Conformational Dependence of the Circular Dichroism of N-Nitrosopyrrolidines[1]

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Abstract: Several substituted N-nitrosopyrrolidines were prepared and their chiroptical spectra studied. The circular dichroism of monocyclic compounds depends on substituents, solvents, and temperature changes. Some of these N-nitrosamines exhibit bisignate CD curves in the region of n–π^* transition. On the contrary, conformationally restricted bi- and tricyclic compounds show monosignate Cotton effects, the magnitudes of which are almost solvent independent. Bisignate CD curves result from two half-chair conformers of the pyrrolidine ring being in equilibrium and contributing with the opposite CD signs. The Cotton effect signs can be predicted with our "lowered symmetry" sector rule developed earlier. Molecular geometries were calculated by the molecular mechanics (MM2) method, and the resulting torsional angles were used to estimate the vicinal coupling constants in the ^{1}H NMR spectra. The crystal structure of (R)-N-nitroso-3-phenylpyrrolidine ((R)-**6**), solved by us, is very close to the calculated minimum energy conformation.

The circular dichroism (CD) associated with the n–π^* transition of the N-nitrosamine chromophore has been the subject of many investigations and speculations during past three decades.[2,3] Substantial research efforts have been directed toward establishing the relation between the Cotton effect (CE) sign and the molecular geometry of N-nitrosamines. The first sector rule was proposed for this purpose by Snatzke et al.[4] However, the predictions based on it appeared incorrect in many cases and Gaffield et al.[5] suggested that the inversion of the signs in the original rule was necessary. Somewhat later, Połoński and Prajer[6] developed a new sector rule, based on the concept of symmetry lowering of the N-nitramine chromophore.[7] This rule appeared to predict correctly the CE sign of many N-nitrosamines. Later, Ferber and Richardson[8] on the basis of semiempirical MO calculations for substituted N-nitrosopiperidines concluded that neither rule is generally applicable for the N-nitrosamine chromophore. More recent studies on N-nitrosopyrrolidines led Gaffield et al.[2] to the suggestion that the CE associated with the π–π^* transition may offer a more reliable basis for stereochemical correlations.

N-Nitrosopyrrolidines were among the most used model compounds for chiroptical investigations. Their CD shows strong substituent and solvent dependence.[2,9] Moreover, many of these compounds show bisignate CD curves within the region of the n–π^* transition,[2,6,9] and this poses difficulties in the interpretation of the spectra. Połoński and Prajer[6] suggested that the vibronic coupling effect[10] may be responsible for this type of CD curve. Recently, Ringdahl[9] reported the CD spectra of some 2- and 3-substituted N-nitrosopyrrolidines and also attributed the bisig-

nate CD to the vibronic coupling. According to him, only the long-wavelength component of the CD reflects the molecular chirality, whereas the higher energy one is due to molecular vibrations. He assumed that the dissymmetrically placed ring substituents determine the CE sign and questioned the validity of our "lowered symmetry" sector rule for the above compounds. Very often bisignate CD curves indicate an equilibrium between two or more conformers contributing with opposite signs to the CE.[11] In the case of five-membered ring compounds, the chiral ring contribution may overweigh that of dissymmetrically placed substituents and determine the CE sign as it occurs in substituted cyclopentanones.[12a–d] Unfortunately, the pyrrolidine ring geometry and its influence on the CD spectra have not received much attention and it was often assumed to be planar and even rigid.[13] Gaffield and co-workers[2] proposed that the ring exists in two rapidly equilibrating envelope conformations with the C-4 atom being above and below the ring plane, so the effective planarity of the ring is achieved on average. On the other hand, the force field calculations of N-acylproline derivatives showed that the five-membered ring is flexible and exists in conformational equilibrium between several half-chair forms.[14]

Our aim was to examine the influence of the ring geometry and conformational equilibria on the chiroptical spectra of N-nitrosopyrrolidines. For this purpose we have prepared compounds **7–11**, in which the pyrrolidine ring condensed with the bicyclo[2.2.1]heptane or cyclopropane systems has very limited conformational flexibility, and compared their CD spectra with those of related, more flexible compounds **5** and **6**. In addition we have measured the low-temperature CD of nitrosamines **3a,b**. Molecular geometries have been studied with use of molecular mechanics (MM2)[15] calculations, and the results have been compared with those obtained from the ^{1}H NMR spectra and the X-ray crystallographic analysis of **6**.

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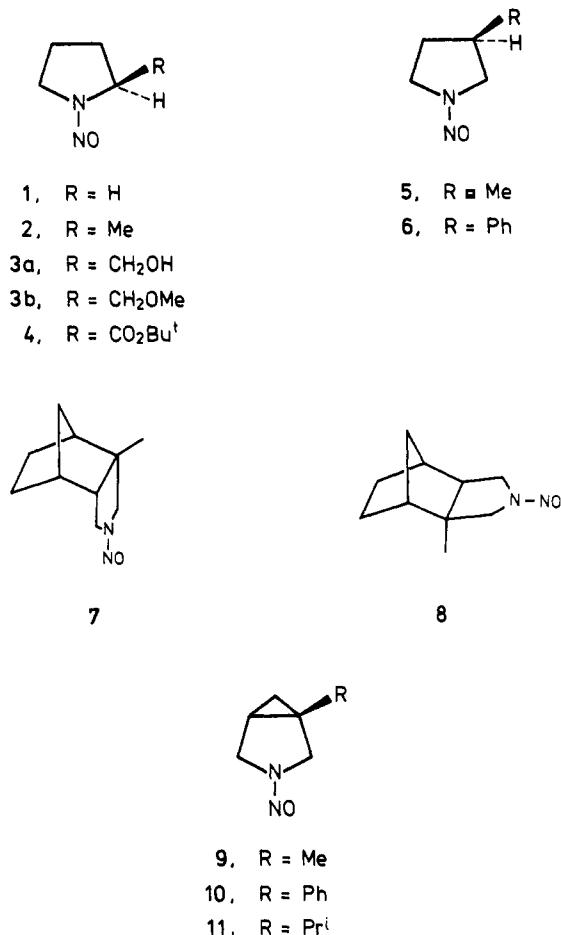(9) Ringdahl, B. *Acta Chem. Scand.* 1990, 44, 42–49.
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Circular Dichroism of N-Nitrosopyrrolidines

J. Am. Chem. Soc., Vol. 115, No. 24, 1993 11411

1, R = H
2, R = Me
3a, R = CH$_2$OH
3b, R = CH$_2$OMe
4, R = CO$_2$Bu^t

5, R = Me
6, R = Ph

7

8

9, R = Me
10, R = Ph
11, R = Pr^i

Results and Discussion

Molecular Geometry and NMR Spectra. Although changes in the Z–E equilibria of N-nitrosopyrrolidines can be easily monitored by NMR spectroscopy, the five-membered ring geometry is more difficult to assign. Since the molecular mechanics[15] method has been shown to be a very reliable and efficient way of determining conformations of a wide variety of compounds, we performed MM2 calculations for several nitrosamines. The original Allinger's parameterization[16] was extended to this class of compounds by following the procedure of Pearlstein and Hopfinger.[17] The calculated geometries (selected torsional angles) are presented in Table I.

The simplest compound of the series, N-nitrosopyrrolidine (1), adopts a half-chair (twisted) conformation,[18] which is the only energy minimum for this molecule. Similarly, the five-membered ring in the 3-substituted N-nitrosopyrrolidines 5 and 6 exists in the half-chair form. The substituent at C-3 prefers an equatorial orientation and does not significantly influence the ring geometry, which has local C_2 symmetry. As expected, the energy difference between Z and E stereoisomers for 3-substituted pyrrolidine ring compounds 5–9 is very low and does not exceed 0.05 kcal/mol. The situation appears to be more complicated for 2-substituted nitrosamine 3; again the E form prefers the half-chair geometry of the ring and the methyl group is located at the equatorial position, whereas the steric interaction between the N-nitroso and methyl group in the Z form causes the axial conformer to be only 0.16 kcal/mol less stable than the equatorial one.

Surprisingly, the pyrrolidine ring in the equatorial Z conformer assumes an envelope conformation with the C-4 atom being out of the plane of the remaining ring atoms, but there is no energy minimum corresponding to the envelope conformation of the opposite ring chirality, as postulated by Gaffield et al.[2]

Since the nitrosamine 6 is a crystalline compound, it was subjected to an X-ray analysis. It was found that 6 crystallizes preferably in the E form and the five-membered ring adopts the half-chair conformation with the phenyl substituent located at the equatorial position (Figure 1). The NNO group is essentially planar. A striking feature of this structure is a significant deformation of the bond angles caused by steric interaction of the N-nitroso oxygen with the neighboring CH$_2$ group; i.e., N-N1-C5 and N-N1-C2 are of 132.3° and 113.7°, respectively.[19] It is noteworthy that the calculated geometry of the half-chair conformer of 6 is very close to that found in the crystal state (Table I).

Due to restrictions imposed by the tri- and bicyclic skeletons in 7–11, the pyrrolidine ring twisting in these compounds is significantly reduced or even ruled out. In the cases of 7 and 8 there are two energy minima corresponding to the *exo* and *endo* conformers; in both compounds the pyrrolidine ring adopts an
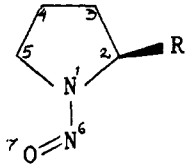

exo - 7

endo - 7

exo - 8

endo - 8
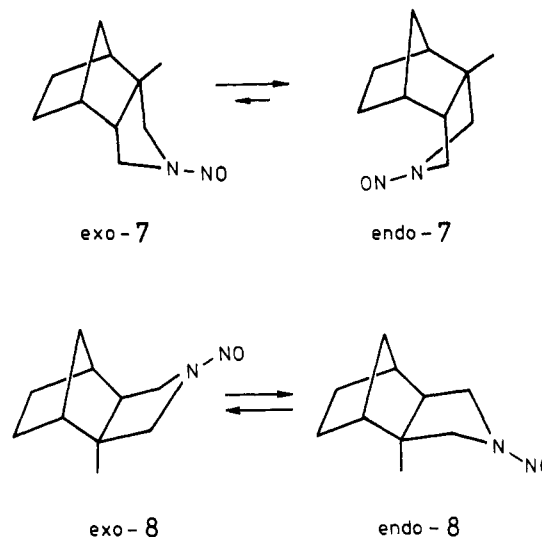
envelope conformation (the nitrogen atom at the tip). Owing to steric interactions between the hydrogens at C-3 and C-9, and at C-5 and C-8, the *exo*-7 is ca. 3 kcal/mol higher in energy than the *endo*-7 conformer, whereas in the absence of such interactions in 8 the *exo* and *endo* conformers differ only by 0.58 kcal/mol. The calculations predict only one energy minimum for compounds 9–11, where the 3-azabicyclo[3.1.0]hexane skeleton assumes a boat-like conformation. This unusual type of geometry is
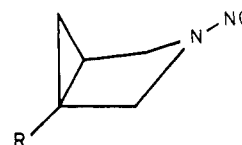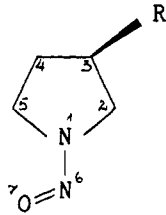

characteristic for bicyclo[3.1.0]hexane[20a,b] and its 3-aza-,[20c] 3-oxa-,[20a,d,e] and 3-oxo-[20f] analogues.

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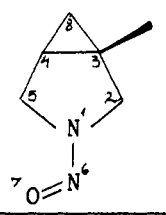(18) Cremer, D.; Pople, J. A. *J. Am. Chem. Soc.* **1975**, *97*, 1354–1358.

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11412 *J. Am. Chem. Soc., Vol. 115, No. 24, 1993*

Połohski et al.

Table I. Selected Torsional Angles (deg) and Relative Energies Calculated by MM2

structure[a]	(2–3–4–5)	(1–2–3–4)	(3–4–5–1)	(5–1–2–R)	(2–1–6–7)	E_{rel}, kcal/mol
1	–40.9	33.4	31.3		–178.9	
(*E*)-**2** (eq)	–41.1	32.3	32.6	–134.5	179.7	0
(*E*)-**2** (ax)	39.3	–29.9	–32.1	–110.2	179.1	0.54
(*Z*)-**2** (eq)	–40.3	26.7	37.0	–124.2	–2.5	0.53
(*Z*)-**2** (ax)	39.6	–30.7	–31.8	–100.7	0.3	0.69

structure[a,b]	(2–3–4–5)	(1–2–3–4)	(3–4–5–1)	(1–2–3–R)	(2–1–6–7)	E_{rel}, kcal/mol
(*E*)-**5** (eq)	41.2	–34.2	–31.0	–157.8	178.9	0
(*E*)-**5** (ax)	–38.6	32.5	28.6	–87.3	–179.7	1.52
(*E*)-**6** (eq)	41.5	–36.0	–29.9	–162.1	179.1	0
(*E*)-**6** (ax)	–40.2	33.7	30.0	–85.9	–178.5	1.28
(*E*)-(*R*)-**6**[c]	–38.4 ± 0.5	31.1 ± 0.5	30.0 ± 0.5	155.3 ± 0.4	–179.4 ± 0.6	
(*E*)-**7** (*endo*)	–2.8	–16.2	20.6	–138.6	–179.0	0
(*E*)-**7** (*exo*)	–10.2	26.3	–10.3	–92.5	179.3	3.05
(*E*)-**8** (*endo*)	–3.3	21.1	–16.0	–99.3	179.4	0.58
(*E*)-**8** (*exo*)	–4.3	–13.2	20.0	–135.8	–179.2	0

structure[a,b]	(2–3–4–5)	(1–2–3–4)	(3–4–5–1)	(1–2–3–8)	(1–2–3–R)	(2–1–6–7)
(*E*)-**9**	0.6	–13.4	12.4	52.2	–156.9	–179.4
(*E*)-**10**	1.4	–13.9	11.7	52.2	–157.4	–179.7
(*E*)-**11**	–0.3	–12.6	13.1	52.8	–156.9	–179.4

[a] eq = equatorial; ax = axial. [b] The dihedral angle and energy values for corresponding *Z* structures differ less than 1.5° and 0.05 kcal/mol, respectively. [c] The X-ray structure.
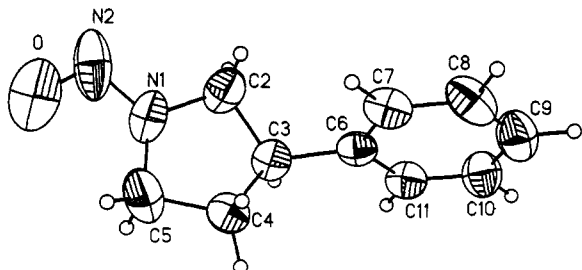
Figure 1. ORTEP drawing of the X-ray structure of (*R*)-**6** (note that this structure is enantiomeric to **6**).

The MM2 results can be correlated with the conformationally averaged ¹H NMR parameters. For this purpose we calculated the vicinal coupling constants $^3J_{HCCH}$ between the C_α and C_β protons of some nitrosamines for each energy minimum conformation on the basis of the corresponding dihedral angles θ obtained from the MM2 method. The equation of Gandour and co-workers[21] was used:

$$^3J_{HCCH} = A + B \cos \theta + C \cos 2\theta + \Delta S_X \cos \theta \cos \phi \quad (1)$$

where $A = 8.17$, $B = -1.96$, $C = 6.30$, $\Delta S_X = 3.72$, and ϕ is the HCCX dihedral angle. This equation improves on the original Karplus relation[22] by including an empirical correlation for the X substituent electronegativity and orientation. The ΔS_X value can be determined on the basis of the observed coupling for the freely rotating ethyl group[21] (i.e., in Et_2NNO in our case):

$$^3J_{HCCH} = A - 0.25\Delta S_X \quad (2)$$

Relation 1 is much simpler than that proposed by Haasnoot et al.[23] Although the accuracy of equation 1 is not high, especially for polycyclic systems, the comparison of calculated and experimental results (Table II) confirms trends predicted by the MM2 method. The calculated $^3J_{HCCH}$ values agree well with those observed for **9–11** existing in the single conformation in solution. The measured vicinal coupling constants for **7** are close to those calculated for the *endo*-**7** conformer, indicating its preference in the equilibrium. Due to the magnetic anisotropy of the NNO

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Circular Dichroism of N-Nitrosopyrrolidines

J. Am. Chem. Soc., Vol. 115, No. 24, 1993 11413

Table II. ^{1}H NMR Vicinal Coupling Constants (Hz) Calculated for Torsional Angles Corresponding to Minimum Energy Conformations and Observed Values

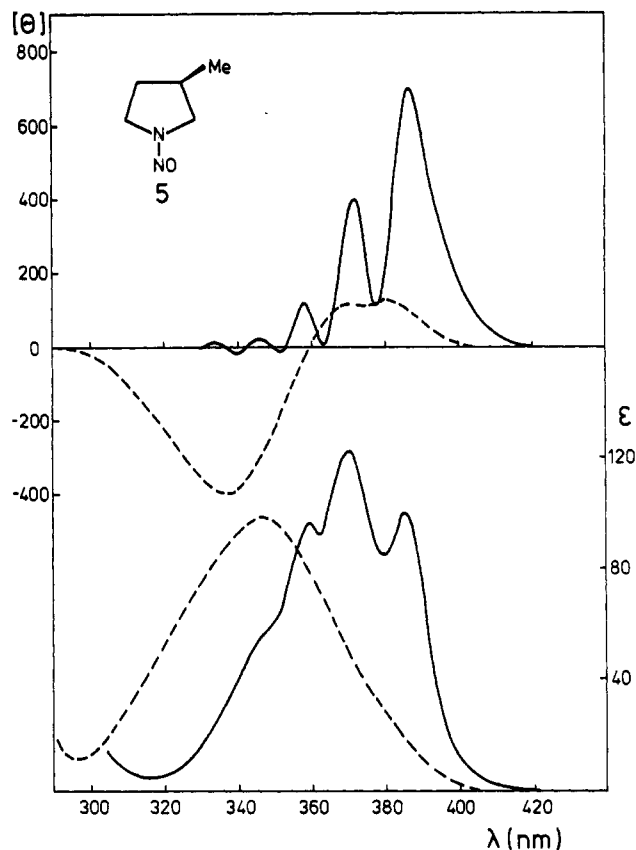| conformer	torsional angle		$^3J_{HCCH}^{calc}$	$^3J_{HCCH}^{obs}$
	θ	ϕ		
endo-7	29.1	142.3	7.21	8.8[a]
	−93.8		2.25	1.6[a]
exo-7	−11.3	108.7	10.89	
	−135.0		10.40	
endo-8	−139.9	105.1	11.35	9.4[a]
	−16.2		10.62	4.3[a]
exo-8	30.1	143.8	7.00	
	−93.2		2.19	
9	44.1	158.9	4.47	4.5
	−79.5		1.29	1.2
10	44.8	158.8	4.36	4.4
	−79.5		1.30	1.2
11	44.9	159.7	4.33	4.4
	78.8		1.28	1.3

[a] Data for an equilibrium mixture of the *exo* and *endo* conformers.

Table III. Electronic Absorption (UV) and Circular Dichroism (CD) Data of N-Nitrosamines 2–11

compd	solvent[a]	UV λ, nm (ε)	CD λ, nm ([θ])[b,c]
2[d]	C	371 (120)	373 (2500)
	M	348 (91)	353 (1500)
3a[e]	CD	370 (102)	393 (170), 364 (−1130)
	M		384 (174), 340 (−1540)
3b[e]	CD	370 (120)	388 (610), 358 (−79)
	M		385 (193), 331 (−1300)
4	CD		364 (2190)[f]
	CD	368 (115)	364 (1450)[g]
	M	351 (91)	348 (2420)[f]
5	C	370 (120)	387 (690)
	M	346 (94)	380 (130), 339 (−390)
6	C	371 (132)	386 (940), 363 (−270)
	M	348 (104)	380 (200), 342 (−780)
7	C	370 (120)	376 (260)
	M	348 (102)	345 (218)
8	C	371 (140)	379 (920)
	M	348 (120)	347 (1020)
9	C	371 (122)	371 (−500)
	M	352 (110)	355 (−540)
10	C	372 (145)	368 (−735)
	M	354 (107)	354 (−690)
11	C	372 (120)	389 (−100), 382 (145), 374 (−35), 366 (105)
	M	353 (105)	368 (−60), 341 (65)

[a] C = cyclohexane, CD = cyclohexane–dioxane (9:1), M = methanol. [b] Molar ellipticity in deg cm²/dmol. [c] The highest intensity vibronic band. [d] Data from ref 9. [e] Data from ref 6. [f] Immediately after dissolution. [g] After 4 h from dissolution.

group,[24] the neighboring axial and equatorial methylene protons show significant differences in their chemical shifts ranging from 1 to 2 ppm. On the contrary, the differences between chemical shifts of the corresponding protons in **8** are much smaller, so the signal of (Z)-CH_2 protons appears as an AB system as a consequence of rapid exchange of the methylene protons between the axial and equatorial positions in equilibrating *endo*-**8** and *exo*-**8** conformers. The observed $^3J_{HCCH}$ value points to predomination of the *endo*-**8** form in equilibrium, though the contribution of the *exo* form cannot be neglected.

Circular Dichroism Spectra. CD data corresponding to the lowest energy n–π* transition of *N*-nitrosamines **2–11** are presented in Table III. A characteristic feature of the CD of monocyclic compounds **2–6** is their sensitivity to solvent changes. Solvents influence not only the CE magnitude, as in **2** and **4**, but also the shape of CD curves, as in **3a,b**, **5**, and **6**. For the latter

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Figure 2. CD and UV spectra of **5** in cyclohexane and methanol (solid and broken lines, respectively).

compounds bisignate CD curves were obtained, where the relative intensity of positive and negative CEs varies with the solvent polarity (Figure 2). In contrast, the CDs of bi- and tricyclic nitrosamines **7–11** do not show significant solvent dependence. Moreover, compounds **7–9**, being conformationally restricted analogues of **5**, exhibit monosignate CD curves (Figures 3 and 4). The nitrosamine **10**, a bicyclic analogue of **6**, behaves similarly; its spectra were already presented in the preliminary communication.[1] In light of the above observations, it seems more likely that conformational effects rather than vibronic coupling[10] are responsible for the bisignate CEs and their solvent dependence. This is further evidenced by the variable-temperature spectra of **3a** (Figure 5) and its *O*-methyl derivative **3b**. The bisignate CD curves of **3a,b** observed at room temperature gradually change to the monosignate ones as the temperature approaches −185 °C. It is noteworthy that, at the same time, the CD peaks corresponding to the vibronic transitions change their positions. Thus the observed lack of correspondence between the CD peak positions and the absorption maxima, which according to Ringdahl[9] is evidence of the vibronic coupling effect,[10] can be simply associated with a superposition of the CE bands with opposite signs. As Wellman et al.[25] have already pointed out, the wavelengths of two oppositely signed extrema on the CD curve do not correspond to the positions of the contributing CEs and depend on their intensities.

Since the Z–E equilibria of the title compounds are only weakly affected by solvent changes,[2,9] as NMR shows (e.g., the Z–E ratios of **5–11** are close to 1 in $CDCl_3$, C_6D_6, and CD_3OD), it seems resonable to assume that the observed solvent and temperature dependences of CD spectra reflect conformational changes within the five-membered ring. Thus the ring geometry should be taken into account in any discussion of chiroptical spectra as an important factor influencing the CE sign.

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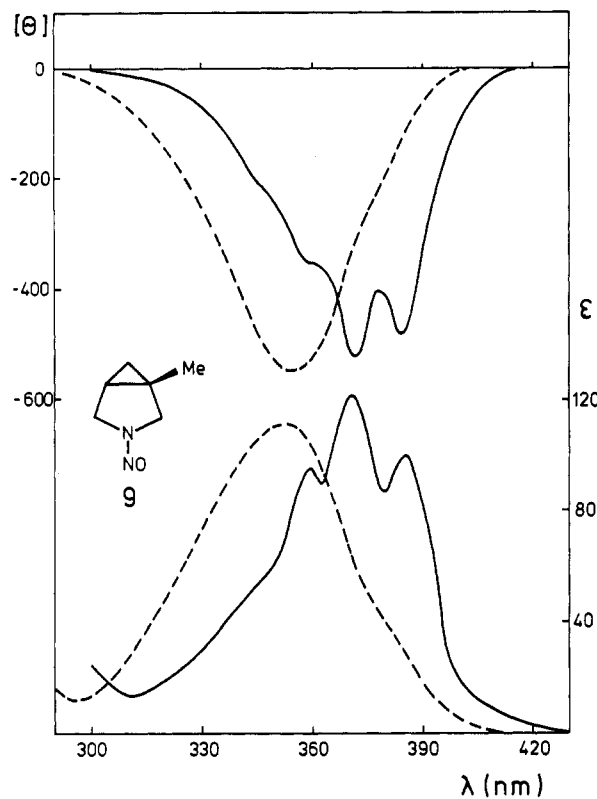
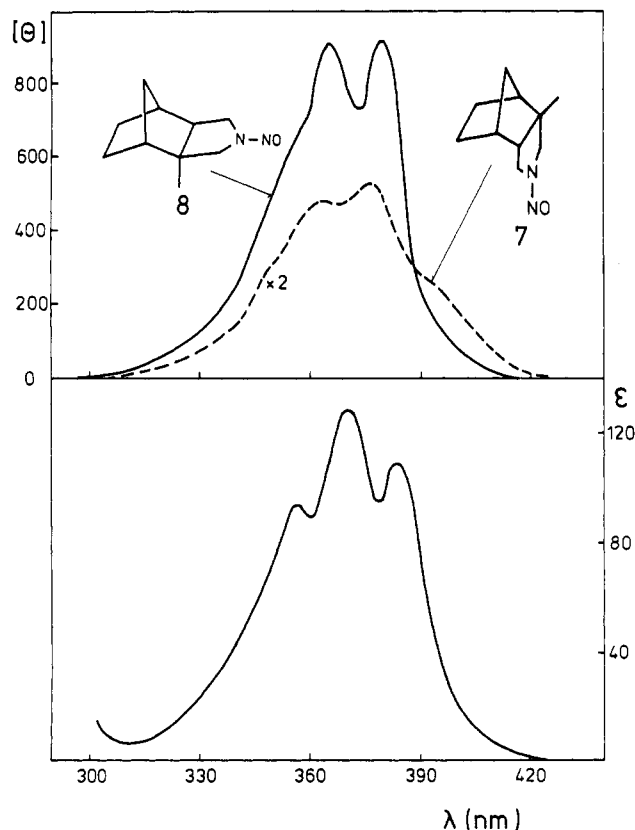**Figure 3.** CD and UV spectra of **9** in cyclohexane and methanol (solid and broken lines, respectively).

Figure 4. CD spectra of **7** and **8** and UV of **7** in cyclohexane.

Figure 5. Variable-temperature (°C) CD spectra of **3a** in EPA.
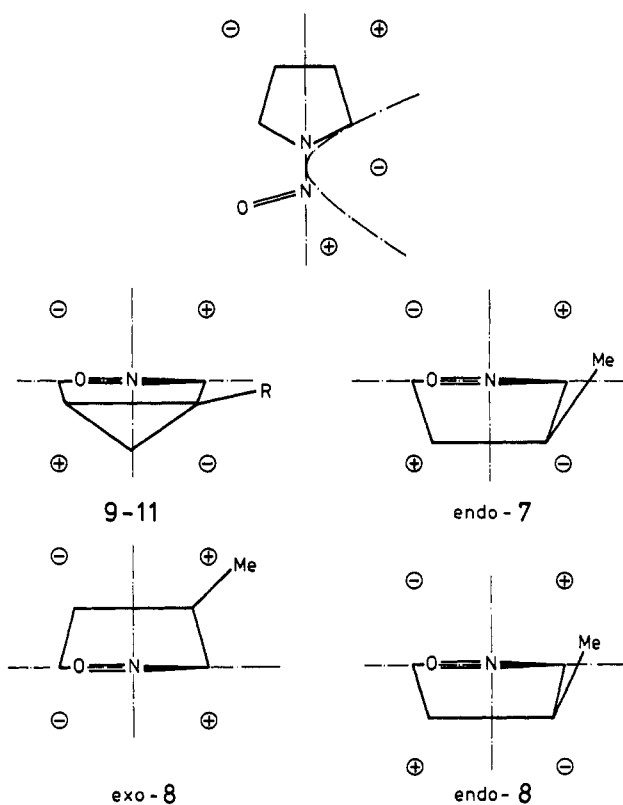
Figure 6. "Lowered symmetry" sector rule[6] projections of nitrosamines **7–11**.

Figures 6–8 show the projections of substituted *N*-nitrosopy-rrolidine molecules according to our "lowered symmetry" sector rule.[6] The analysis of the CD spectra is simplified especially for nitrosamines **9** and **10** existing in a single ring conformation, and generally for all 3-substituted pyrrolidine ring compounds, like

5–11. In the above cases, the rule predicts the same CE signs for both Z and E stereoisomers, which are almost equally populated according to the NMR spectra. The methyl substituent placed unequivocally in the negative sector, though close to the nodal surface (Figure 6), is responsible for the weak negative CE of **9**. The phenyl group in **10** behaves analogously, but the CE magnitude is slightly higher than that of **9** due to a stronger

Circular Dichroism of N-Nitrosopyrrolidines

J. Am. Chem. Soc., Vol. 115, No. 24, 1993 11415

Figure 7. Projections of two half-chair conformers of N-nitrosopyrrolidine substituted at C-3.

Figure 8. Projections of equatorial Z and E conformers of N-nitroso-pyrrolidine substituted at C-2.

dissymmetric perturbation exerted by this substituent. Surprisingly, nitrosamine 11 exhibits only a very weak and bisignate CE. This result can probably be attributed to the contribution from two rotamers of the isopropyl group. The rotation about the C–C bond changes the location of methyls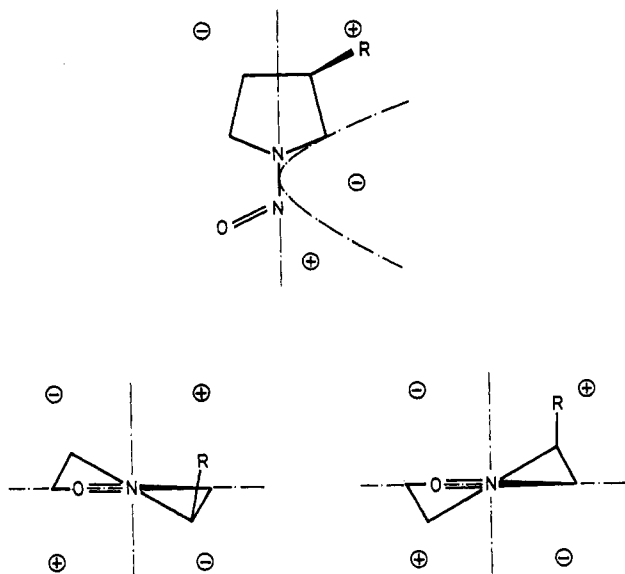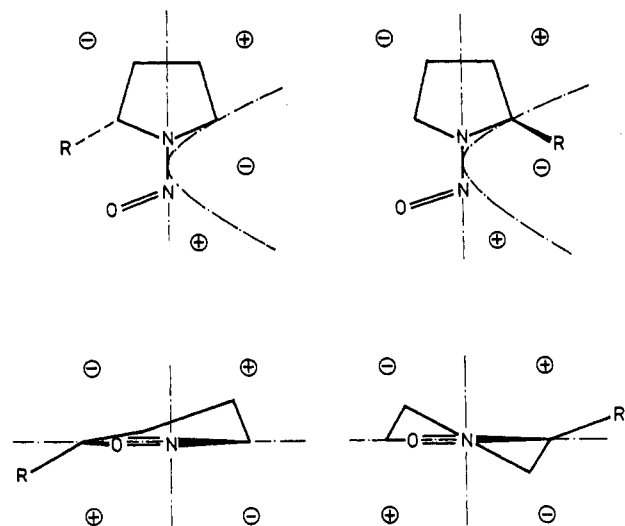, constituting this group, from the lower positive to the upper negative sector, which results in the positive and negative CE signs, respectively. The importance of a rotational isomerism of the isopropyl substituent for the CD of ketones has been shown by Djerassi and co-workers.[26]

Although the sector diagrams for *endo* conformers of tricyclic nitrosamines 7 and 8 are almost the same (Figure 6), compound 8 shows a much stronger CE than the isomeric nitrosamine 7 (Figure 4). This may be attributed to a significant contribution of the *exo* from to the conformational equilibrium of 8, whereas in the case of 7 the population of the *exo* from is negligible according to the MM2 calculations. The *exo*-8 conformer has the Me group in the upper positive sector far from the nodal plane and causes a relatively strong CE, whereas both *endo* conformers of 7 and 8 show this group to be very close to the nodal surface and thus their contributions to the CE are very weak.

(26) Wellman, K. M.; Briggs, W. S.; Djerassi, C. *J. Am. Chem. Soc.* **1965**, *87*, 73–81.

The bisignate CD curves shown by monocyclic 5 and 6 may be explained by contribution from two half-chair (twisted) conformers of the five-membered ring being in equilibrium and showing the opposite CE signs; the negative CE is due to the axial conformer and the positive CE to the equatorial one. The CE signs are determined by the ring chirality (the chiral second sphere according to Snatzke),[27] the contribution of which overweighs that of the substituent at C-3 (the chiral third sphere) located quite far from the chromophore (Figure 7). An analogous explanation has been given for stereochemically related substituted cyclopentanones,[12a–d] pyrrolidine nitroxyls,[12e] and some other five-membered ring compounds.[12f]

Predictions for monocyclic N-nitrosopyrrolidines substituted at C-2 are more complicated than for those substituted at C-3, since the contributions from the four conformers of different populations should be taken into account. The vicinal effect of the substituent at C-2, which is less clear than that of the substituent at C-3, poses additional difficulties. Assuming that the most stable conformer of 2, i.e., the twisted E stereoisomer with the Me group at the equatorial position, decides the CE sign, and that the chiral ring contribution prevails over the effect of the Me group (Figure 8), a positive CE is expected, in agreement with the observed CD spectrum. The bisignate CEs shown by 3a,b at room temperature (Figure 5) point to a significant contribution from the axial conformer to the equilibrium; however, its concentration diminishes upon temperature lowering and finally the equatorial E form dominates at -185 °C, as shown by the monosignate and positive CE.

The proline ester 4, which crystallizes preferably in the Z form, equilibrates slowly in solution, affording a mixture of both Z and E stereoisomers, as the ^{1}H NMR spectra show. Simultaneously the CE magnitude decreases gradually after dissolution of 4 until the equilibrium is reached. This behavior is characteristic also for other N-nitrosoproline derivatives[2] and can be explained by our sector rule. The ester group of the Z stereoisomer occupying the positive sector contributes with the same sign as the chiral pyrrolidine ring, whereas the ester group in the E stereoisomer located in the negative sector exerts a contribution of the opposite sign to that of the ring (Figure 8). In effect, the positive and initially relatively strong CE decreases as the concentration of the E form increases.

It should be stressed that our sector rule can be applied only to the planar nitrosamine chromophore. Any twisting of the NNO moiety and pyramidal distortion of the amino nitrogen results in intrinsic chirality of the chromophore and its strong contribution to the CE (the chiral first sphere[27]). The nonplanar nitrosamine group was found in some strained ring compounds, where the CE sign follows a so-called "spiral rule".[3,28] In our case only the equatorial Z conformer of 2-substituted N-nitrosopyrrolidines exhibits marked pyramidalization of the amino nitrogen according to the MM2 calculations.

Concluding Remarks

Our CD studies of substituted N-nitrosopyrrolidines showed that knowledge of the five-membered ring geometry is extremely important for predictions of the CE sign based on sector rules. The chiral ring contribution may overweigh the effect of dissymmetrically placed substituents and determines the n–π^* CE sign. The analysis of chiroptical spectra of some compounds with rigid skeletons showed that our "lowered symmetry" sector rule[6] correctly explains the CD signs. Bisignate CD curves observed for some flexible compounds result from two or more conformers being in equilibrium and contributing with opposite signs to the CE.

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(28) Shustov, G. V.; Kadorkina, G. K.; Varlamov, S. V.; Kachanov, A. V.; Kostyanovsky, R. G.; Rauk, A. *J. Am. Chem. Soc.* **1992**, *114*, 1616–1623.

11416 *J. Am. Chem. Soc., Vol. 115, No. 24, 1993*

Połoński et al.

Table IV. Force Field Parameters[a]

Natural Bond Lengths and Stretching Constants

bond	l_o, Å	k, mdyn/Å	dipole, D
1–9	1.46	4.23	0.9
9–9	1.34	8.08	4.46
7–9	1.235	13.06	4.48

Natural Bond Angles and Bending Constants[b]

angle	θ_o, deg	k_θ, mdyn Å rad^{-2}
1–9–1	123.2	0.63
1–9–9	120.0	0.29
5–1–9	108.5	0.36
1–1–9	109.5	0.50
9–9–7	113.6	1.55

Torsional Parameters (kcal/mol)

torsional angle	V_1	V_2	V_3
1–9–9–7	0.0	7.7	0.0
9–1–1–5	0.0	0.0	0.52
1–1–1–9	0.4	0.2	0.52
1–1–9–1	0.0	0.0	0.46
9–9–1–5	0.0	0.0	–0.20

[a] MM2 atom types are used: $1 = C_{sp^3}$, $5 = H$, $9 = N_{sp^2}$, $7 = O$ (NO group). [b] Out of plane bending constant for 9–9–X angles = 0.05.

Methods

The molecular mechanics calculations were performed using the MM2 program of Allinger and Yuh,[16] employing their force field for the hydrocarbon part of the molecules. Some additional parameters, which pertain to bond lengths, bond angles, and torsional angles, involving the NNO functional group, needed to deal with *N*-nitrosamines, were settled upon and are given in Table IV. We have assigned a value of 7.7 kcal/mol to the V_2 torsional parameter for the N–N bond on the basis of the barrier to rotation about this bond (ca. 23 kcal/mol).[29] Some other parameters involving the N_{sp^2} atom and the cyclopropane ring atoms were taken from the set used for azoalkanes[30] and the MMX program,[31] respectively. The remaining stretching and bending parameters for the NNO moiety were estimated according to the procedure of Pearlstein and Hopfinger,[17] where the corresponding potential energy functions for the *N*-nitrosodimethylamine molecule, taken as a model, were calculated by the MNDO method.[32] The corresponding minimum energy bond lengths and angles were taken from the gas-phase structure of the above compound assigned by the electron diffraction method.[33] Bond dipole moments were estimated from the point charges calculated by the *ab initio* SCF method.[34] The MM2 calculations showed that introduction of the lone pair on the N_{sp^2} atom into the force field does not influence significantly the resulting geometries.

Experimental Section

CD spectra were recorded on a JASCO J-20 spectropolarimeter. Low-temperature CD was measured in ethyl ether–isopentane–ethanol (5:5:2 v/v/v (EPA)) on a Jouan Dichrograph II. UV measurements were performed on a Beckman 3600 spectrophotometer. ¹H and ¹³C NMR spectra were determined with a Bruker MSL-300 spectrometer operating at 300 and 75 MHz, respectively, and on a Bruker AM-500 instrument (500 MHz). The synthesis of compounds 3a,b was described earlier,[4] and nitrosamines 5 and 6 were prepared according to literature methods.[9] Compounds 7–11 were obtained by LiAlH₄ or [(MeOCH₂CH₂O)₂AlH₂]·Na (Red-Al, Aldrich) reduction of corresponding imides of the known absolute configuration[35,36] followed by N-nitrosation with HNO₂.

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(*S*)-N-Nitrosoproline *tert*-Butyl Ester (4). To a solution of (*S*)-proline *tert*-butyl ester hydrochloride[37] (0.6 g, 2.9 mmol) and NaNO₂ (0.62 g, 9 mmol) in water (2 mL) was added one drop of concentrated hydrochloric acid at 0 °C. After standing for 10 min at 0 °C, the product was extracted with benzene, dried (MgSO₄), evaporated to dryness, and crystallized from toluene–hexane: yield 0.43 g (74%); mp 75 °C; [α]²⁰₅₇₈ –138° (*c* 2, C₆H₆); ¹H NMR (CDCl₃) (immediately after dissolution) δ 4.5–4.3 (complex m, 3 H), 2.35–2.1 (complex m, 2 H), 2.05 (m, 2 H), 1.44 (s, 9 H, CMe₃); ¹H NMR (CDCl₃) (3 h after dissolution, equilibrated sample) δ 5.16 (dd, *J* = 3.3 and 7.6 Hz, 0.4 H, (*E*)-H-2), 4.48–4.30 (complex m, 1.8 H, (*Z*)-H-2 + (*E*)-H-5), 3.75–3.58 (complex m, 0.8 H, (*Z*)-H-5), 2.35–2.13 (complex m, 2 H), 2.10–1.96 (complex m, 2 H), 1.48 (s, 3.6 H, (*E*)-CMe₃), 1.44 (s, 5.4 H, (*Z*)-CMe₃).

Anal. Calcd for C₉H₁₆N₂O₃: C, 53.99; H, 8.05; N, 13.99. Found: C, 54.08; H, 8.07; N, 14.25.

(1*S*,2*S*,6*R*,7*R*)-2-Methyl-4-azatricyclo[5.2.1.0²,⁶]decane. To a solution of (1*S*)-2-methyl-*endo,endo*-bicyclo[2.2.1]heptane-2,3-dicarboximide[35] (0.80 g, 4.5 mmol) in THF (10 mL) was added LiAlH₄ (1.0 g), and the mixture was refluxed for 12 h. A standard workup gave the title amine, which was converted into the hydrochloride: yield 0.56 g (66%); mp 218–219 °C (CCl₄); [α]²⁴₅₄₆ –3.5° (*c* 4, CHCl₃); ¹H NMR (CDCl₃) 10.16 (br s, 1 H, ⁺NH₂), 8.96 (br s, 1 H, ⁺NH₂), 3.43 (m, 1 H), 3.31 (m, 2 H), 2.87 (m, 1 H), 2.28 (m, 2 H), 2.02 (s, 1 H), 1.84 (m, 1 H), 1.75–1.45 (complex m, 5 H), 1.24 (s, 3 H, Me); ¹³C NMR (CDCl₃) δ 52.05, 51.96, 50.16 (C-2), 46.67, 45.70, 41.50, 27.57, 23.79, 21.72.

Anal. Calcd for C₁₀H₁₈NCl: C, 63.99; H, 9.66; N, 7.46. Found: C, 63.92; H, 9.91; N, 7.41.

(1*S*,2*S*,6*R*,7*R*)-N-Nitroso-2-methyl-4-azatricyclo[5.2.1.0²,⁶]decane (7) was obtained from the above amine by N-nitrosation with HNO₂: mp 104–105 °C (after sublimation); [α]²¹₅₇₈ –20.4° (*c* 0.88, cyclohexane); ¹H NMR (500 MHz, CDCl₃) δ 4.71 (dd, *J* = 13.3 and 1.4 Hz, 0.5 H, (*E*)-H-3), 4.54 (ddd, *J* = 13.3 and 1.6 Hz, 0.5 H, (*E*)-H-5), 4.48 (dd, *J* = 15.1 and 1.4 Hz, 0.5 H, (*Z*)-H-3), 4.29 (ddd, *J* = 15.0 and 1.6 Hz, 0.5 H, (*Z*)-H-5), 4.03 (dddd, *J* = 13.3, 8.8, and 1.6 Hz, 0.5 H, (*E*)-H-5), 3.60 (m, *J* = 13.3 Hz, 0.5 H, (*E*)-H-3), 3.06 (dddd, *J* = 15.1, 8.8, and 1.6 Hz, 0.5 H, (*Z*)-H-5), 2.64 (m, *J* = 15.1 Hz, 0.5 H, (*Z*)-H-3), 2.39 (m, 0.5 H), 2.23 (m, 0.5 H), 2.16 (complex m, 1 H, H-6), 2.09 (m, 0.5 H), 1.95 (m, 0.5 H), 1.75 (m, 1 H), 1.5–0.85 (complex m, 5 H), 1.22 (s, 1.5 H, (*E*)-Me), 1.19 (s, 1.5 H, (*Z*)-Me).

Anal. Calcd for C₁₀H₁₆N₂O: C, 66.64; H, 8.95; N, 15.54. Found: C, 66.94; H, 9.01; N, 15.32.

(1*S*,2*S*,6*R*,7*S*)-2-Methyl-4-azatricyclo[5.2.1.0²,⁶]decane was obtained by LiAlH₄ reduction of (1*S*)-2-methyl-*exo,exo*-bicyclo[2.2.1]heptane-2,3-dicarboximide[35] and converted into the hydrochloride: mp 183–185 °C (CCl₄); [α]²²₅₄₆ +8.6° (*c* 5, CHCl₃); ¹H NMR (CDCl₃) δ 9.56 (br s, 2 H, ⁺NH₂), 3.62 (m, 1 H, CHN), 3.12 (m, 1 H, CHN), 2.86 (m, 1 H, CHN), 2.70 (m, 1 H, CHN), 2.05 (d, *J* = 4.6 Hz, 1 H), 2.00 (d, *J* = 4.1 Hz, 1 H), 1.70 (t, 1 H), 1.57 (m, 3 H), 1.35 (m, 1 H), 1.23 (s, 3 H, Me), 1.20 (m, 1 H), 1.06 (m, 1 H); ¹³C NMR (CDCl₃) δ 56.85, 53.11, 50.78, 49.25 (C-2), 44.24, 40.78, 34.58, 26.74, 23.34, 22.97.

Anal. Calcd for C₁₀H₁₈NCl: C, 63.99; H, 9.66; N, 7.46. Found: C, 63.91; H, 9.81; N, 7.55.

(1*S*,2*S*,6*R*,7*S*)-N-Nitroso-2-methyl-4-azatricyclo[5.2.1.0²,⁶]decane (8) was obtained by N-nitrosation of the above amine with HNO₂: oil; [α]²²₅₄₆ –16.3° (*c* 2.8, MeOH); ¹H NMR (500 MHz, CDCl₃) δ 4.59 (dddd, *J* = 13.3, 9.4, and 1.3 Hz, 0.5 H, (*E*)-H-5), 4.21 (m, *J* = 13.3 Hz, 0.5 H, (*E*)-H-3), 4.1–4.0 (complex m, 1.5 H, (*E*)-H-5 + (*E*)-H-3 + (*Z*)-H-5), 3.50 (AB system, *J* = 15.4 Hz, 1 H, (*Z*)-H-3), 3.25 (dddd, *J* = 15.5, 4.3, and 1.4 Hz, 0.5 H, (*Z*)-H-5), 2.20 (m, 2 H, H-1 + H-7), 1.82 (m, 0.5 H, (*E*)-H-6), 1.69 (m, 0.5 H, (*Z*)-H-6), 1.65–1.1 (complex m, 6 H), 1.24 (s, 1.5 H, (*E*)-Me), 1.16 (s, 1.5 H, (*Z*)-Me).

Anal. Calcd for C₁₀H₁₆N₂O: C, 66.64; H, 8.95; N, 15.54. Found: C, 66.78, H, 9.12; N, 15.48.

(1*S*,5*R*)-1-Methyl-3-azabicyclo[3.1.0]hexane was obtained by reduction of (1*S*,2*R*)-1-methyl-1,2-cyclopropanedicarboximide[36] with Red-Al (Aldrich) in toluene and converted into the oxalate: mp 158–160 °C (EtOH); [α]²¹_D –8° (*c* 1, MeOH); ¹H NMR (DMSO-d₆) δ 9.03 (br s, 2 H, ⁺NH₂), 3.45–3.1 (complex m, 4 H), 1.51 (q, *J* = 3.9, Hz, 1 H, H-5), 1.34 (s, 3 H, Me), 0.79 (m, 1 H, H-6), 0.67 (m, 1 H, H-6); ¹³C NMR (MeOD) δ 165.67 (CO), 51.57, 48.22, 23.51 (C-1), 21.99, 16.85, 13.09.

Anal. Calcd for C₈H₁₃NO₄: C, 51.33; H, 7.00; N, 7.48. Found: C, 51.28; H, 7.13; N, 7.29.

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(1S,5R)-N-Nitroso-1-methyl-3-azabicyclo[3.1.0]hexane (9) was obtained by N-nitrosation of the above amine with HNO_2: oil; $[\alpha]^{21}_{546}$ −28.9° (c 0.9, C_6H_6); ^{1}H NMR (C_6D_6) δ 4.07 (d, J = 11.6 Hz, 0.5 H, (E)-H-2), 4.01 (d, J = 11.7 Hz, 0.5 H, (E)-H-2), 3.92 (d, J = 13.8 Hz, 0.5 H, (Z)-H-2), 3.84 (d, J = 13.9 Hz, 0.5 H, (Z)-H-2), 3.70 (ddd, J = 11.7, 4.5, and 1.0 Hz, 0.5 H, (E)-H-4), 3.48 (ddd, J = 11.6 and 1.2 Hz, 0.5 H, (E)-H-4), 2.94 (dddd, J = 13.8, 4.6, and 1.2 Hz, 0.5 H, (E)-H-4), 2.72 (ddd, J = 13.8 and 1.3 Hz, 0.5 H, (E)-H-4), 0.79 (s, 1.5 H, (E)-Me), 0.76 (s, 1.5 H, (Z)-Me), 0.70 (m, 1 H, H-5), 0.19 (m, 1 H, H-6), −0.20 (dd, J = 5.5 and 4.6 Hz, 1 H, H-6).

Anal. Calcd for $C_6H_{10}N_2O$: C, 57.12; H, 7.99; N, 22.20. Found: C, 57.01; H, 8.05; N, 22.02.

(1S,5R)-1-Phenyl-3-azabicyclo[3.1.0]hexane was obtained by LiAlH$_4$ reduction of (1S,2R)-1-phenyl-1,2-cyclopropanedicarboximide[36] and converted to the hydrochloride: mp 170–172 °C; $[\alpha]^{20}_D$ −73° (c 3, CHCl$_3$) [lit.[38] mp 170–172 °C; $[\alpha]^{25}_D$ −67° (c 1, MeOH)]; ^{1}H NMR (CDCl$_3$) 10.20 (br s, 1 H, $^+$NH), 9.74 (br s, 1 H, $^+$NH), 7.26 (m, 5 H, Ph), 3.90–3.55 (complex m, 4 H), 1.94 (m, 1 H, H-5), 1.59 (dd, J = 4.6 and 6.5 Hz, 1 H, H-6), 1.20 (m, 1 H, H-6); δ ^{13}C NMR (CDCl$_3$) δ 137.99, 128.70, 127.21, 127.01, 50.65, 47.53, 31.22 (C-1), 23.04, 15.46.

(1S,5R)-N-Nitroso-1-phenyl-3-azabicyclo[3.1.0]hexane (10) was obtained by N-nitrosation of the above amine with HNO_2: oil; $[\alpha]^{20}_D$ −162° (c 2.6, CHCl$_3$); ^{1}H NMR (C_6D_6) δ 7.09 (m, 2.5 H, (E)-Ph), 6.75 (m, 2.5 H, (Z)-Ph), 4.38 (d, J = 11.7 Hz, 0.5 H, (E)-H-2), 4.32 (d, J = 13.7 Hz, 0.5 H, (Z)-H-2), 4.07 (d, J = 11.7 Hz, 0.5 H, (Z)-H-2), 3.99 (d, J = 13.8 Hz, 0.5 H, (Z)-H-2), 3.87 (dd, J = 11.6 and 1.2 Hz, 0.5 H, (E)-H-4), 3.62 (ddd, J = 11.7, 4.4, and 0.8 Hz, 0.5 H, (E)-H-4), 3.15 (ddd, J = 13.8 and 1.1 Hz, 0.5 H, (Z)-H-4), 2.89 (ddd, J = 11.7, 4.4, and 1.1 Hz, 0.5 H, (E)-H-4), 1.12 (m, 1 H, H-5), 0.62 (m, 1 H, H-6), 0.10 (t, J = 5.2 Hz, H-6).

Anal. Calcd for $C_{11}H_{12}N_2O$: C, 70.19; H, 6.43; N, 14.88. Found: C, 70.16; H, 6.49; N, 14.78.

(1R,5R)-1-Isopropyl-3-azabicyclo[3.1.0]hexane was obtained by reduction of (1R,2R)-1-isopropyl-1,2-cyclopropanedicarboximide[36] with Red-Al (Aldrich) and converted into the oxalate: mp 142–143 °C (EtOH); $[\alpha]^{22}_{546}$ −25° (c 1, MeOH); ^{1}H NMR (DMSO-d_6) δ 8.90 (br s, 2 H, $^+$NH$_2$), 3.31 (m, 4 H), 1.75 (sep, J = 6.9 Hz, 1 H, CHMe$_2$), 1.59 (m, 1 H, H-5), 1.04 (d, 1 H, J = 6.8 Hz, 3 H, Me), 0.95 (d, J = 6.9 Hz, 3 H, Me), 0.73 (m, 2 H, H-6); ^{13}C NMR (MeOD) δ 165.57 (CO), 48.38, 48.15, 33.53 (C-1), 30.35, 20.28, 19.33, 19.23, 11.08.

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Anal. Calcd for $C_{10}H_{17}NO_4$: C, 55.80; H, 7.96; N, 6.51. Found: C, 55.72; H, 7.98; N, 6.53.

(1R,5R)-N-Nitroso-1-isopropyl-3-azabicyclo[3.1.0]hexane (11) was obtained by N-nitrosation of the above amine with HNO_2: mp 25–26 °C (pentane); $[\alpha]^{22}_{546}$ −88° (c 0.5, CH$_2$Cl$_2$); ^{1}H NMR (CDCl$_3$) δ 4.48 (d, J = 12.1 Hz, 0.5 H, (E)-H-2), 4.44 (d, J = 12.1 Hz, 0.5 H, (E)-H-2), 4.30 (ddd, J = 12.0, 4.4, and 1.0 Hz, 0.5 H, (E)-H-4), 4.18 (ddd, J = 12.0 and 1.3 Hz, 0.5 H, (E)-H-4), 4.04 (d, J = 14.3 Hz, 0.5 H, (Z)-H-2), 4.01 (d, J = 14.3 Hz, 0.5 H, (Z)-H-2), 3.37 (dddd, J = 14.3, 4.6, and 1.2 Hz, 0.5 H, (Z)-H-4), 3.27 (ddd, J = 14.3 and 1.4 Hz, 0.5 H, (Z)-H-4), 1.62 (sep, J = 6.9 Hz, 0.5 H, (E)-CHMe$_2$), 1.59 (sep, J = 6.8 Hz, 0.5 H, (Z)-CHMe$_2$), 1.48 (q, J = 4.1 Hz, 0.5 H, (E)-H-5), 1.41 (q, J = 4.1 Hz, 0.5 H, (Z)-H-5), 1.04 (d, J = 6.9 Hz, 1.5 H, (E)-CHMe$_2$), 0.98 (d, J = 6.8 Hz, 1.5 H, (Z)-CHMe$_2$), 0.89 (d, J −= 6.9 Hz, 1.5 H, (Z)-CHMe$_2$), 0.82 (m, 1 H, H-6), 0.21 (dd, J = 5.6 and 4.1 Hz, 1 H, H-6).

Anal. Calcd for $C_8H_{14}N_2O$: C, 62.31; H, 9.15; N, 18.17. Found: C, 62.11; H, 9.28; N, 18.02.

Crystal Structure Determination. The (R)-6 monocrystals were obtained by slow evaporation of the heptane solution. The sample was closed in a thin-wall quartz capillary to avoid sublimation. The unit-cell parameters were determined by a least-squares fitting to the setting angles of 25 automatically centered reflections (2θ in the range 10–21°). The reflection intensities were measured on a KM-4 diffractometer with graphite-monochromated irradiation. The 2θ–θ scan mode and variable scan speed depending on reflection intensity (1.9–24.0 deg/min) were used. Only Lorentz and polarization corrections were applied. No systematic variation in intensity was observed. The structure was solved by direct methods using the SHELXS-86 program[39] and refined by a full-matrix least-squares method with the SHELX-76 program.[40] The hydrogen atom positions were calculated from the molecular geometry.

Supplementary Material Available: Tables of X-ray crystallographic data for (R)-6 including details of data collection, atomic coordinates, bond lengths and angles, and anisotropic thermal parameters (3 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS. Ordering information is given on any current masthead page.