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THE STABLE CONFORMATION OF N-METHYLACETANILIDE

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The conformation of N-methylacetanilide both in solution and in the solid itself has been studied in connection with work on some related X-ray contrasting agents going on in our laboratory. The conformation found in the solid has also been found to dominate in solution. The conformational behavior in solution (pyridine) is based on the interpretation of the high resolution proton magnetic resonance spectrum, while the molecular conformation found in the solid has been obtained from three-dimensional X-ray diffraction data through the determination of the crystal structure.

The problem connected to the conformation of N-methylacetanilide is two-fold. 1. As is well known, the amido-group is planar[1], or nearly so[2], giving rise to two isomers (cis, trans) with a stability in solution which usually is high enough so that each isomer gives its own distinct NMR-spectrum[3], but the stability is in general too low to separate the two isomers chemically. 2. The planes of the amido-group and the benzene ring can make an arbitrary angle with each other. The equilibrium value of this angle will be a compromise

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[1] L. Pauling. The Nature of the Chemical Bond, Cornell University Press, Ithaca, New York 1960, p. 281

[2] C.C. Costain and J.M. Dowling, J. Chem. Phys. 32 (1960) 158

[3] M.T. Rogers and J.C. Woodbrey, J. Phys. Chem. 66 (1962) 540

between two main effects: π -electron communication and steric interactions between the benzene ring and the acetamido-group. As the contributions to the total energy of the molecule from these two effects are phase shifted 90°, the actual conformation observed tells us which one of the two is the most important in determining the shape of the molecule.

Solution. In the X-ray contrasting agents we have studied the acetamido-group in the molecule is surrounded by two iodine atoms in the ortho positions[4]. These large atoms force the acetamido-group to be orthogonal to the benzene ring. Even in this orthogonal position the distances between atoms in the acetamido-group and the iodine atoms are somewhat smaller than the van der Waals' distances. Furthermore, the iodine atoms stabilize in some, still not clearly understood way, the cis and trans isomers, so that these can be chemically separated and isolated. Due to the different orientation of the methyl groups in the two isomers relative to groups in the molecule which are magnetically anisotropic (the benzene ring and the carbonyl group), it is possible, univocally, to determine the actual conformation of each isomer from its NMR-spectrum. In the investigation of these X-ray contrasting agents it was found that the unmethylated acetamido-groups were preferentially in the conformation with the carbonyl oxygen cis to the benzene ring, this conformation has been named endo-(I)[5]. When the acetamido-group is methylated, however, the other conformation, named exo-(II)[5], is found to be the most stable. In solution both N-methylacetamido-isomers can be detected with approximately 20 parts exo- to 1 part endo-.

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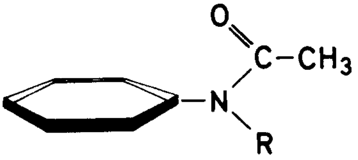
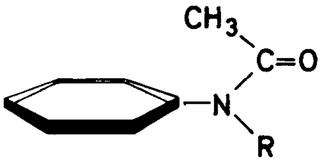
4. B. Pedersen, H. Holtermann, and J. Haavaldsen, to be published in Acta Chem. Scand.
5. H. Holtermann, L.G. Haugen, J. Haavaldsen, V. Nordal, K. Wille, and K. Tjønneland, Resuméer av sektionsforedrag 11. Nordiske Kjemikermøte, Åbo 1962, p. 34

This behavior has been observed both in pyridine and in water solution.



I

endo-



II

exo-

As N-methylacetanilide dissolves readily only in pyridine, the present discussion will be limited to this solvent. In the NMR-spectra of a series of X-ray contrasting agents containing one or two N-methylacetamido groups, the methyl-peaks were found at the positions given in Table I. These positions were found to vary only slightly with substitution in the remaining positions, in accordance with expectation from the assumed orthogonal conformation. When the acetamido-group is orthogonal to the benzene ring the electron distribution in the acetamido-group will be rather insensitive to substitution in the benzene ring except for inductive effects.

TABLE I

Methyl-peak Positions in the NMR-spectrum of Compounds[4] containing a N-methylacetamido-group, measured relative to a TMS-peak in c/sec at 60 mc/sec*

	exo	endo
CH_3-C-O	113	134
CH_3-N	195	193

* The spectra were recorded on a Varian asc. DP-60 NMR-spectrometer.

The NMR-spectrum of N-methylacetanilide in pyridine solution contains two large peaks at 112 c/sec and 195 c/sec, and two much smaller peaks at 126 c/sec and 177 c/sec. From the relative intensities of these two peak sets we estimate that only 0.5 % of the molecules are in the conformation responsible for the small peaks. The NMR-spectrum therefore strongly suggests that 99.5 % of the N-methylacetanilide molecules in pyridine solution are in the conformation with the N-methylacetamido group in the exo-configuration (II), and with the plane of this group orthogonal to the benzene ring. The other isomer does not give methyl peaks at the expected positions from the data in Table I. This indicates that the endo-N-methylacetamido group is not orthogonal to the benzene ring, as we will discuss more fully at the end of this note.

The exo-conformation of the N-methylacetamido group in N-methylacetanilide has also been inferred by Thompson and Hallberg[6] from measurements of the electric dipole moment in dioxane solution. The NMR-spectrum of N-methylacetanilide in benzene solution has been studied earlier by Gutowsky and Holm[7]. They detected only one isomer and were unable to decide whether this was the exo- or endo-isomer or a rotamer.

Solid. N-methylacetanilide crystallizes with orthorhombic symmetry, space group *Pnma* or $Pn2_1a$, as determined from systematic absences of X-ray reflections. The cell dimensions are: a = 17.151 Å, b = 7.328 Å, c = 6.779 Å. The main difference between the two space groups is a mirror plane normal to the b-axis in *Pnma* which is reduced to a two-fold screw axis in $Pn2_1a$. The three-dimensional Patterson map indicated

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6. H.B. Thompson and K.M. Hallberg, J. Phys. Chem. 67 (1963) 24[illegible]6
7. H.S. Gutowsky and C.H. Holm, J. Chem. Phys. 25 (1956) 122[illegible]

that the correct space group is Pnma, and the structure has been satisfactorily refined by least-squares and Fourier methods in this space group to a final reliability index, R, equal to 8.4 % (unobserved reflections not included). As there are four N-methylacetanilide molecules in the unit cell, the space group symmetry requires that the molecule has a mirror plane. The only reasonable molecular configuration is then the one with the N-methylacetamido group in the mirror plane, and the benzene ring oriented normal to the mirror plane. The structure was solved by interpretation of the Patterson map. The final composite three-dimensional Fourier map is shown in Fig. 1.

The details of the structure determination will be published later, together with a full discussion of the different aspects of this structure. We will only point out here that the conformation shown in Fig. 1 is the same as inferred being the stable in solution. This conclusion follows both from the relative intensity of the peaks in Fig. 1 and from the interatomic distances.

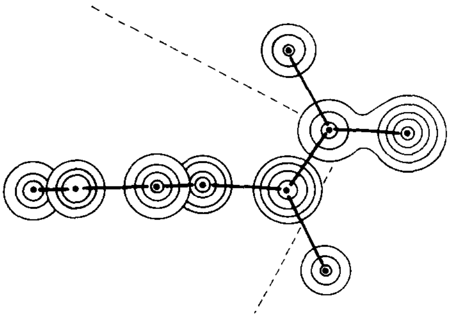

FIG 1

Composite Fourier map of N-methylacetanilide viewed normal to the mirror plane

The conformation shown in Fig. 1 should be compared to the conformation found for acetanilide by Brown and Corbridge[8] several years ago, also from a three-dimensional X-ray diffraction study. In acetanilide the acetamido group is in the endo-configuration (I), and the plane of the acetamido group and the benzene ring is making an angle of 38°. Hence, the stable conformation of N-methylacetanilide is completely different from the conformation of acetanilide. It is difficult to understand why the methylation of acetanilide should completely reverse the relative stability of the exo- and the endo-isomer, and no attempt at an explanation will be given here. It is easier to understand that the angle between the acetamido group and the benzene ring is larger when the acetamido group is in the exo-configuration than in the endo-configuration. The van der Waals' radius of a carbonyl oxygen is about 1.5 Å, while the van der Waals' radius of a methyl group is 2.0 Å. Furthermore, the methyl group is closer to the benzene ring as the C-C distance is 0.3 Å longer than the C-O distance. The increase in the angle from 38° to 90° must therefore be ascribed to the larger van der Waals' interaction between the benzene ring and the exo-acetamido group than between the benzene ring and the endo-acetamido group. Brown and Corbridge[8] pointed out that the carbon atom in the benzene ring closest to the carbonyl oxygen is forced a little out of the ring plane due to the van der Waals' interaction between these two atoms. Similarely,in N-methylacetanilide the bond between the benzene ring and the nitrogen atom is bent about 6°, revealing the existence of strain in the molecule induced by the van der Waals' interaction between the methyl group and the benzene ring.

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[8] C.J. Brown and D.E.C. Corbridge, Acta Cryst. 7 (1954) 711

We can now better understand why the positions of the two small peaks in the NMR-spectrum of N-methylacetanilide deviated from the predicted positions. The predicted positions were based on data collected from molecules with iodine atoms in the ortho positions, which forces the acetamido group to be normal to the plane of the benzene ring. But in endo-N-methylacetanilide the conformation probably is as observed for acetanilide, and hence, the observed positions will be different from the predicted ones both because of mesomeric effects, and because of a different orientation of the methyl groups relative to the benzene ring. The positions of the peaks in the spectrum of acetanilide dissolved in pyridine are also shifted away from the corresponding peaks from orthogonal unmethylated endo- and exo-acetamido groups. The former spectrum contains a strong peak at 131 c/sec and a small (0.1 %) at 105 c/sec, compared to peaks at 141 c/sec and 116 c/sec in the latter spectra.