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CONFORMATION OF 1,4-DIBENZOYL-2,5-DIALKYLPIPERAZINE. TWIST-BOAT RING CONFORMATION.

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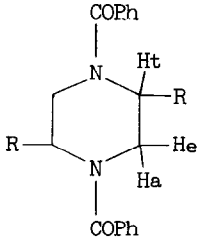
Only relatively few nitrogen-containing six-membered rings have been shown to exist in non-chair conformation.[1] We now present evidence that 1,4-dibenzoyl-*cis*-2,5-dialkylpiperazines (*cis*-I) possess twist-boat (TB) form in both solution and crystal.

During an NMR spectral study of ring flattening effects in chiral piperazines synthesized in our laboratory,[2] it was found that the pattern of the spectra of *cis*-I was very different from that of *trans*-I. As shown in Table I, no drastic spectral change is observed in *cis*-Ia within 150° ~ -58°, except for changing $\Delta\delta_{ae}$. On the other hand, the NMR data of *trans*-I indicated strong temperature dependence, as well as other N,N'-diacylated analogues.[3] The spectra of *cis*- and *trans*-Ib containing the ethyl group as C-substituent are compared in Fig. 1. Since no appreciable differences are found in the pattern of spectra in the methyl and ethyl derivatives, only the latter will be discussed here.



Ia; R = CH_3

Ib; R = C_2H_5

Table I. Chemical shifts (δ in ppm) and coupling constants (J in Hz) of the ring protons in 1,4-dibenzoyl-2,5-dialkylpiperazines (I).

Piperazine	R	Solvent	Temp. °C	Ha	He	Ht	Δδae	Jae	Jat	Jet
cis-Ia	CH_3	$CDCl_3$	33	2.98	3.95	4.44	0.97	14.0	11.0	7.0
"	"	"	-58	3.25	3.83	4.63	0.58	14.2	11.6	7.0
"	"	DMSO-d_6	30	3.10	3.78	4.16	0.68	14.0	11.0	7.0
"	"	"	150	3.03	3.81	4.20	0.78	13.5	10.0	7.0
trans-Ia*	"	"	150	3.35	3.72	4.34	0.37	14.0	4.0	2.0
cis-Ib	C_2H_5	$CDCl_3$	30	2.98	3.98	4.34	1.00	14.0	11.0	7.0
trans-Ib**	"	DMSO-d_6	150	3.30	3.88	4.15	0.58	14.0	4.0	1.8

* No NMR data in $CDCl_3$ are available owing to the poor solubility.
** The spectra in $CDCl_3$ and in DMSO-d_6 are shown in Fig. 3.

The spectrum of *cis*-isomer reveals one set of sharp resonances which are readily assignable. The ^{13}C-NMR spectrum of *cis*-Ib was similarly constituted, and little change was noted down to -48°. The result indicates that only one conformer is present at the temperature and the conformation exhibits C_2 symmetry, with pairs of magnetically equivalent groups and protons. On the other hand, *trans*-Ib shows a complicated pattern that is characteristic of a dynamic process involved, and the contribution of three or more conformers to the spectrum is suggested. The following interpretation is consistent with the observed spectra.

If the chiral piperazine ring exists as the usual chair form, the molecule may undergo three different dynamic processes; nitrogen inversion, ring reversal, and N-R bond rotation around the amide bond. In all cases studied, the carbonyl group conjugates with the ring nitrogen atom so that nitrogen inversion is NMR-fast. In addition, there are evidences that steric interactions between the amide group and the vicinal C-substituent in alkylpiperidine amides and 1,4-diacetyl-*trans*-2,5-dimethylpiperazine are sufficient to cause conformational bias, resulting in the preference for axial alkyl conformation.[4,5] Furthermore, conformational energy estimates[6] regarding the *trans*-isomer of I lead to the conclusion that the conformational equilibrium is strongly biased toward diaxial alkyl conformations (Form A-1 ~ A-4 as shown in Fig. 2), and rotation around either C-N or C-C bond in the amide group should be required in order to decrease of the strain. Only N-R bond rotation process, therefore, should be considered (i.e., Form A-1 ~ A-4) and these four forms, in which A-3 and A-4 are enantiomers, are expected to contribute to the spectrum. The *trans*-Ib presents a typical spectum. In these three well-separated triplets of methyl protons in 1 : 2 : 1 ratio, for example, the low-field signal is assigned to the methyl in A-1 and that of high field is A-2 which are

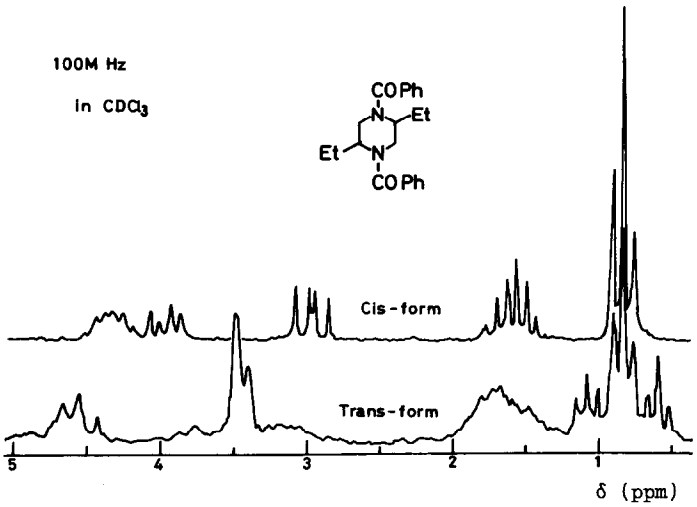


Fig. 1. ^1H-NMR spectra of 1,4-dibenzoyl-*cis*- and *trans*-2,5-diethylpiperazines (Ib) at room temperature, except for the signal of aromatic protons.

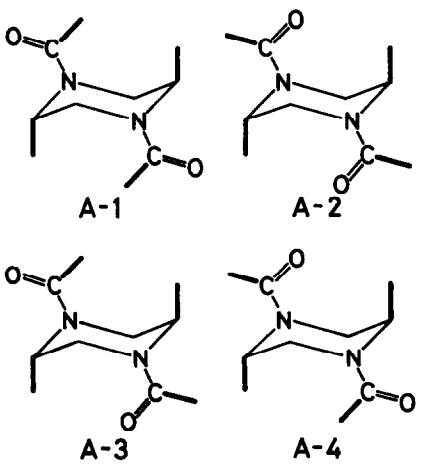


Fig. 2. Possible rotamers of 1,4-dibenzoyl-*trans*-2,5-dialkyl-piperazines

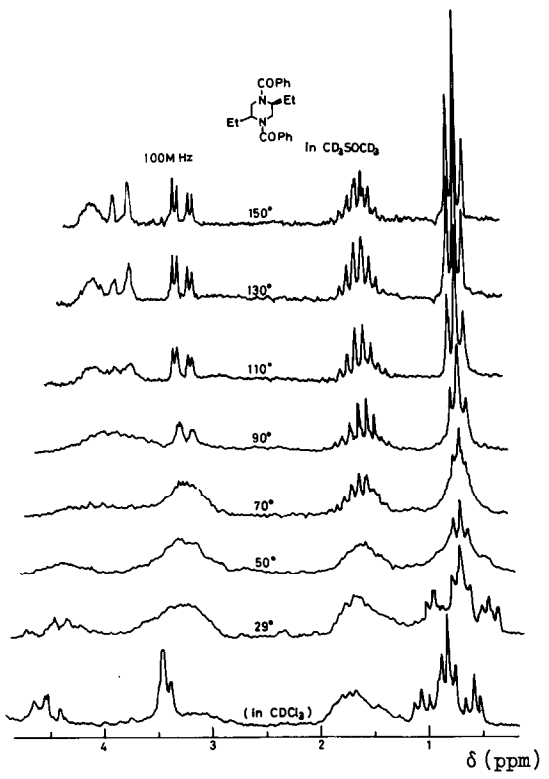


Fig. 3. The 100 MHz ^{1}H-NMR spectra of 1,4-dibenzoyl-*trans*-2,5-diethylpiperazine (*trans*-Ib) in DMSO-d_6 as a function of temperature, except for signals of aromatic protons.

subjected to a deshielding or shielding effect of the carbonyl group or phenyl ring, respectively. The both methyl protons in A-3 and A-4 correspond to the triplet at 0.9 ppm. This spectral feature clearly shows that the molecule exists as a nearly equal amount of mixture of four axial alkyl rotamers. As temperature is raised, the spectrum broadens, coalesces, and emerges as one set of resonances, which shows AMX type pattern for the ring protons (Fig. 3). At a low-temperature, the methyl and methylene carbons in the ^{13}C-NMR spectrum indicated consisting of two and three lines, respectively. No further appreciable changes were observed down to -21° in both ^{1}H- and ^{13}C-NMR spectra.

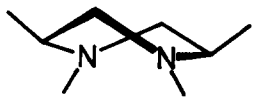


Fig. 4. Conformation of twist-boat piperazine ring.

If the above conclusion applies to the case of *cis*-isomer, there is no possibility to take the chair form, and the molecule is forced into non-chair conformation by the strain between the amide group and the vicinal equatorial alkyl group. From above consideration, the result seems to be best rationalized by the presence of thermodynamically stable twist-boat form of *cis*-I (Fig. 4). On the basis of vicinal coupling constants ($^3J_{HH}$ = 7.0 Hz) in the ring protons, we assumed that the torsion angle (ϕ_1) of N-C-C-N in the ring was nearly 40°, and designed several models of the TB form and estimated the minimum conformational energy.[6]

The result is confirmed by X-ray diffraction analysis of the single crystals of racemic *cis*-Ia. The crystal is monoclinic, a = 11.220, b = 14.571, c = 10.668 Å, β = 99.38°, Z = 4, D_x = 1.24, space group $P2_1/a$, and stereoscopic view of the molecule with (R)-configuration is in Fig. 5.

The structure was solved by a direct phasing method and all hydrogen atoms were deduced from successive difference Fourier syntheses. The structure was

refined by the block diagonal least squares method. The final R index was 5.6%. The bond lengths and angles in the pairs were equal within the experimental errors.

In agreement with the NMR study, the piperazine ring takes TB form in which ϕ_1 is nearly -40° for (R)-molecule in the racemic crystal and the methylenes locate at the bows. The important torsion angles, average bond angles and the bond distances are shown in Fig. 6. The amide group is almost planer and the lengths of C-N bond and carbonyl-phenyl bond are 1.35 and 1.50 Å, respectively. These mean that the carbonyl group conjugates strongly with the ring nitrogen but does not with phenyl ring, and the above-mentioned strain decreases through the rotation about the latter C-C single bonds. The orientations of the phenyl ring plane with respect to the amide bond plane are 56.8° and -51.8°, respectively. Although the conformation in the crystal lacks the two fold symmetry, the conformation in solution exhibits C_2 symmetry on the NMR time scale.

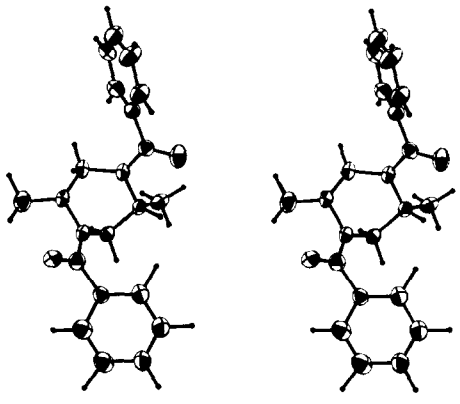


Fig. 5. Stereoscopic view of (R)-1,4-dibenzoyl-*cis*-2,5-dimethylpiperazine in the racemic crystal.

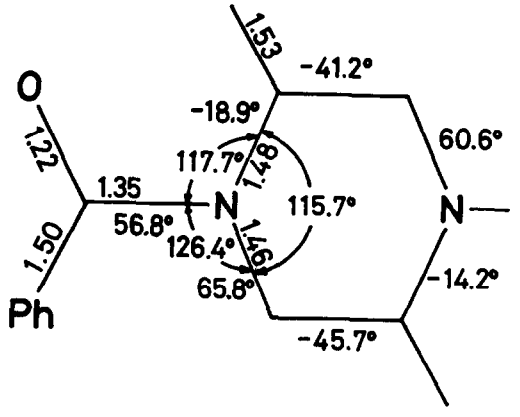


Fig. 6. Important torsion angles, bond angles, and bond lengths (Å) of (R)-1,4-dibenzoyl-*cis*-2,5-dimethylpiperazine in the racemic crystal.

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