note however the considerable influence of the solvent in that in D_2O solution this is reduced to 0·7 kcal mol^{-1}.

However, the most interesting effect is the marked preference for the *gauche*-conformation of the C_α–C_β fragment in the hydrochloride (ΔE — 1·2 kcal mol^{-1}) in $CDCl_3$ solution, which again is considerably reduced in D_2O solution (ΔE −0·3 kcal mol^{-1}).

The remarkable conclusion which emerges from this study is that the side-chain of imipramine hydrochloride in a non-aqueous medium such as $CDCl_3$ exists almost entirely in one fixed conformation, with a *gauche*-C_α–C_β and a *trans*-C_β–C_γ fragment. This fixed conformation is less favoured (though still preferred) in D_2O solution whilst in the free base there is very little conformational preference.

Pharmacological Properties of Benzazepines.—The therapeutic actions of depressant and anti-depressants are not well understood although a common structural feature of both types of drug is attachment of a γ-aminopropyl function to a tricyclic ring system.

Anti-depressant drugs must be administered in large doses and taken for up to two weeks before becoming effective. At least two possible modes of action have been considered.[19,20]

Curzon [21] has implicated imipramine and/or its metabolites in the biosynthetic pathway leading to the neurotransmitter 5-hydroxytryptamine, and suggests that imipramine may act by inhibiting the liver enzyme tryptophan pyrrolase. An alternative interpretation is that tricyclic anti-depressants rely for effect on their capacity to block the re-uptake of neurotransmitters released upon stimulation of the nerve terminal which leads to an accumulation of neurotransmitter at the reception and a consequent increase in activity.

It is at least possible therefore that the detailed molecular conformation of imipramine, now adduced from n.m.r. analysis, may be important in understanding its blocking or inhibiting effects.

EXPERIMENTAL

^1H Spectra were obtained on Varian HA 100 and A 56/60 spectrometers, at probe temperatures of 28 and 35° respectively. ^{13}C Spectra were obtained on *ca.* 1M solutions in $CDCl_3$ on a Varian XL-100 spectrometer operating at 25·2 MHz in the Fourier transform mode with noise-modulated ^1H decoupling. The sample temperature for these spectra was *ca.* 35°. Spectra were usually obtained over a 5 kHz width, with 2048 real points in the transformed spectrum providing an accuracy of 0·1 p.p.m. Sample tubes (12 mm) were used with an inner 5 mm tube of D_2O for the field-frequency lock.

5-Methyl-, m.p. 106—107° (lit.,[22] 107—108°), 5-acetyl-, m.p. 85—86° (lit.,[3,23] 98°), 5-chloroacetyl-, m.p. 96—98° (lit.,[24] 97—100°), 5-ethoxycarbonyl-, m.p. 94—95° (lit.,[23,24] 95°), and 3,5-diacetyl-10,11-dihydrodibenz[*b*,*f*]azepine, m.p. 140—142° (lit.,[23] 143—144°), were prepared as outlined in the literature. 1,2,6,7-Tetrahydroindolo[1,7a,7-*ab*]benz[1]-azepin-1-one (10), m.p. 196—198° (lit.,[25] 198°), was prepared by intramolecular Friedel–Crafts alkylation of 5-chloroacetyl-10,11-dihydrodibenz[*b*,*f*]azepine.

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