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Z-E CONFORMATIONAL DEPENDENCE OF THE N-NITROSAMINE CIRCULAR DICHROISM. THE NEED OF REVISION OF THE NITROSAMINE SECTOR RULE

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The N-nitrosamine sector rule which correlates the stereochemistry of the N-nitrosamines to their Cotton effects was originally proposed in 1966 by Snatzke <u>et al.</u>[1] /1a and 1b/. Although the rule has been used for stereochemical assignments of secondary chiral amines its general applicability was questioned in 1971[2]. In 1972, Gaffield <u>et al.</u>[3], on the basis of CD spectra of N-nitrosoproline and N-nitrosopipecolic acid, and in 1976, Ringdahl and Dahlbom[4], on the basis of CD data of N-nitroso-2-methylpyrrolidine suggested that the signs of sectors should be reversed. In the meantime a paper in support of the original signs of sectors has also appeared[5].

In order to test the general validity of the nitrosamine sector rule and to obtain reliable information on chiroptical properties of N-nitrosoamino acids[6] we have separated N-nitroso-L-proline, I, into the conformationally pure Z /<u>syn</u>/ and E /<u>anti</u>/ isomers by column chromatography at low temperatures[7-9]. The other studied compound was monomethylamide of N-nitroso-L-proline, II, /Z-E equilibrium mixture, and mixture of conformers of known Z:E ratio displaced from equilibrium on the side of the Z form by crystallization[10-12]/. The molecule of our model compounds I and II in both Z and E conformations should be nearly planar and relatively free from ring conformational mobility, at least puckered conformations deviating from ring planarity should have no profound effect on chiroptical properties. Conformational purity of the studied compounds was checked by low temperature tlc[8-9], the ratio of Z-E isomers in mixtures by ^{1}H NMR spectroscopy[10-11].

The results of our studies are summarized in Table.

According to Snatzke <u>et al.</u> both Z and E isomers of I and II should display negative $n \longrightarrow \pi^*$ band[1], according to the reverse sign N-nitrosamine sector rule of Gaffield <u>et al.</u>[3], and Ringdahl and Dahlbom[4] the Cotton effects of the Z and E isomeric forms should be positive /1a and 1b/.

Table

Chiroptical properties of the Z and E isomers of N-nitroso-L-proline and its monomethylamide

Compound	Solvent	λ max. $n \rightarrow \pi^*$ [nm]	Molecular ellipticity [θ]			Equilibrium constant[a] $K = \frac{[E]}{[Z]}$
			E	Z	Equilibrium mixture	
N-nitroso-L-proline	acetone	345^Z	-1415^c	$+2040^b$	$+546^b$	0.76
	chloroform	346^E 344^Z	-1690^b	$+1952^b$	$+422^b$	0.72
	pyridine	348^Z	-1565^c	$+3265^b$	$+1190^b$	0.75
monomethylamide of N-nitroso-L-proline	water	327^{Eq}	-3300^d	$+4240^d$	$+1337^b$	0.62
	pyridine	348^{Eq}	-1080^d	$+4140^d$	$+1527^b$	1.0

Eq = equilibrium mixture; a/ determined by ^{1}H NMR spectroscopy;

b/ obtained directly from CD-spectra recorded with a Jasco J-20 automatic recording spectropolarimeter;

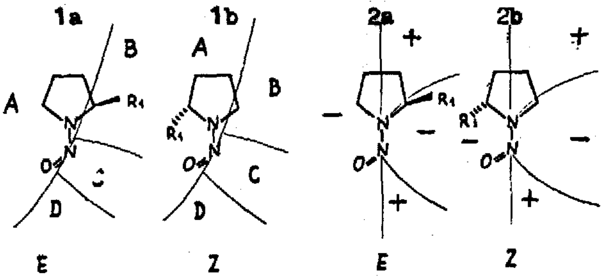
c/ calculated from the equilibrium constant K, and molecular ellipticity of equilibrium mixture and of the Z isomer

d/ calculated from molecular ellipticity of equilibrium mixture and the equilibrium K value, and molecular ellipticity of a mixture of the Z and E conformers of known E : Z ratio;

Our results support neither of these sector rules. The dichroic absorption bands associated with the $n \longrightarrow \pi^*$ transition of the N-nitrosamine group are of opposite signs, positive for the Z conformers and negative for the E isomers.

In our opinion the discussion about the signs of sectors is useless and one should be warned against too great reliance on CD measurements performed with mixtures of Z-E conformers even of constant[4] E : Z ratio. If the nodal properties of the N-nitrosamine chromophore are not altered significantly by perturbing influence of substituents in the Z and E conformation / the methyl[4], carboxyl[3] and N-methylcarboxamide groups in the α-position of the pyrrolidine ring/ the problem seems to be reduced to defining new vertical nodal surfaces separating sectors /1a, 1b, 2a and 2b/.

Recently Połoński and Prajer[13] proposed a new sector rule relating the optical activity of the lowest energy electronic transition of the N-nitrosamine chromophore to the spatial configuration of atoms and groups lying outside the chromophore /2a and 2b/. The CD characteristic of the Z and E isomers of N-nitroso-L-proline and its methylamide is in agreement with this new sector rule[14].



R_1 $-CONHCH_3$ or $-COOH$

Figs. 1a, 1b, 2a and 2b. Sector rules for the n $\longrightarrow \pi^*$ transition of the N-nitrosamine chromophore; A,B,C and D sectors above the plane of the paper; A',B',C' and D' sectors below the plane of the paper; 1a and 1b – Signs of sectors in the original Snatzke's rule[1] A +, B −, C +, D − and A' −, B' +, C' −, D' +; 1a and 1b – Signs of sectors according to Gaffield[3], and Ringdahl and Dahlbom[4] A −, B +, C −, D +, and A' +, B' −, C' +, D' −; 2a and 2b – New sector rule proposed by Połoński and Prajer[13]. Signs of sectors above the plane of the paper shown in drawings.

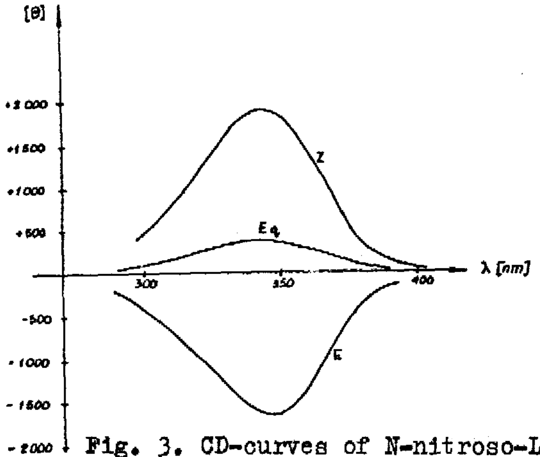


Fig. 3. CD-curves of N-nitroso-L-proline in $CHCl_3$ recorded with a Jasco J-20 automatic spectropolarimeter; Z and E – CD-curves recorded immediately after dissolution of the Z and E isomers; Eq – CD-curve of equilibrium mixture recorded several hrs after dissolution; Z-E conformer interconversions can be easily followed by scanning the CD-spectra.

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12. Compound II shows preference for crystallization in the Z conformation. The crystals are, however, conformationally unpure and contain usually a considerable proportion of the E isomer. On dissolution partial interconversion to the E isomer results till conformational equilibrium is established.
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14. Studies with N-nitroso-4-hydroxy-L-proline /2S,4R/ and its monomethylamide revealed also the positive and negative CD-bands for the Z and E isomers, respectively. The attempts to interpret the perturbing influence of the remote 4-hydroxy group on the basis of the Połoński's N-nitrosamine sector rule showed randomness. It seems that for the low symmetry N-nitrosamine chromofore the planar vertical nodal surface in the Połoński's rule / vertical straight line in Figs. 2a and 2b/ should deviate from planarity.