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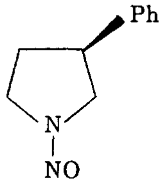
BISIGNATE n-π^* CIRCULAR DICHROISM OF N-NITROSOPYRROLIDINES

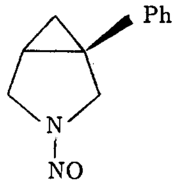
T. Połoński* and M. J. Milewska
Department of Organic Chemistry, Technical University,
80-952 Gdańsk, Poland

Summary - The bisignate Cotton effect of substituted N-nitrosopyrrolidines results from conformational changes within the five-membered ring. The CD sign can be predicted by our "lowered symmetry" sector rule.

Substantial research efforts have been devoted toward the understanding of the chiroptical properties of the N-nitrosamine chromophore. N-Nitrosopyrrolines were among the most used test systems for existing sector rules correlating the Cotton effect (CE) sign with molecular geometry.[1-4] Many of these compounds show bisignate CD curves within the region of n-π^* transition. Usually such a two-branched curve is an indication of a conformational equilibrium between conformers contributing with opposite signs to the CE.[5] Although the Z-E isomerism of N-nitrosopyrrolidines has been extensively studied, the five-membered ring conformation and its influence on the CD has not received too much attention.[6] Very often it was assumed to be planar and even rigid.[2] Recently Ringdahl,[4] basing on this assumption, stated that the CE sign of (S)-N-nitroso-2-methylpyrrolidine is determined by the asymmetrically placed methyl group and questioned validity of our "lowered symmetry"[7] sector rule for N-nitrosopyrrolidines. Moreover, he attributed bisignate CD of these compounds to the vibronic coupling.[8] According to him the "allowed" long-wavelength component of the CD reflects molecular chirality and the other one - "forbidden" is due to molecular vibrations. However, both theoretical and experimental studies of a variety of substituted pyrrolidines, like N-acyl-proline derivatives reveal the five-membered ring to be very far from planarity, significantly twisted and flexible.[9] Strong substituent, solvent,[1,4] and temperature dependence[10] of the CD of the title compounds points, in our opinion to conformational changes of the ring as a source of bisignate CEs. The contribution from the skewed ring may outweigh the effects due to substituents and then govern the CE sign similarly as in the case of substituted cyclopentanones.[11]



(1)



(2)

In order to verify this hypothesis we prepared the structurally related N-nitroso compounds: (S)-3-phenylpyrrolidine (**1**) and (1R)-3-azabicyclo[3.1.0]hexane (**2**)[12] and compared their CD spectra. Next we performed molecular mechanics (MM2)[13] calculations for these compounds. The five-membered ring being a part of the 3-azabicyclo[3.1.0]hexane skeleton in (**2**) has very limited conformational flexibility, especially ring twisting is impossible. Actually compound (**2**) exists in a boat-like sofa conformation (Fig. 1) and its geometry is very similar to that of bicyclo[3.1.0]hexane, its 3-oxa- and 3-oxo-analogues.[14]

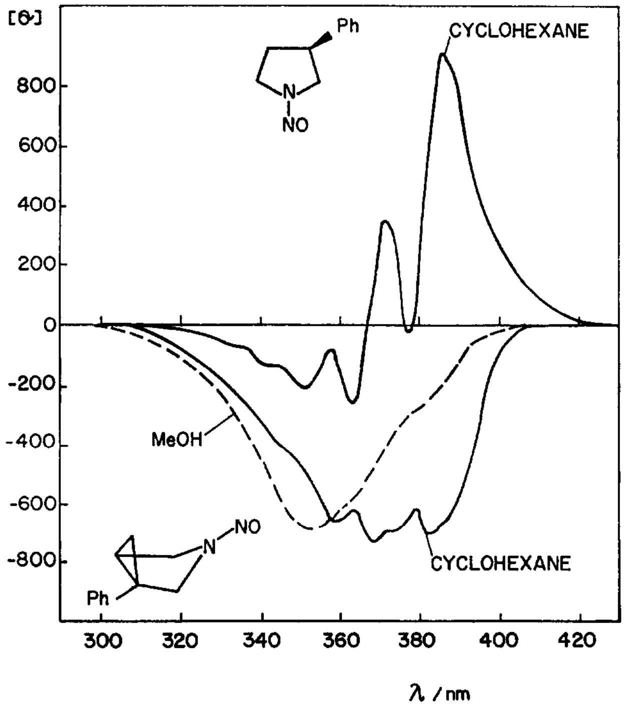


Fig. 1. CD spectra of compounds (**1**) and (**2**)

On the contrary the pyrrolidine ring in (**1**), according to MM2 calculations, adopts two half-chair (twisted) conformations separated in energy by 0.8 kcal/mol; one with the phenyl group in pseudo-equatorial position and the second with the substituent in pseudo-axial position. The n-π^* CE of (**2**) (Fig. 1) is monosignate and almost solvent independent, which contrasts with the bisignate and strongly solvent dependent CE of (**1**) (compare Fig. 5 in ref. 4). The CD sign of (**1**) is determined by the ring chirality (chiral second sphere)[15] and according to our "lowered symmetry" sector rule[7] the positive CE corresponds to the half-chair pseudo-equatorial (e) conformer and the negative one to the pseudoaxial (a) conformer (Fig. 2). The phenyl group lying in the negative sector (close to the nodal plane) is responsible for the negative CE of (**2**). It is noteworthy that the rule predicts the same CE signs for both Z and E isomers of (**1**) and (**2**), which are almost equally populated according to the NMR spectra. Assuming that the chiral ring makes a stronger contribution to the CE than the substituent, which plays important role in deciding conformer populations, the CD sign of 2-substituted N-nitrosopyrrolidines may be explained by this rule as well.

In conclusion, the bisignate CD of N-nitrosopyrrolidines reflects the conformational equilibrium of the pyrrolidine ring and the CE sign can be easily predicted by our sector rule.

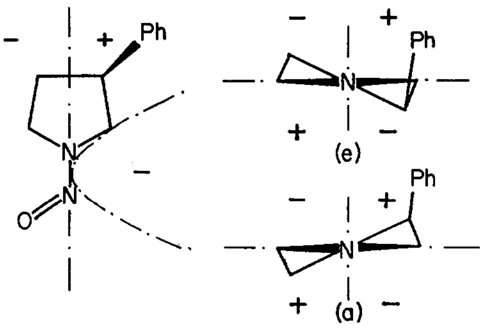


Fig. 2. The sector projections of skewed conformers of N-nitrosamine (**1**).

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