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STEREOCHEMISTRY OF N-METHYLBENZANILIDE AND BENZANILIDE

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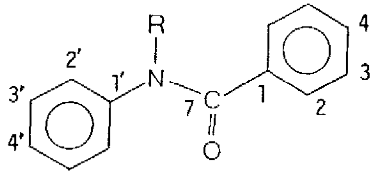
Abstract: The structure of N-methylbenzanilide was elucidated by X-ray analysis and examination of ^{1}H- and ^{13}C-nmr spectra. The stereochemistry of the amide bond was proved to be cis in the crystal and in solution, whereas that of benzanilide is trans.

The amide moiety is one of the most important structural fragments found in biologically active organic compounds. Studies on the stereochemistry of amide bonds are important not only in pure chemistry but also in biological or medicinal chemistry. Since the consideration of amide structure by Pauling in 1948,[1] a number of experimental and theoretical studies on the cis-trans stereochemistry of amide bond have been made.[2] The stereochemistry of the amide bond can be a determinant of the biological activity in amide compounds,[3] a critical example being seen in a series of synthetic retinoids:[4] N-methylation of aromatic anilide derivatives with potent retinoidal activity abolished the potency, due to the structural change of the amide stereochemistry from trans to cis. This paper shows that N-methylbenzanilide exists in cis conformation in solution as well as in the crystal, whereas benzanilide has trans conformation in the crystal.[5]



$R=CH_3$ N-methylbenzanilide (1)
R=H benzanilide (2)

An X-ray structure analysis was performed on a crystal of N-methylbenzanilide, obtained by recrystallization from n-hexane solution, mp. 56.5-57.5°. The crystal belongs to an orthorhombic space group Pbca, with eight molecules in a unit cell of a=12.588, b=12.309 and c=14.654 Å. Reflection data were collected on a Philips PW1100 four-circle diffractometer using CuKα radiation monochromated by a graphite plate. A total of 1835 non-zero, independent reflections were measured by a θ-2θ scanning method at a speed of 4°/min in the range of $3<\theta<78^\circ$. The corrections for Lorentz and polarization factors were applied in a conventional way, but no correction was made for absorption. The structure was solved by the direct method using the MULTAN80 program[6]. The structure was refined by block-diagonal least-squares calculations assuming anisotropic thermal motions for non-hydrogen atoms and isotropic ones for hydrogen atoms. The final R-factor was 0.075. The molecular structure of N-methylbenzanilide (1) is shown in Figure 1, together with that of benzanilide (2) drawn by the PLUTO program[7]. A clear difference is seen between the two molecules, mainly due to the amide conformation. Bond lengths and angles, and torsion angles related to the amide bond are shown in Figure 2. The torsion angle of the amide group (C_1'-N-C_7-C_1) was 13.5°. Partial double bond character of the amide bond, as in other nonmethylated amide bonds, is confirmed by the bond length of N-C_7, 1.355 Å, as well as by the sp^2 bond angles around the nitrogen atoms and the coplanarity of the amide atoms. It is unlikely that the cis amide structure is caused by the crystal packing forces, because we have already found three examples of cis amide structure for the N-methylated anilides, whose corresponding free amides took trans amide structures. Both the anilide and benzoyl moieties deviate from planar conjugative form, as indicated by the large torsion angles of C_2'-C_1'-N-C_7 (60.0°) and N-C_7-C_1-C_2 (47.9°).

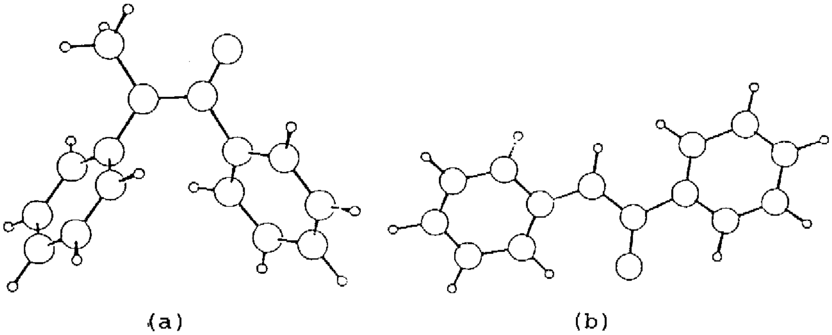


Figure 1. Computer-generated drawings of
(a) N-methylbenzanilide and
(b) benzanilide molecules.

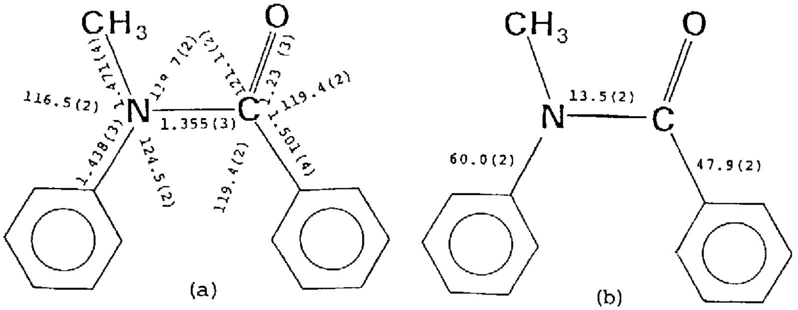


Figure 2. (a) Bond lengths (Å) and angles (°), (b) torsion angles (°) related to the amide bond in N-methylbenzanilide. Standard deviations are given in parentheses.

The ^1H-nmr spectra of N-methylbenzanilide (1) and benzanilide (2) in $CDCl_3$ are shown in Figure 3. The spectra are essentially the same in methanol and DMSO. The signals were assigned on the basis of decoupling experiments and deuterium substitution of benzene hydrogens. The protons of both benzene rings of N-methylbenzanilide showed significant shifts to higher field. This chemical shift difference seems to be mainly due to the mutual ring current anisotropic effects of the of benzene rings. Calculation of the shielding effect of the ring current anisotropy on several probable models using the Johnson-Bovey

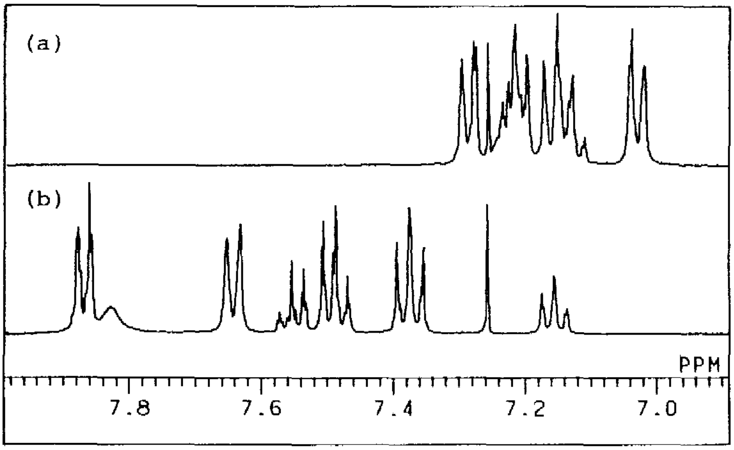


Figure 3. ^{1}H-nmr spectra in $CDCl_3$.
(a) N-methylbenzanilide
(b) benzanilide

equation[8] gave a good agreement with the observed values for an energetically stable structure which is close to the crystal structure, as shown in Table 1. This strongly indicates that the N-methylbenzanilide molecule adopts a folded <u>cis</u>-structure in solution, too, with the two benzene rings partially facing each other.

Table 1. ^{1}H-nmr chemical shifts (ppm) of N-methylbenzanilide (1) and benzanilide (2) in $CDCl_3$, and comparison of observed and calculated chemical shift differences between them.
Δobs: difference of observed chemical shifts
Δcal: difference of calculated shielding effects (ppm)

	H_2	H_3	H_4	H_2'	H_3'	H_4'
1	7.29	7.16	7.23	7.04	7.22	7.12
2	7.88	7.49	7.56	7.64	7.38	7.16
Δobs	-0.59	-0.33	-0.33	-0.60	-0.16	-0.04
Δcal	-0.66	-0.15	-0.10	-0.56	-0.20	-0.10

*The structure used for calculation:
$C_2'-C_1'-N-C_7=45.0^\circ$; $C_1'-N-C_7-C_1=0.0^\circ$;
$N-C_7-C_1-C_2=45.0^\circ$

Similarity of stereochemistries in the crystal and in solution was further confirmed by comparing the ^{13}C-nmr spectra of crystals with that of a solution, as shown in Figure 4. Although the correct assignment of the spectra in the crystalline state is difficult because of the line broadening and stereochemical non-equivalency of carbon atoms which are equivalent in

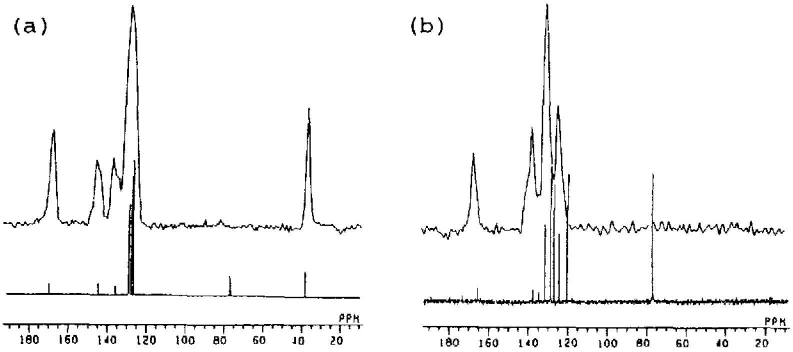


Figure 4. ^{13}C-nmr spectra in solid state (upper) and in $CDCl_3$ (lower).
(a) N-methylbenzanilide
(b) benzanilide

solution, the two spectra showed reasonably good correspondence with each other. It is deduced that the amide stereochemistries in the crystal are well maintained in solution for both compounds.

Furthermore, in order to confirm that *cis* predominance in N-methylanilide is not fortuitous, but intrinsically preferred, *ab initio* molecular orbital calculations were performed using the Gaussian program.[9] The structures for the crystallographically unobservable isomers were built by computer molecular modelling on the basis of energetic considerations. It was found that the *cis* conformation is more stable than the *trans* by 3.12 kcal/mol in N-methylbenzanilide using the STO-3G basis set, whereas the *trans* conformation is more stable than the *cis* by 5.90 kcal/mol in benzanilide.

Thus, the amide stereochemistry of N-methylbenzanilide should be *cis* not only in the crystal but also in solution and as an isolated molecule in vacuo, whereas that of benzanilide is *trans* in all states. This conclusion is in good agreement with the results obtained for three retinoidal-active benzanilide derivatives. The results seems to provide an important concept for understanding aromatic amide stereochemistry, and could give a basis for designing molecular structures in medicinal chemistry. This result is also very helpful for understanding the unusual fluorescence and phosphorescence properties of benzanilides[10] and N-methylbenzanilide[11]. The long wave length fluorescence could be caused by twisting of the excited state, exciplex emission or other factors. In any case, the Frank-Condon excited state structures of N-methylbenzanilide and benzanilide must be very close to the *cis* and *trans* structures, respectively, contrary to those adopted by Kasha et al.[10,11] Without a correct understanding of the ground state structures, we cannot hope to interpret the electronic spectra of benzanilides.

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