# Bisignate $n\rightarrow\pi^*$ Cotton Effects in the Circular Dichroism Spectra of 2- and 3-Substituted *N*-Nitrosopyrrolidines

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The $^1$H NMR, electronic absorption and circular dichroism spectra of several 2- and 3-substituted *N*-nitrosopyrrolidines have been studied in solvents of varying polarity. The 2-substituted *N*-nitrosopyrrolidines prefer the *E* isomer in solution whereas the 3-substituted derivatives exist as roughly equimolar mixtures of *E* and *Z* isomers. The circular dichroism spectra show pronounced fine structure and cross the zero-line within the region of the $n\rightarrow\pi^*$ transition of the nitrosamine chromophore. The origin of the bisignate CD curves is ascribed to *E*–*Z* isomerism or to vibrational–electronic coupling. In the latter case, the long-wavelength branches of the bisignate CD curves are associated with the 'allowed' character rotatory strength which was analyzed using a published [*Tetrahedron 32* (1976) 847] sector rule for the $n\rightarrow\pi^*$ transition of the nitrosamine chromophore. The general validity of this sector rule is questioned.

The nitroso group can be easily introduced into chiral secondary amines. The sign of the Cotton effect (CE) associated with the weak UV band near 370 nm ($n\rightarrow\pi^*$) of the resulting nitrosamines has been used in stereochemical correlations among chiral secondary amines (for a review, see Ref. 1). Snatzke and coworkers first proposed a sector rule relating the sign of the 370 nm CE to the configuration of the nitrosamine.[2] Difficulties in the application of this sector rule soon became apparent.[3–5] Careful conformational analysis of 2-methyl-*N*-nitrosopiperidine,[6] the model compound used by Snatzke *et al.*[2] in the designation of the sector signs, as well as circular dichroism (CD) measurements on more rigid nitrosamines suggested that the sector signs should be reversed.[4,5]

Polonski and Prajer[7] proposed a different sector rule for the nitrosamine chromophore based upon the concept of symmetry lowering.[8,9] This sector rule appeared to predict correctly the sign of the $n\rightarrow\pi^*$ CEs of chiral *N*-nitrosopyrrolidines and *N*-nitrosopiperidines.[7,10] Because of their propensity to equilibrate at room temperature,[11] *Z* and *E* isomers of *N*-nitrosamines have generally not been isolated and CD measurements have been performed on equilibrium mixtures of isomers. Despite the presence of two distinct molecular species in such mixtures, there is normally only one band apparent in the $n\rightarrow\pi^*$ region of their CD spectra. When separated at low temperatures, the *E* and *Z* isomers of *N*-nitroso-L-proline displayed CEs of opposite sign.[10] On the other hand, (*S*)-*N*-nitrosoprolinole which was claimed to exist as a fixed *E* isomer because of intramolecular hydrogen bonding, displayed a negative CE centered around 340 nm along with a positive CE at longer wavelength. The sign of the short-wavelength CE agreed with that predicted by the lowered-symmetry sector rule and the CE was ascribed to the usual $n\rightarrow\pi^*$ transition of the nitrosamine chromophore. The long-wavelength CE was tentatively assigned to an $n\rightarrow\pi^*$ transition from an excited vibrational ground state.[7] More recent studies by Gaffield *et al.*,[12] however, showed that in dilute solutions of (*S*)-*N*-nitrosoprolinole, the *Z* isomer was present in appreciable amounts (about 15 %). Thus the possibility that the bisignate CD curve for (*S*)-*N*-nitrosoprolinole was caused by *Z*–*E* isomerism cannot be excluded. With the aim of exploring further the influence of conformational isomerism and vibrational effects on the chiroptical properties of *N*-nitrosamines, the CD spectra of some chiral *N*-nitrosopyrrolidines (**1–6**; Scheme 1, Table 1) have been recorded and analyzed.

## Results

*Synthesis of* N-*nitrosamines* **1–6**. The *N*-nitroso derivatives of 2-methylpyrrolidine [(*S*)-**1**], 2-phenylpyrrolidine [(*R*)-**2**], 3-methylpyrrolidine [(*S*)-**3**] and 3-phenylpyrrolidine [(*R*)-**4**] were prepared by nitrosation[2] of the respective amines the absolute configurations of which are known.[13–16] (+)-*N*-Nitroso-3-pyrrolidinecarboxylic acid methyl ester [(*S*)-**5**] and (−)-*N*-nitroso-3-methoxymethylpyrrolidine [(*S*)-**6**] were synthesized from (−)-3-hydroxymethylpyrrolidine obtained by debenzylation of (−)-*N*-benzyl-3-hydroxymethylpyrrolidine,[17] the absolute configuration of which is known to be *S* from chemical correlation to (+)-*N*-benzyl-3-methylpyrrolidine[17] and to (+)-methylsuccinic acid.[14,18]

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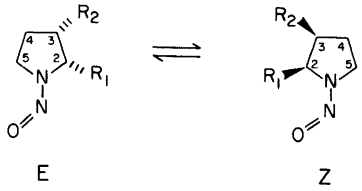
*Table 1.* Electronic absorption and circular dichroism spectra of *N*-nitrosamines.

| Compound | UV; λ/nm (ε) | | CD; λ/nm ([θ]) | | | |
|---|---|---|---|---|---|---|
| | Methanol | Hexane | Methanol | Acetonitrile | Dioxane | Hexane |
| (*S*)-**1** | 348 (91) | 385 (101)<br>372 (123)<br>360 (93) | 354 (−1,800) | 364 (−2,030) | 378 (−2,590)<br>367 (−2,720) | 387 (−2,450)<br>373 (−2,550)<br>362 (−1,770)$^{sh}$ |
| (*R*)-**2** | 355 (88) | 388 (100)<br>374 (122)<br>363 (94)$^{sh}$<br>~350 (50)$^{sh}$ | 389 (−360)<br>374 (−270)<br>342 (+1,120) | 387 (−780)<br>374 (+585)$^{sh}$<br>360 (+1,405)<br>348 (+1,230)$^{sh}$ | 390 (−1,000)<br>378 (+940)<br>363 (+1,810)<br>352 (+1,470) | 398 (−925)<br>386 (+1,775)<br>372 (+2,600)<br>359 (+1,900)<br>347 (+1,075)$^{sh}$ |
| (*S*)-**3** | 348 (99) | 384 (105)<br>370 (131)<br>359 (100)<br>~347 (50)$^{sh}$ | 381 (−140)<br>368 (−115)<br>339 (+378) | 379 (−280)<br>364 (+235)$^{sh}$<br>353 (+385) | 382 (−460)<br>372 (+50)<br>367 (−67)<br>358 (+190)<br>347 (+150) | 386 (−830)<br>372 (−590)<br>358 (−230)<br>347 (−70)<br>336 (−25) |
| (*R*)-**4** | 347 (103) | 385 (107)<br>371 (133)<br>360 (104)<br>~348 (60)$^{sh}$ | 381 (−200)<br>369 (−120)<br>342 (+730) | 380 (−400)<br>364 (+545)$^{sh}$<br>355 (+735) | 383 (−735)<br>372 (+235)<br>359 (+440)<br>349 (+305)$^{sh}$ | 387 (−970)<br>380 (+55)<br>372 (−500)<br>365 (+215)<br>359 (−70)<br>352 (+155)<br>342 (+85)<br>332 (+30) |
| (*S*)-**5** | 350 (103) | 385 (102)<br>371 (127)<br>360 (102)<br>~349 (65)$^{sh}$ | 348 (+290) | 360 (+384) | 383 (−211)<br>372 (+80)<br>359 (+116)<br>349 (+70) | 388 (−270)<br>373 (−180)<br>359 (−75)<br>348 (−30)<br>337 (−18) |
| (*S*)-**6** | 347 (95) | 384 (105)<br>370 (131)<br>359 (103)<br>~350 (60)$^{sh}$ | 381 (−70)<br>370 (−12)$^{sh}$<br>342 (+350) | 381 (−115)<br>363 (+320)$^{sh}$<br>354 (+395) | 382 (−260)<br>372 (+58)<br>366 (−11)<br>358 (+135)<br>348 (+90) | 386 (−480)<br>371 (−350)<br>358 (−150)<br>347 (−60)<br>337 (−23)<br>326 (−12) |

*$^1$H NMR studies of* E–Z *equilibria.* The nitrosamines **1–6** exist in solution as equilibrium mixtures of *E* and *Z* isomers as evident from their $^1$H NMR spectra (Scheme 1). It is well known that many *N*-nitrosamines give rise to separate resonance signals for α-protons located *cis* and *trans* to the nitrosamino group.[6,19–21] In general, protons positioned *trans* to the nitroso oxygen are more deshielded than those located *cis* to the oxygen. *trans* α-protons also show a preferential upfield shift in benzene solution.[19] In agreement with these observations, the *trans* α-methine (*E*-H2) and *trans* α-methylene protons (*Z*-H5) of (*S*)-**1** were centered around δ 4.45 and 4.33, respectively, whereas the corresponding *cis* protons (*Z*-H2 and *E*-H5) were located at δ 4.18 and 3.60, all in methanol-$d_4$ (see the Experimental). In benzene-$d_6$, the *trans* α-protons of (*S*)-**1** were shifted upfield (0.66–0.88 ppm) more than the *cis* α-protons (0.15–0.41 ppm). Integration over the α-methine, α-methy-




| Cmpd. | $R_1$ | $R_2$ |
|---|---|---|
| (*S*)-**1** | $CH_3$ | H |
| (*R*)-**2** | $C_6H_5$ | H |
| (*S*)-**3** | H | $CH_3$ |
| (*R*)-**4** | H | $C_6H_5$ |
| (*S*)-**5** | H | $COOCH_3$ |
| (*S*)-**6** | H | $CH_2OCH_3$ |

*Scheme 1.*

lene and methyl resonances belonging to the *E* and *Z* isomers of (*S*)-**1** gave an *E*–*Z* ratio of 87/13 in both methanol and benzene. In a similar manner, the intensity of the signals originating from the α-methylene protons of (*R*)-**2** was used to determine the *E*–*Z* ratio of its equilibrium mixtures which was found to be 76/24. The upfield shift in benzene was 0.55–0.74 ppm for the *Z*-H5 protons and 0.36–0.41 ppm for the *E*-H5 protons (Experimental).

Compound (*R*)-**4**, which, in contrast with the other nitrosamines studied, was crystalline, appeared to crystallize preferentially as one isomer. Thus its $^1$H NMR spectral properties and its sodium D line rotation changed with time after dissolution until equilibrium was reached. Analogous behaviour has been described for crystalline *N*-nitrosoamino acids.[11] $^1$H NMR peak assignments for *E* and *Z* isomers of the 3-substituted nitrosamines were not possible because of isomeric ratios close to unity. Thus (*S*)-**3** and (*R*)-**4** had ratios of 55/45 and 60/40, respectively, in methanol-$d_4$. Whether these ratios were *E*–*Z* or *Z*–*E* ratios could not be established. Likewise, compounds (*S*)-**5** and (*S*)-**6** existed in solution as roughly equimolar mixtures of *E* and *Z* isomers.

*Electronic absorption and circular dichroism spectra.* In methanol, all of the nitrosamines gave a single absorption peak for the $n\rightarrow\pi^*$ transition (Table 1). The absorption maximum of (*R*)-**2** was at longer wavelength (5–8 nm) than those of the other compounds studied. In hexane solution, the absorption bands of **1**–**6** showed clear fine structure (Fig. 1). The spectra in hexane, except that of (*R*)-**2**, were virtually identical in wavelength position and relative intensity of the vibrational peaks. The long-wavelength peak fell within 384–385 nm, the most intense peak within 370–372 nm and the short-wavelength peak within 359–360 nm. On the other hand, the spectrum of (*R*)-**2** in hexane was shifted 3–4 nm compared with the others.

The CD spectra of **1**–**6** were recorded in methanol, acetonitrile, dioxane and hexane (Table 1). The nitrosamines substituted in the 3-position of the pyrrolidine ring, i.e. (*S*)-**3**, (*R*)-**4**, (*S*)-**5** and (*S*)-**6**, displayed very similar spectra in all the solvents. For example, the CD curves of (*S*)-**3** in methanol and acetonitrile crossed the zero-line within the absorption band associated with the $n\rightarrow\pi^*$ transition (Fig. 2). In dioxane, and especially in hexane, the vibrational fine structure was sharper and the relative intensity of the long-wavelength negative band was enhanced (Fig. 3). The long-wavelength CD peak of (*S*)-**3** in hexane was located at longer wavelength than the long-wavelength peak in the UV absorption spectrum (Table 1). This observation was confirmed independently by simultaneous measurements (on a single instrument) of the CD and UV absorption of (*S*)-**3** in hexane. These measurements (which were performed by Professor H. P. J. M. Dekkers, Department of Theoretical Organic Chemistry, University of Leyden, The Netherlands) showed the CD peak to be located at 387.3 ± 0.5 nm whereas the UV peak was at 384.1 ± 0.5 nm. The CD spectra of (*S*)-**6** (Fig. 4) were

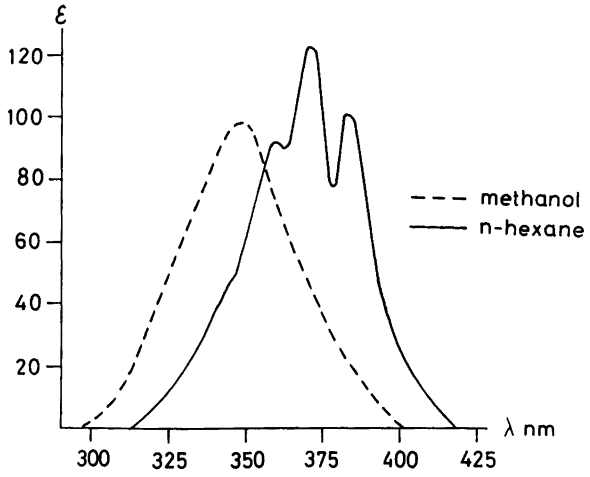



*Fig. 1.* Ultraviolet absorption spectra of (*S*)-2-methyl-*N*-nitrosopyrrolidine, (*S*)-**1**.

virtually identical in band shape and position with those of (*S*)-**3**. As observed with (*S*)-**3**, the CD spectrum of (*S*)-**6** in hexane was shifted to longer wavelength as compared with the UV spectrum. In the hexane spectra of (*S*)-**3** and (*S*)-**6**, as well as in the spectrum of (*S*)-**5**, no short-wavelength positive CD band was readily apparent. For the 3-phenylpyrrolidine derivative (*R*)-**4**, two differently signed components of the CD were clearly evident, also in hexane (Fig. 5). Again, the long-wavelength peak of (*R*)-**4** in hexane was at longer wavelength than the UV peak. Simultaneous recording of CD and UV peaks showed the peaks to be located at 387.5 ± 0.5 nm and 384.5 ± 0.5 nm, respectively.

The 2-methylpyrrolidine derivative (*S*)-**1** did not show bisignate CD curves in any of the solvents used. The CD spectrum in hexane (Fig. 6) was displaced towards longer

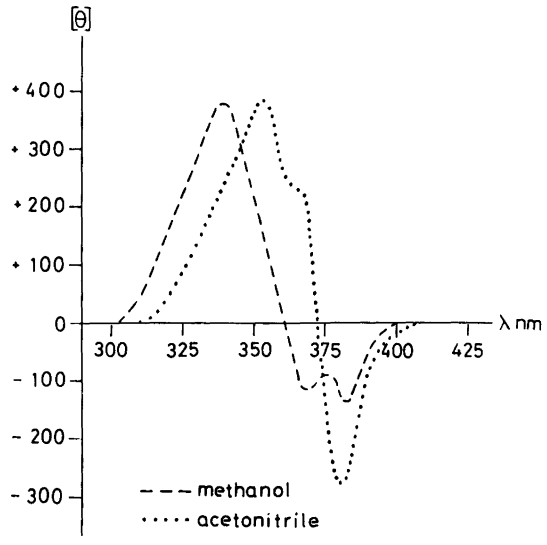



*Fig. 2.* Circular dichroism spectra (*S*)-3-methyl-*N*-nitrosopyrrolidine, (*S*)-**3**.

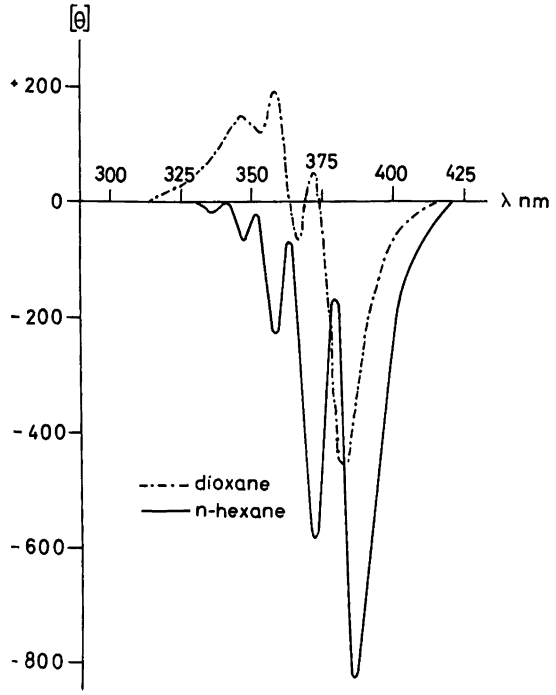



*Fig. 3.* Circular dichroism spectra of (*S*)-3-methyl-*N*-nitrosopyrrolidine, (*S*)-**3**.

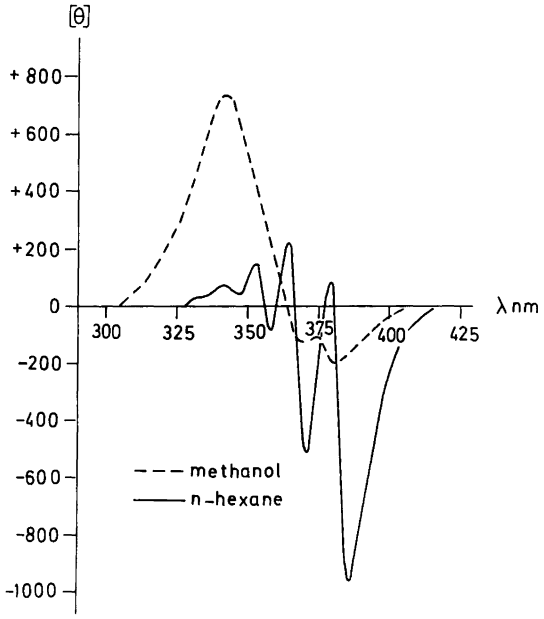



*Fig. 5.* Circular dichroism spectra of (*R*)-*N*-nitroso-3-phenylpyrrolidine, (*R*)-**4**.

wavelength as compared with the UV spectrum. Measurements on a single instrument showed that the long-wavelength peaks were at 388.0 ± 0.5 nm (CD) and 385.3 ± 0.5 nm (UV). The 2-phenylpyrrolidine (*R*)-**2**, in contrast, displayed bisignate CD curves in all solvents investigated. The spectra obtained in methanol and hexane are depicted in Fig. 7. Simultaneous recording of CD and UV spectra in hexane gave positions for the long-wavelength peak of 397.5 ± 0.5 nm and 387.8 ± 0.5 nm, respectively.

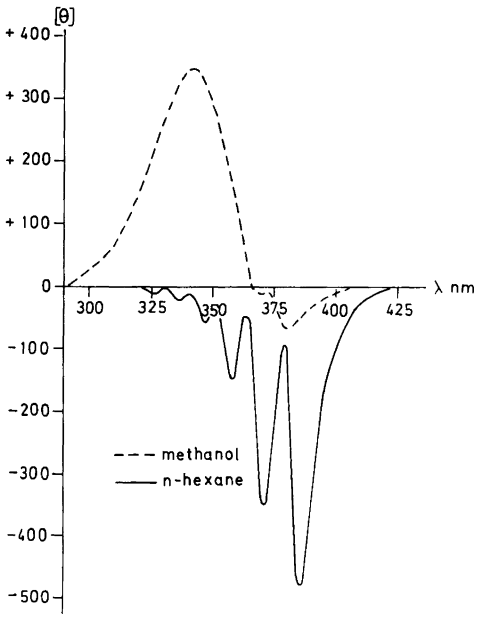



*Fig. 4.* Circular dichroism spectra of (*S*)-3-methoxymethyl-*N*-nitrosopyrrolidine, (*S*)-**6**.

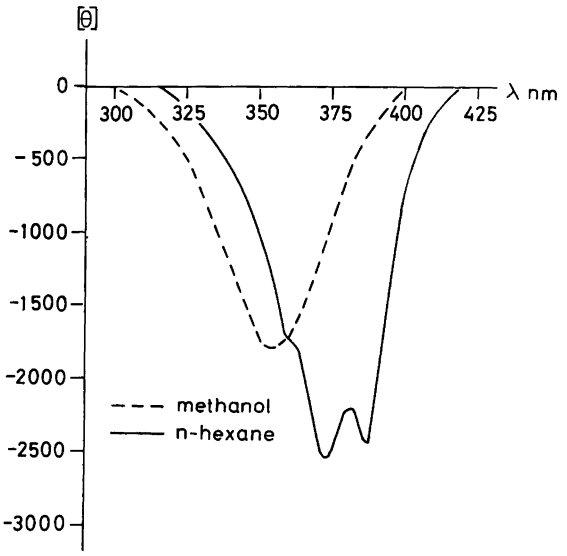



*Fig. 6.* Circular dichroism spectra of (*S*)-2-methyl-*N*-nitrosopyrrolidine, (*S*)-**1**.

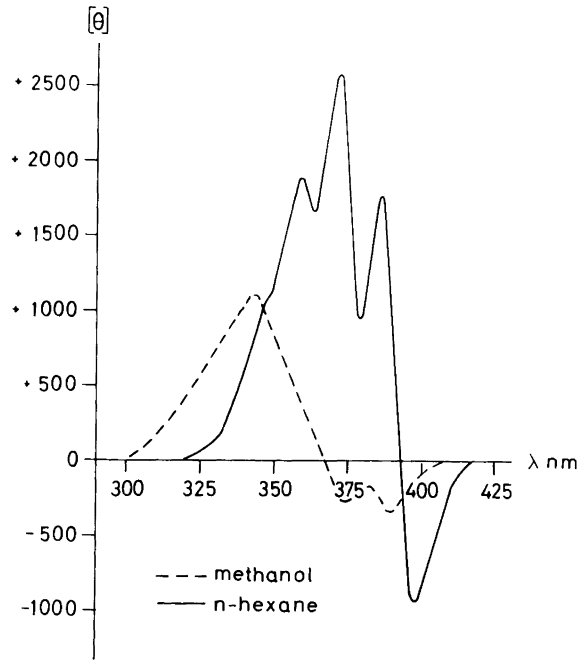



*Fig. 7.* Circular dichroism spectra of (*R*)-*N*-nitroso-2-phenylpyrrolidine (*R*)-**2**.

## Discussion

Successful application of a sector rule to these nitrosamines requires knowledge of the origin of their bisignate CD curves. Perhaps the most straightforward explanation for the differently signed components of the CD is a superposition of two molecular spectra (*E* and *Z* isomers), different in frequency position of the vibrational structure as well as in sign. However, the great sensitivity of the intensities of the positive and negative CD bands of (*S*)-**3**, (*R*)-**4**, (*S*)-**5** and (*S*)-**6** to solvent variation does not appear to be due to changes in *E*–*Z* equilibria since the *E*–*Z* ratios of the nitrosamines studied are virtually independent of solvent as shown by $^1$H NMR measurements. Energetic differences between *E* and *Z* isomers would be expected to reveal themselves in the UV absorption spectra although less clearly than in the CD spectra. The UV spectrum in hexane shows a shift of no more than 1 nm for (*S*)-**1** as compared with (*S*)-**3**, (*R*)-**4**, (*S*)-**5** and (*S*)-**6**; yet the equilibrium ratio is about 1/7 for the first compound but close to 1 for the last four. On the other hand, the UV spectrum of (*R*)-**2** is shifted 3–4 nm compared with the above spectra. This compound perhaps shows the greatest potential for *E* and *Z* forms having CD spectra shifted in wavelength relative to one another. Even with (*R*)-**2**, however, the bisignate curve is present at low temperatures (down to −130 °C where solubility problems are encountered), suggesting that *E*–*Z* equilibria are not solely responsible for the bisignate CD.

An alternative explanation of the bisignate CD curves may be provided by vibrational effects. According to Weigang, the rotatory strength of a symmetrical chromophore can be ascribed to two intensity sources.[9,22-24] One is the 'allowed' character rotatory strength that is caused by the perturbation brought about by the asymmetric environment i.e., it contains the optical activity due to static molecular structure. The 'allowed' character rotatory strength reflects the molecular chirality and can be analyzed using sector rules. The other component is the 'forbidden' character rotatory strength that is due entirely to vibrations, i.e., deviations from equilibrium geometry. As such it shows vibronic (vibrational–electronic) coupling. The more pronounced vibrational structure observed in the CD curves (Figs. 2–7) as compared with the UV curves (Fig. 1) is characteristic of such vibronic coupling. The sign of the 'forbidden' character rotatory strength may differ from that of the rotatory strength 'allowed'.[22-26]

Returning to the nitrosamines studied here, we may proceed by assuming that each molecular spectrum has an 'allowed' and a 'forbidden' component, most often of different sign. The observed spectrum for each equilibrium mixture is a superposition of two such molecular spectra the extrema of which coincide closely in wavelength. For purposes of simplification, let us also assume that only one member of each *E*–*Z* equilibrium pair is responsible for the observed CD spectrum, due either to the larger concentration of the one or due to the much greater rotatory strength of the one. Then one may compare the characteristics of the nitrosamine CD spectra to a published analysis of the CD of nitrite esters.[23] As for all the nitrite esters analyzed, the UV spectra *in hexane* of all the nitrosamines, except (*R*)-**2**, are identical in band shape and wavelength position to a high degree of approximation. Based in part on the low extinction coefficient ($\varepsilon \sim 120$), this UV spectrum is associated with a 'pure forbidden' spectrum. The CD spectra of (*S*)-**3**, (*S*)-**5** and (*S*)-**6** *in hexane*, based in part on their shape, as well as a slight shift to longer wavelength compared with the UV spectra, are associated with a 'pure allowed' spectrum. Then each CD spectrum is a sum of 'forbidden' and 'allowed' components, at least for the hexane spectra. For all of the nitrosamines, the longest-wavelength CD peak in hexane is located at longer wavelength than the UV absorption. The relevant conclusion of this analysis is that the longer-wavelength component of the CD is 'allowed' and should give the correct sign and magnitude of the dichroism that relates to the ground state geometry of the molecule, as a correct sector rule should do. A similar analysis for the other solvents used is complicated by peak broadening, especially in methanol. The experimental evidence available for hexane solution appears to favour vibronic coupling (as opposed to *E*–*Z* isomerism) as the origin of the bisignate CD but both mechanisms may very well operate simultaneously. Measurements on conformationally pure *E* and *Z* isomers should provide more conclusive evidence.

According to the lowered-symmetry sector rule of Polonski and Prajer (Fig. 8), *E* and *Z* conformers of 2-substituted *N*-nitrosopyrrolidines should display $n \rightarrow \pi^*$ CEs of

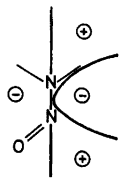


*Fig. 8.* Lowered-symmetry sector rule for the $n \rightarrow \pi^*$ transition of the *N*-nitrosamine chromophore.[7] Signs are for the upper sectors.

opposite sign. It appears reasonable to assume that the sign of the CE of the 2-methylpyrrolidine derivative (*S*)-**1** is determined by the more abundant (87 % at equilibrium) *E* isomer. Under this assumption, the strong negative CE observed for (*S*)-**1** appears inconsistent with the above sector rule. As noted previously,[5] the sector rule proposed by Snatzke *et al.*[2] and later modified by Gaffield *et al.*[4] predicts a negative CE for (*S*)-**1**.

Similarly, the long-wavelength negative CD band ('allowed') displayed by (*R*)-**2** is in disagreement with the sign predicted by the lowered-symmetry sector rule for the more abundant (76 % at equilibrium) *E* isomer. However, this 2-phenyl substituted nitrosamine might not follow the sector rule because it may have access to a mechanism for generation of rotational strength ($\mu - m$)[27] that is less readily available to the other compounds. The sector rule predicts negative CEs for both *E* and *Z* isomer of 3-substituted *N*-nitrosopyrrolidines, in agreement with the negative long-wavelength CD bands observed for (*S*)-**3**, (*R*)-**4**, (*S*)-**5** and (*S*)-**6**.

The observation that 2-substituted *N*-nitrosopyrrolidines do not appear to obey the lowered-symmetry sector rule is at odds with the findings of Polonski and Prajer.[7] (*R*)-*N*-Nitroso-2-hydroxymethylpyrrolidine and its methyl ether, the latter being isomeric with (*S*)-**6**, exist in solution mainly as the *E* isomers. They display CD and UV spectra that are very similar, both in shape and wavelength position, to the spectra of the compounds included in this study.[7] In contrast with the assignment suggested here, Polonski and Prajer assigned the 'allowed' component of the bisignate CD curves of the above two compounds to their short-wavelength branches. In other words, the publication of Polonski and Prajer appears to reverse the location of 'forbidden' and 'allowed' components and the generality of their sector rule thus may be disputed. The general applicability of this sector rule has been questioned previously on other grounds.[12,28]

## Experimental

Optical rotations at the sodium D line were measured in a 1 dm tube with a Perkin-Elmer 141 spectropolarimeter. Electronic absorption spectra were recorded with a Shimadzu MPS-5000 spectrophotometer and circular dichroism spectra with a Jasco J-41 spectropolarimeter at 20 °C. $^1$H NMR spectra were obtained with a Bruker AM/360Wb spectrometer (360 MHz) at 23 °C or with a Perkin-Elmer R12 B instrument (60 MHz) at 37 °C. Chemical shifts are reported in parts per million (δ) downfield from internal $Si(CH_3)_4$ standard. Mass spectra were recorded on a Hewlett-Packard 5981A mass spectrometer at 70 eV. Elemental analyses were carried out at the Microanalytical Laboratory, Royal Agricultural College, Uppsala, Sweden. Unless otherwise indicated, values obtained were within ±0.4 % of the theoretical values. *N*-Nitrosamines are toxic and carcinogenic. Therefore extreme caution must be exercised in their preparation and handling. Appropriate precautions have been described; cf. *J. Chem. Educ. 52,* (1975) A 419.

(S)-(+)-*2-Methyl*-N-*nitrosopyrrolidine* [(*S*)-**1**] was prepared by nitrosation[2] of (*S*)-2-methylpyrrolidine;[14] b.p. 75 °C (3 mmHg), $n_D^{22}$ 1.4828, $[\alpha]_D^{22}$ + 62° (*c* 1.1, ethanol), yield 74 %. Lit.[12] b.p. 104–105 °C (18 mmHg) for (*R*)-**1**. $^1$H NMR (360 MHz, $CD_3OD$) δ 4.50–4.41 (m, 0.8 H, *E*-H2), 4.36–4.29 (m, 0.3 H, *Z*-H5, *Z*-H5′), 4.21–4.16 (m, 0.1 H, *Z*-H2), 3.71–3.63 (m, 0.8 H, *E*-H5), 3.58–3.50 (m, 0.8 H, *E*-H5′), 2.32–1.69 (m, 4 H, H3, H3′, H4, H4′), 1.55 (d, 2.7 H, $J$ = 6.8 Hz, *E*-$CH_3$), 1.20 (d, 0.4 H, $J$ = 6.4 Hz, *Z*-$CH_3$). $^1$H NMR (360 MHz, $C_6D_6$) δ 4.07–3.98 (m, 0.1 H, *Z*-H2), 3.85–3.72 (m, 0.9 H, *E*-H2), 3.49–3.41 (m, 0.2 H, *Z*-H5, *Z*-H5′), 3.32–3.24 (m, 0.9 H, *E*-H5), 3.17–3.09 (m, 0.9 H, *E*-H5′), 1.35–0.76 (m, 4 H, H3, H3′, H4, H4′), 1.18 (d, 2.6 H, $J$ = 6.8 Hz, *E*-$CH_3$), 0.91 (d, 0.4 H, $J$ = 6.1 Hz, *Z*-$CH_3$). MS: *m/z* 115 [$M^+$ + 1] (48 %), 114 [$M^+$] (100 %), 99 (17 %), 84 (18 %), 69 (48 %). Anal. $C_5H_{10}N_2O$: C, H, N.

(R)-(+)-N-*Nitroso-2-phenylpyrrolidine* [(*R*)-**2**]. (±)-2-Phenylpyrrolidine was prepared from 3-benzoylpropiononitrile[29] or from 5-phenyl-2-pyrrolidone[30] and resolved with (+)-tartaric acid in ethanol[15] to give a tartrate salt of m.p. 135–136 °C. Liberation of the free amine followed by distillation gave (*R*)-2-phenylpyrrolidine, b.p. 105 °C (10 mmHg), $[\alpha]_D^{22}$ + 71.6° (neat, *d* 1.004), $n_D^{22}$ 1.5482. Lit.[15] $[\alpha]_D^{17}$ + 71.2° (neat).

Nitrosation[2] of (*R*)-2-phenylpyrrolidine yielded (*R*)-**2**; b.p. 120 °C (0.4 mmHg), $n_D^{22}$ 1.5697, $[\alpha]_D^{22}$ + 197° (*c* 1.7, ethanol), yield 82 %. $^1$H NMR (360 MHz, $CD_3OD$): δ 7.40–7.00 (m, $C_6H_5$), 5.67–5.56 (m, 0.6 H, *E*-H2), 5.24–5.15 (m, 0.2 H, *Z*-H2), 4.64–4.53 (m, 0.2 H, *Z*-H5), 4.47–4.37 (m, 0.2 H, *Z*-H5′), 3.90–3.78 (m, 0.8 H, *E*-H5), 3.75–3.64 (m, 0.8 H, *E*-H5′), 2.57–1.86 (m, 4.1 H, H3, H3′, H4, H4′). $^1$H NMR (360 MHz, $C_6D_6$): δ 5.22–5.15 (m, 0.6 H, *E*-H2), 5.03–4.97 (m, 0.2 H, *Z*-H2), 4.08–4.00 (m, 0.2 H, *Z*-H5), 3.72–3.64 (m, 0.2 H, *Z*-H5′), 3.53–3.43 (m, 0.8 H, *E*-H5), 3.34–3.24 (m, 0.8 H, *E*-H5′), 1.70–1.05 (m, 4.1 H, H3, H3′, H4, H4′). MS: *m/z* 176 [$M^+$] (21 %), 146 [$M^+ - NO$] (43 %), 104 (100 %). Anal. $C_{10}H_{12}N_2O$: C, H, N.

(S)-(−)-*3-Methyl*-N-*nitrosopyrrolidine* [(*S*)-**3**] was obtained similarly from (*S*)-3-methylpyrrolidine;[14] b.p. 80 °C

(5 mmHg), $n_D^{22}$ 1.4813, $[\alpha]_D^{22} - 42°$ (*c* 1.0, ethanol), yield 75 %. $^1$H NMR (360 MHz, $CD_3OD$): δ 4.48–4.41 (m, 1.0 H), 4.19–4.11 (m, 0.46 H), 3.84–3.68 (m, 1.56 H), 3.53–3.44 (m, 0.56 H), 3.06–3.00 (m, 0.44 H, 2.49–2.35 (m, 0.9 H), 2.25–2.13 (m, 1.0 H), 1.76–1.58 (m, 1.0 H), 1.13 (two overlapping doublets, 3.0 H, *E*-$CH_3$ and *Z*-$CH_3$). $^1$H NMR (360 MHz, $C_6D_6$): δ 3.85–3.78 (m, 0.96 H), 3.46–3.38 (m, 0.94 H), 3.36–3.29 (m, 0.56 H), 3.11–3.00 (m, 1.1 H), 2.68–2.62 (m, 0.45 H), 1.50–1.38 (m, 0.8 H), 1.23–1.15 (m, 1.0 H), 0.79–0.65 (m, 0.9 H), 0.46 (d, 3.0 H, $J = 6.5$ Hz, *E*-$CH_3$ and *Z*-$CH_3$). MS: *m/z* 114 [$M^+$] (100 %). Anal. $C_5H_{10}N_2O$: C, H, N.

(R)-(+)-N-*Nitroso-3-phenylpyrrolidine* [(*R*)-**4**]. (±)-3-Phenylpyrrolidine was prepared by $LiAlH_4$ reduction of 3-phenylsuccinimide obtained[31] from 2-phenylsuccinic acid. The amine was resolved with (+)-dibenzoyltartaric acid in methanol[16] to give a dibenzoyltartrate of m.p. 158.5–159.5 °C. The liberated (*R*)-3-phenylpyrrolidine had b.p. 88 °C (2 mmHg), $[\alpha]_D^{22} - 37.0°$ (neat, *d* 1.013), $n_D^{22}$ 1.5567. Lit.[16] $[\alpha]_D - 40°$ (neat).

Nitrosation[2] of (*R*)-3-phenylpyrrolidine yielded (*R*)-**4**; m.p. 55–57 °C (from ether–light petroleum), $[\alpha]_D^{22} + 19°$ (*c* 1.1, ethanol), yield 80 %. $^1$H NMR (360 MHz, $CD_3OD$): δ 7.42–7.22 (m, 5 H, $C_6H_5$), 4.80–4.75 (m, 0.6 H), 4.63–4.56 (m, 0.4 H), 4.30–4.07 (m, 1.4 H), 3.90–3.83 (m, 0.6 H), 3.65–3.42 (m, 2.0 H), 2.50–2.37 (m, 1.0 H), 2.26–2.07 (m, 1.0 H). $^1$H NMR (360 MHz, $C_6D_6$): δ 4.20–4.13 (m, 0.4 H), 4.00–3.92 (m, 0.4 H), 3.76–3.68 (m, 0.4 H), 3.52–3.36 (m, 1.3 H), 3.20–3.05 (m, 0.9 H), 2.61–2.50 (m, 0.6 H), 1.50–1.40 (m, 0.9 H), 1.35–1.16 (m, 1.0 H). MS: *m/z* 176 [$M^+$] (11 %), 146 (80 %), 91 (100 %). Anal. $C_{10}H_{12}N_2O$: C, H, N.

(S)-(−)-*3-Hydroxymethylpyrrolidine.* (*S*)-*N*-Benzyl-3-hydroxymethylpyrrolidine (6.3 g, 0.033 mol) dissolved in ethanol was treated with hydrogen in the presence of palladium (10 %) on charcoal (1 g) for 48 h at a pressure of 60 psi. The catalyst was removed by filtration, the solvent was evaporated *in vacuo* and the product was distilled, b.p. 79 °C (0.6 mmHg), $n_d^{22}$ 1.4952, $[\alpha]_D^{22} - 28.5°$ (*c* 3.4, ethanol), yield 86 %. Anal. $C_5H_{11}NO$: C, H, N. Lit.[32] $[\alpha]_D^{20} - 19.1°$ (*c* 4.5, ethanol).

(S)-(+)-*3-Pyrrolidinecarboxylic acid* was prepared by chromic acid oxidation of (*S*)-3-hydroxymethylpyrrolidine as described previously,[32] m.p. 187–188 °C (from ethanol), $[\alpha]_D^{22} + 19°$ (*c* 0.6, water). Lit.[32] m.p. 188–190 °C, $[\alpha]_D^{20} + 18.5°$ (*c* 3.1, water).

(S)-(+)-N-*Nitroso-3-pyrrolidinecarboxylic acid methyl ester* [(*S*)-**5**]. (*S*)-3-Pyrrolidinecarboxylic acid was esterified using methanol saturated with HCl. The crude ester hydrochloride was nitrosated as described[33] to give (*S*)-**5**, b.p. 105 °C (0.2 mmHg), $n_D^{22}$ 1.4912, $[\alpha]_D^{22} + 37°$ (*c* 0.7, ethanol). $^1$H NMR (60 MHz, $CDCl_3$): δ 4.2–4.7 (m, 2 H, *E*-H2, *Z*-H5), 3.4–4.0 (m, 2 H, *E*-H5, *Z*-H2), 3.76 (s, 3.0 H, *E*-$CH_3$, *Z*-$CH_3$), 2.9–3.5 (m, 1.0 H, *E*-H3, *Z*-H3), 2.1–2.6 (m, 2.0 H, *E*-H4, *Z*-H4). (Found: C, 44.5; H, 6.3; N, 17.6. $C_6H_{10}N_2O_3$ requires C, 45.6; H, 6.4; N, 17.7 %).

(S)-(−)-*3-Methoxymethyl*-N-*nitrosopyrrolidine* [(*S*)-**6**]. (*S*)-3-Hydroxymethylpyrrolidine was transformed into the corresponding *N*-nitroso derivative according to a method described in the literature.[33] The crude product was *O*-methylated as described for the preparation of (*S*)-*O*-methyl-*N*-nitrosoprolinole;[7] b.p. 110 °C (1 mmHg), $[\alpha]_D^{22} - 12°$ (*c* 0.1, ethanol). $^1$H NMR (60 MHz, $CDCl_3$): δ 3.39 and 3.36 (two singlets of roughly equal intensity, 3 H, *E*-$CH_3$ and *Z*-$CH_3$). Anal. $C_6H_{12}N_2O_2$: C, H, N.

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