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CHIROPTICAL PROPERTIES OF NITROSAMINO ACIDS AND THEIR RELATIONSHIP TO THE NITROSAMINE SECTOR RULE

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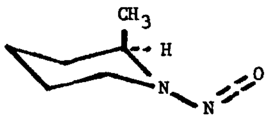
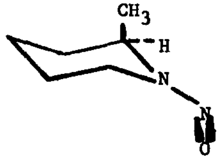
The Cotton effect associated with the weak u.v. band at 330-370 nm of the nitrosamino chromophore has been useful in stereochemical correlations[1] of chiral nitrosamines and hence of the derived amines. In order to permit assignments of absolute configuration to be made directly from the optical data for a single compound (i.e., without comparison to related compounds of known configuration), Snatzke, et al.[2], have proposed a sector rule for this chromophore based upon the nodal properties of the orbitals involved in the high wavelength n → π^* transition. This communication summarizes our CD results (Table) on a series of nitrosamino acids and presents our reasons for suggesting that the signs of the sectors must be reversed from the original assignments.

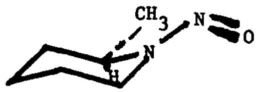
The discrepancy probably derives from the question of the conformation of nitrosopipecoline (1), which was the model compound used by Snatzke and coworkers[2] in empirically designating the sector signs. Little specific information was available at the time these assignments were made concerning the conformations of this kind of compound, and these workers made the reasonable assumption that the methyl group must be predominantly equatorial. More recently, Harris and Spragg[3] have concluded from the n.m.r. spectrum of 1 that its methyl group is primarily axial, as in 1a and 1b, and that it exists in CCl_4 solution 27% in configuration 1a, at least 37% in 1b and the remainder in 1c. Summing over all three conformations, one



1a



1b



1c

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might expect the C-4 and C-5 methylene groups of 1b, which lie in sector A' (Figure), to predominate in determining the sign of the Cotton effect. If so, the observed positive Cotton effect for R-nitrosopipecoline yields a + sign for A', which is opposite of that previously[2] assigned.

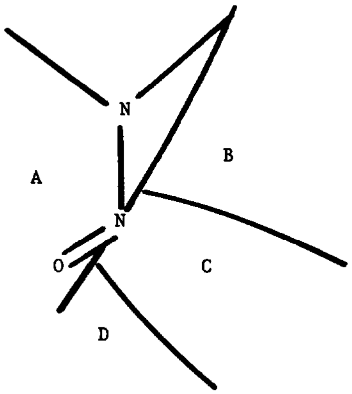
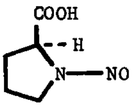


Figure. Sector rule for nitrosamine n → π* transition according to G. Snatzke, H. Ripperger, C. Horstmann and K. Schreiber, Tetrahedron 22, 3103 (1966). These authors have given sectors A, B, C and D (above the plane of the paper) signs +, -, + and -, respectively and sectors A', B', C' and D' (below the plane of the paper) opposite signs. The N-N=O atoms and α,α'-carbon atoms are in the plane of the paper.

This conclusion is far from unequivocal[4] and we have sought confirmation in model compounds of less questionable conformation. Proline derivatives, 2 and 3, are much better model compounds since they are nearly planar and are free from the conformational mobility of piperidine derivatives. Syn/anti ratios of these compounds, and others studied herein, have been determined by n.m.r. measurements[5] on freshly dissolved crystalline material at 0°. CD measurements were performed immediately after dissolving at 0° before the n.m.r. spectra indicated any isomerization had occurred. Thus CD results were obtained on the same syn/anti ratio as in the crystalline material.

Both 2 and 3 clearly have the carboxyl group in sector A' since the syn nitroso conformer (2a and 3a) predominates[5] in each compound. The positive Cotton effects observed for 2a[6] and 3a argue strongly for a reversal of the previously designated[2] signs.



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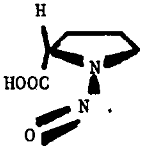
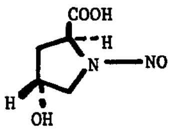
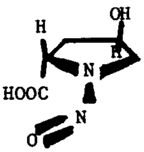


2a



3



3a

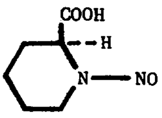
S-Nitroso-pipecolic acid (4), the n.m.r. spectrum[5] of which suggests that it exists in freshly prepared solutions with the carboxyl group axial and with the nitroso oxygen atom predominantly syn to the α-substituent, also exhibits a positive Cotton effect. As with 1, the conformer having predominant contribution in sector A' (similar to 1b) should determine the sign of the Cotton effect for compound 4. Thus the data for 4 also suggest[7] that the signs for sectors A, B, C and D should be reassigned as -, +, - and +, respectively. Accordingly sectors A', B', C' and D' should be given signs of +, -, + and -.

Table. Circular Dichroism of 2-S-Nitrosamino Acids

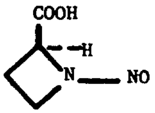
Compound	Syn/anti[a]	CD[b]
1-Nitroso-2-S-Proline (2)	80/20	$[\theta]_{342}+1800$
1-Nitroso-4-R-Hydroxy-2-S-Proline (3)	95/5	$[\theta]_{342}+3200$
1-Nitroso-2-S-Pipecolic Acid (4)	82/18	$[\theta]_{348}+5800$
1-Nitroso-2-S-Azetidine Carboxylic Acid (5)	10/90	$[\theta]_{333}-2800$

a - Syn/anti ratio in the crystalline material as determined by the method of Lijinsky, et al. (Ref. 5).

b - CD spectra were measured immediately after dissolving in water at 0°C.



4



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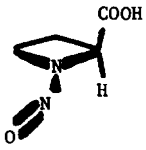

5a

1-Nitroso-2-S-azetidine carboxylic acid (5) exhibited a negative CD band at the n → π* transition. In contrast to nitrosamino acids 2, 3 and 4, the anti nitroso conformer (5a) predominated[5] in the crystalline form of 5. The negative Cotton effect of 5a is probably due to the carboxyl group being mainly in sector A rather than in sector B due to constraints imposed by the four-membered ring. Thus a knowledge of nitroso group conformation is essential when making stereochemical correlations, since an α-axial substituent may lie near the nodal plane between sectors A and B.

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1. B. Sjöberg in "Optical Rotatory Dispersion and Circular Dichroism in Organic Chemistry," G. Snatzke, Ed., Heyden and Son Ltd., London, 1967, p. 173.
2. G. Snatzke, H. Ripperger, C. Horstmann and K. Schreiber, Tetrahedron, **22**, 3103 (1966).
3. R. K. Harris and R. A. Spragg, J. Mol. Spectry., **23**, 158 (1967).
4. Since the n.m.r. results[3] were run in CCl_4 and the CD results[2] in dioxane the two measurements may not be compared quantitatively.
5. W. Lijinsky, L. Keefer and J. Loo, Tetrahedron, **26**, 5137 (1970).
6. Since highly polar solvents are known to exert strongly perturbing influences upon $n \rightarrow \pi^*$ transitions, an additional set of measurements was obtained in a non-polar solvent. In ether compound 2a gave $[\theta]_{366} + 2110$.
7. Regional symmetry rules owe their success to the fact that the idealized nodal topology of the chromophore is preserved when it is buried in a chiral environment. Groups with lone pairs and other functionality can interact electronically to significantly alter the nodal structure. Until nitrosamines having established conformation and alkyl perturbing groups are studied, the remote possibility exists that carboxyl groups give a rotatory contribution of opposite sign to that of alkyl groups.