Stereochemistry and chiroptical properties of 1,3-dialkylaziridinones (α-lactams). Chiral rules for the nonplanar amide chromophore

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Structural features, configurational stability, and chiroptical properties of the nonplanar amide group in α-lactams were investigated by means of ab initio (6-31+G*) molecular orbital calculations on (1*R*)-aziridinone **1**, (1*R*)-1-methylaziridinone **2**, (1*R*,3*R*)-3-methylaziridinone **3**, (1*R*,3*R*)-1,3-dimethylaziridinone **4*a***, its *cis* diastereomer (1*S*,3*R*)-1,3-dimethylaziridinone **4*b***, and (1*R*,3*R*)-3-*tert*-butyl-1-methylaziridinone **5**, and by experimental CD spectra of 1-*tert*-butyl- and 1-(1′-adamantyl)-substituted 3(*R*)-3-*tert*-butylaziridinones **6** and **7**. The nitrogen inversion barriers of **4*a*** and **4*b*** are 2.8 and 1.6 kcal mol^{-1}, respectively. The lowest excited singlet state of all of the aziridinones is a valence state (the n_O–π_{CO}* transition); the second is a Rydberg state (the n_N–3*s* transition). The signs of the first and second Cotton effects in the CD spectra of the compounds **6** and **7** coincide with the calculated ones for **1** and **2** and the *trans* isomers **3**, **4*a***, and **5**. According to the calculated and experimental data for aziridinones **1–7** as well as to the well-known data for other nonplanar amides, the sign of the first Cotton effects is determined by the intrinsic chirality of the nonplanar amide chromophore and obeys a spiral rule. For cases where the chromophore has the conformation around the N—C(O) bond, which is close to the antiperiplanar, a reverse octant rule is proposed.

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On a étudié les caractéristiques structurales, la stabilité configurationelle et les propriétés chiroptiques du groupe amide non planaire des α-lactames en faisant appel à des calculs d'orbitales moléculaires ab initio au niveau (6-31+G*) sur la (1*R*)-aziridinone **1**, la (1*R*)-1-méthylaziridinone **2**, la (1*R*,3*R*)-3-méthylaziridinone **3**, la (1*R*,3*R*)-1,3-diméthylaziridinone **4*a*** ainsi que son diastéréoisomère *cis*, la (1*S*,3*R*)-1,3-diméthylaziridinone **4*b*** et la (1*R*,3*R*)-3-*tert*-butylazirinidone **5** et à des expériences de dichroïsme circulaire (DC) sur 1-*tert*-butyl- et 1-(1′-adamantyl)-(3*R*)-3-*tert*butylaziridinones **6** et **7**. Les barrières à l'inversion de l'azote pour les composés **4*a*** et **4*b*** sont respectivement de 2,8 et 1,6 kcal mol^{-1}. L'état singulet excité le plus bas pour toutes les aziridinones est un état de valence (la transition n_O–π_{CO}*) et le deuxième est un état de Rydberg (la transition n_N–3*s*). Les signes des premier et deuxième effets Cotton (EC) observés dans les spectres de DC des composés **6** et **7** coïncident avec ceux calculés pour **1** et **2** et les isomères *trans* **3**, **4*a*** et **5**. Sur la base des données expérimentales et calculées pour les aziridinones **1–7** ainsi que les données bien connues pour d'autres amides non planaires, le signe du premier EC est déterminé par la chiralité intrinsèque du chromophore de l'amide non planaire et il obéit à la règle de la spirale. Dans les cas où la conformation autour de la liaison N—C(O) du chromophore est pratiquement anti-périplanaire, on propose une inversion de la règle de l'octant.

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Introduction

A nonplanar amide group is contained in β-lactam antibiotics (1) and found in peptides (2). Unusual chemical and spectroscopic properties associated with the group, as well as the potential pharmacological activity of nonplanar amides, have attracted a great deal of attention (3). Most recently, these compounds were used for modelling the action of proteolitic fermenting reagents (4*a*), with respect to the problem of the origin of rotation barriers (4*b*), and as effective chiral reagents (4*c*). Hence there is great importance to recognition of the presence of the nonplanar amide group and to the determination of the absolute stereochemistry of compounds containing it. Both problems can be solved simultaneously by means of CD spectroscopy on the basis of the wavelength of the first (long wavelength) Cotton effect (CE) (3*a*) and using chiral rules connecting the sign of the CE with the stereochemistry of a molecule (3*a*, 5). It goes without saying that for the confident application of these rules and for the establishment of their limits, it is necessary to study the chiroptical properties of as a wide a range of nonplanar amides as possible. From this standpoint, 1,3-dialkylaziridinones (α-lactams), obtained earlier (6) in optical active form, are of special interest. The pyramidal configuration of the nitrogen atom and, therefore, the nonplanarity of the amide group in the ground state of α-lactams are established by X-ray diffraction (7) and confirmed by quantum chemical calculations (3*c*, 8). Weakening of the amide conjugation follows from the data of IR (3*a*, 3*c*, 9*a*), UV (9*b*), and PE spectra (9*a*, 9*c*).

A peculiarity of α-lactams, in comparison with other nonplanar amides, is incorporation of the N—C(O) amide bond into the strained three-membered ring. In the present work, an attempt to elucidate an influence of this peculiarity on the stereochemistry and the chiroptical properties of the amide chromophore was undertaken. For this purpose, ab initio quantum chemical calculations have been carried out on a series of aziridinones, including the parent molecule **1**, *N*-methylaziridinone **2**, (3*R*)-3-methylaziridinone **3**, the *cis* and *trans* isomers of (3*R*)-1,3-dimethylaziridinone **4*a*** and **4*b***, and (3*R*)-1-methyl-3-*tert*-butylaziridinone **5**. The structure of the transition state to nitrogen inversion in **4**, **4-TS**, was also determined. For all compounds, the theoretical chiroptical properties were calculated. Experimentally, the CD spectra of two (3*R*)-1,3-dialkylaziridinones, **6**, and **7**, have been studied. The compounds **6** and **7**

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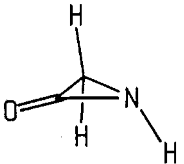

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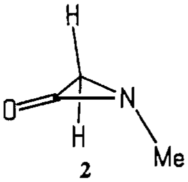

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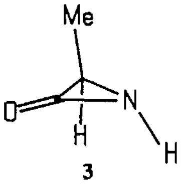

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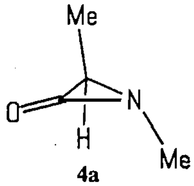
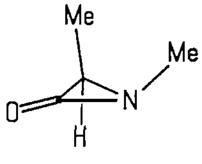
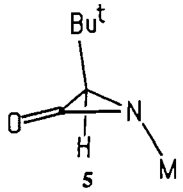


4a

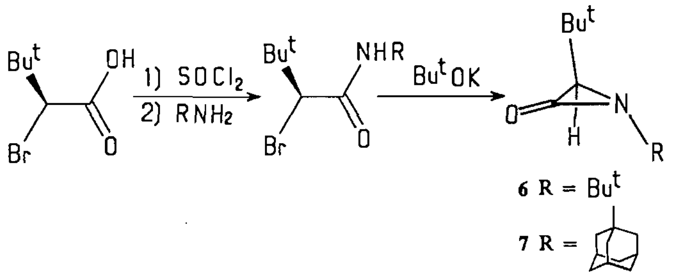


4b



5

were obtained by cyclization of the corresponding amides of (*S*)-α- bromo-3,3-dimethylbutyric acid (Scheme 1). The (*R*)-absolute configuration at the C3 atom of aziridinones **6** and **7** follows from the stereochemistry of the cyclization.

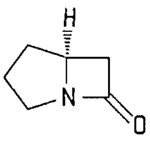


6 R = Bu^t

7 R =

SCHEME 1

The possibilityof the application of a spiral rule (3*a*, 5) and a reverse octant rule (5*b*) to different instances of the nonplanar amide chromophore have been analyzed on the basis of the present aziridinone study, as well as by existing data on the chiroptical properties of other relatively rigid nonplanar amides, i.e., (1*S*,4*R*)-1-azabicyclo[3.2.0]heptan-7-one **8** (10*a*) (1*R*,5*R*)-1-azabicyclo[3.3.1]nonan-2-one **9** (10*b*), and (1*R*,4*S*)-6,6-dimethyl-1-azabicyclo[2.2.2]octan-2-one **10** (footnote 2).



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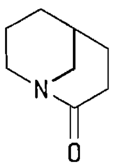

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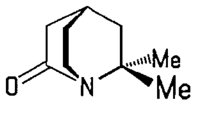

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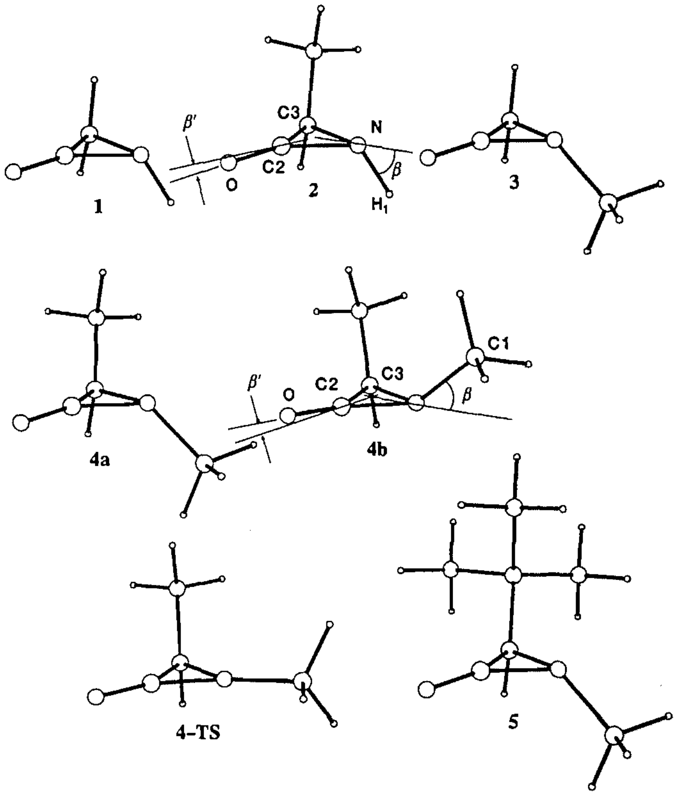

FIG. 1. Structures optimized at the 6-31 + G* level. Selected structural parameters (bond lengths in Å, bond angles in degrees) in the order **1**, **2**, **3**, **4***b*, **4-TS**, **5**, respectively: O—C2, 1.179, 1.181, 1.183, 1.184, 1.186, 1.190, 1.185; N—C2, 1.346, 1.349, 1.331, 1.334, 1.326, 1.297, 1.335; C2—C3, 1.456, 1.456, 1.462, 1.461, 1.465, 1.487, 1.460; N—C3, 1.497, 1.500, 1.485, 1.488, 1.491, 1.462, 1.488; $\angle$OC3N, 143.8, 143.3, 144.2, 143.6, 144.0, 145.9, 143.4; $\angle$OC2C3, 151.4, 151.8, 151.2, 151.6, 150.9, 151.1, 151.9; β, 51.0, 43.3, 50.9, 43.3, 38.6, 44.0; β′, 3.5, 4.5, 3.2, 4.4, 5.1, 0.7, 4.6. Relative energies (kcal mol^{-1}): **4***a*, 0.0; **4***b*, 1.2; **4-TS**, 2.8.

Results and discussion

Ab initio calculations were carried out earlier (3*c*, 8*b*) only for the parent aziridinone **1**, and only for its stationary states. We have carried out calculations on the parent, as well as on a number of alkylsubstituted aziridinones (Fig. 1). In particular, (3*R*)-1,3-dimethylaziridinone **4** and (3*R*)-1-methyl-3-*tert*-butylaziridinone **5** are more realistic models of the obtained α-lactams, which are stable only with N and C3 substituents (6, 11). Owing to constraints imposed by the small ring, the nitrogen atom has a pyramidal configuration in the ground state of aziridinones and, together with the carbonyl, forms the intrinsically chiral nonplanar amide group (Fig. 1). The out-of-plane angle (β, Fig. 1) is 51° for the two N—H aziridinones **1** and **3**, and 43°, 43°, and 44° for the *N*-methyl and *trans*-dialkylaziridinones **2**, **4***a*, and **5**, respectively. The nitrogen pyramid in the *cis*-dimethylaziridinone **4***b* is more flattened (β = 39°) owing to steric repulsion of the methyl groups. Even the modest flattening of the nitrogen pyramid in the *cis* isomer **4***b* leads to strengthening of the $n_{N}-\pi_{CO}^{*}$ amide conjugation that is expressed in some shortening of the N—C(O) bond (−0.008 Å). Only a slight lengthening of the C═O bond (+0.002 Å) is calculated. The largest change of the bond lengths along this line is observed at reaching the nitrogen inversion transition state **4-TS**, which has the maximum amide conjugation. Nevertheless, even in the transition state **4-TS**, the nitrogen arrangement is not exactly planar (β = 2°), a consequence of the nonsymmetrical substitution at the C3 atom. The methyl group at the nitrogen atom has the *cis* orientation with respect to the methyl group at C3. Thus, the transition state **4-TS** is closer to the *cis* isomer **4***b* than to *trans*-**4***a* on the inversion coordinate.

It is of interest to note the nonplanarity of the carbonyl C2 atom in all of the computed structures, the distortion from planarity being always to the same side of the ring as the

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[2] P. Malon, private communication.

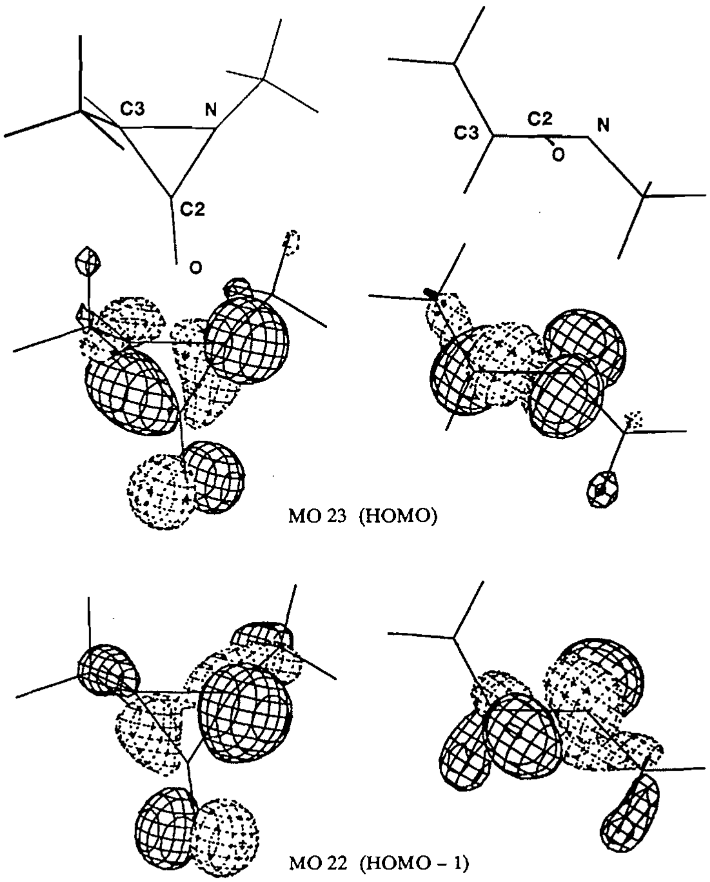


FIG. 2. The two upper occupied MOs involved in the electronic transitions of aziridinone 4*a*. Contour values, 0.075.

N-substituent or *anti* to the orientation of the N lone pair. It can be supposed that the nonplanarity of the C2 atom is connected with the asymmetrical environment on the side of the nitrogen atom or rather with the sp^n hybridization of the nitrogen lone electron pair, but not with the effect of the C2 atom insertion into the three-membered ring, because the transition to **4-TS** with almost planar nitrogen arrangement and with almost pure *p*-character of the nitrogen lone pair leads to the virtually complete flattening of C2 atom ($\beta' = 0.7°$ in **4-TS**). It is well known that in three-membered rings an overlapping of *cis*-oriented vicinal sp^n orbitals (the dihedral angle between the orbital axes is 0°) is more than the overlap of *trans*-oriented orbitals (12) (the dihedral angle is about 110°). Therefore, the *cis* orientation of the carbonyl with respect to the *N*-methyl group in compounds **1–5** is as expected for maximum n_N–π_{CO}* overlap.

The inequality of the outer valence angles at the carbonyl C2 atom, which is more pronounced than observed for other lactams (13), is a general structural feature of aziridinones. Evidently, as also observed elsewhere (13), the positive difference $\angle$C3C2O − $\angle$NC2O = 7.8 ± 0.9° in the valence angles (Fig. 1) is caused by the interaction of the nonbonding n_O orbital of the carbonyl oxygen with the Walsh orbitals of the aziridinone ring: a destabilizing interaction with the occupied orbital of the C2—C3 bond and a stabilizinginteraction with the antibonding orbital of the C2—N bond. An admixture of the Walsh orbitals with the n_O orbital in MO 23 (HOMO) and MO 22 (HOMO-1) may be seen on Fig. 2.

The nitrogen inversion barriers were determined for the *trans* and *cis* isomers of 1,3-dimethylaziridinone (4*a* and 4*b*). The barriers, 2.8 kcal mol^{-1} and 1.6 kcal mol^{-1}, which should be typical for 1,3-dialkylaziridinones, in general, are less than that calculated for *N*-formylaziridine (≈6 kcal mol^{-1}) (5*a*). Undoubtedly in both the cases (aziridinone **4** and *N*-formylaziridine), the stabilization of the inversion transition state by the n_N–π_{CO}* amide conjugation is the main reason of the low pyramidal stability of the nitrogen atom, as is the case with unstrained amides. A characteristic feature of the electronic structure of the *N*-acylaziridine moiety, namely a stabilizing interaction between the π_{CO}* orbital and an occupied Walsh orbital of the ring, may be responsible for the higher barrier to inversion in *N*-acylaziridines. This interaction is not available in any conformation of aziridinones or in the (nearly) planar transition state to inversion in the *N*-acyl compounds.

Thus, the nonplanar amide group in α-lactams is more configurationally labile than in *N*-acylaziridines. However, unlike the latter, the inversion of the intrinsic chirality of this group is carried out only by the nitrogen inversion path and can be effectively controlled by the steric interaction of substituents at the N and C3 atoms. Indeed, assuming $\Delta S^0 = 0$, the calculated difference in energies of the *trans* and *cis* isomers **4***a* and **4***b* (Fig. 1) gives their ratio 88.7:11.3. Although we did not pursue the point with **5** because of its size, it is reasonable to expect that in the case of more bulky *tert*-alkyl N and C substituents in aziridinones **6** and **7**, the equilibrium is shifted completely towards the *trans* isomer.

An intense negative band of the dichroic absorption is observed in the 250-nm region of the CD spectra of (3*R*)-aziridinones **6** and **7** (Table 1, Figs. 3 and 4). The band sign coincides with the calculated sign for the CE of the first (lowest energy) electronic transition of each of the aziridinones investigated theoretically, with the exception of the *cis* diastereomer **4b** (Table 2). Aziridinones **1** and **2** do not possess an asymmetric carbon atom, but the sense of twist of the α-lactam chromophore is the same as in **3**, **4***a*, and **5**, and opposite to that found in **4***b*. The (3*R*)-*cis* isomer **4***b* has the rotational strength of the first transition with opposite sign. Therefore, the first CE sign in the CD spectra of aziridinones is determined only by the nitrogen configuration. The latter determines the chirality of the whole amide group. Right-spiral chirality (positive torsion O═C—N—C1 angle) corresponds to the (*S*)-absolute configuration of the nitrogen atom in aziridinones **1–3**, **4***a*, and **5**, and vice versa (**4***b*).

At first glance, there appears to be a discrepancy between the calculation and experiment in respect of the second CE of (3*R*)-*trans*-aziridinones. Thus, according to the calculation, the second CE of **4***a* and **5** has the same sign (negative) as the first CE (Table 2), while the short-wavelength part (at 200 nm) of the experimental CD spectra of aziridinones **6**, and **7** is characterized by a positive dichroic absorption (Table 1, Fig. 3). However, the moderate asymmetry of the 250-nm CD absorption band of both **6** (Fig. 3) and **7** (Fig. 4) suggests the possibility of a second negative component to the short-wavelength side of the first. Decomposition of the observed band at 250 nm in the CD and UV spectra of aziridinones **6** and **7** into their Gaussian components permits an additional CE near 230 nm, coinciding in sign with the first CE (Table 1, Fig. 4). Nevertheless, the experimental ratio of both the rotational and oscillator strengths of the first and second Gaussian components (Table 1) is significantly different from the ratio that is predicted theoretically (Table 2) for both **4***a* and **5**. It is of interest to note that the coincidence in sign between the first and second transitions is pre-

TABLE 1. Chiroptical properties[a] of aziridinones **6** and **7**

			CD and UV maxima					
			Observed		Gaussian components			
Compound	Solvent	Method	λ, nm	Δε or ε	λ, nm	Δλ, nm[b]	Δε or ε	[*R*][c] or *f*[c]
6	*n*-Heptane	CD	255	−8.946	254.9	19.1	−8.828	−31.39
					234.1	13.4	−1.558	−3.95
			205p[d]					
		UV	250	213	255	19.6	185	0.0042
					231.6	15.7	129	0.0029
	Gaseous phase	CD	251	−6.9[e]				
			195p					
	MeOH	CD	243	−6.363				
			202p					
7	*n*-Heptane	CD	254	−9.581	255.1	19.6	−9.374	−31.44
					232.8	13.3	−2.045	−5.11
		UV	251	194	254.9	20.3	181.5	0.0043
					232.9	13.1	102.5	0.0019
	MeOH	CD	243	−8.787				
			205p					

[a] Values of Δε and [*R*] are not corrected to 100% enantiomeric purity.
[b] Half-width of a Gaussian band at (1/*e*) × Δε or (1/*e*) × ε.
[c] [*R*] ≈ 1.08 × 10^{40} × *R* in CGSE; *f* in CGSE.
[d] p, positive CD but without a maximum.
[e] Δ*D*, in cm, was measured in a 1-cm cell (sensitivity, 0.002 deg/cm) at 17°C.

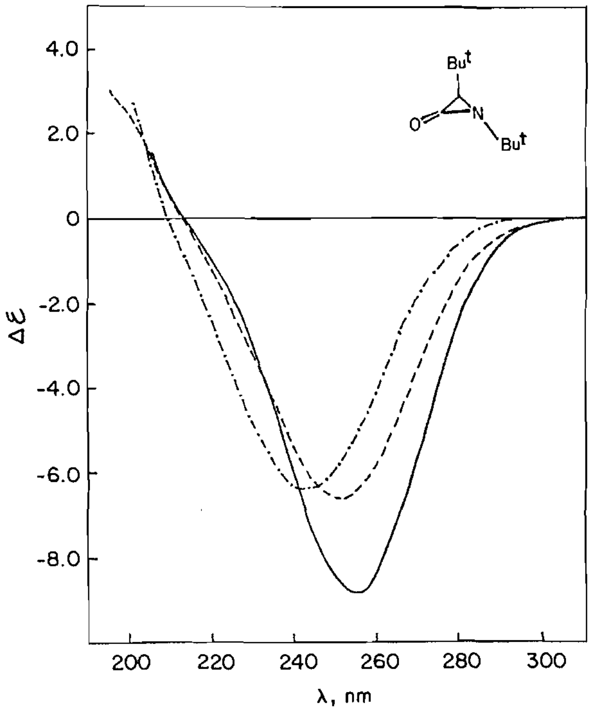
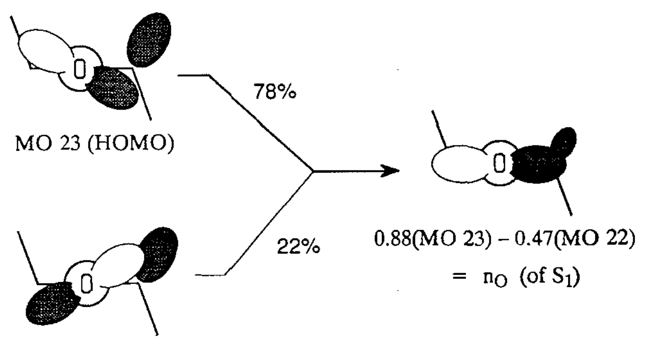


FIG. 3. The CD spectra of aziridinone **6** in heptane (—), gaseous phase (---) (see footnote *d* in Table 1), and MeOH (-·-).

dicted for the three *N*-alkylated aziridinones **2**, **4***a*, and **5**. In the case of the N—H aziridinones **1** and **3**, a strong CE of opposite sign is predicted for the second transition.

According to the calculations, only the first excited singlet state of aziridinones is a valence state. The next higher excited states have been determined as Rydberg states (Table 2). The first electronic transition is to the antibonding π_{CO}* orbital and the second one is to a diffuse orbital which may be loosely described as a molecular 3*s* orbital (Fig. 5).Unlike the Rydberg transition, the first transition is not pure in the sense that it originates from a single canonical MO. One may deduce the initial orbital of the first electronic transition (i.e., the lower singly occupied MO), by examining the configurational mixing (5*b*) which comprises the lowest excited singlet state. The state description is dominated by two sets of configurations, one with MO 23 as the initial orbital and the other with MO 22 (Fig. 2). Both sets terminate in the same MO, the π_{CO}* orbital (Fig. 5). As a result of such treatment, for example for *trans*-aziridinone **4***a* (Scheme 2), the initial orbital of the first transition is found as almost pure 2*p* orbital of the carbonyl oxygen, lying in the ring plane and containing a minimum contribution of the nitrogen orbitals. Therefore, the first electronic transition of aziridinones can be described as the $n_O \rightarrow \pi_{CO}$* transition. The low values for the computed and experimental oscillator strengths (Tables 1 and 2) are consistent with such an assignment. Thus



SCHEME 2

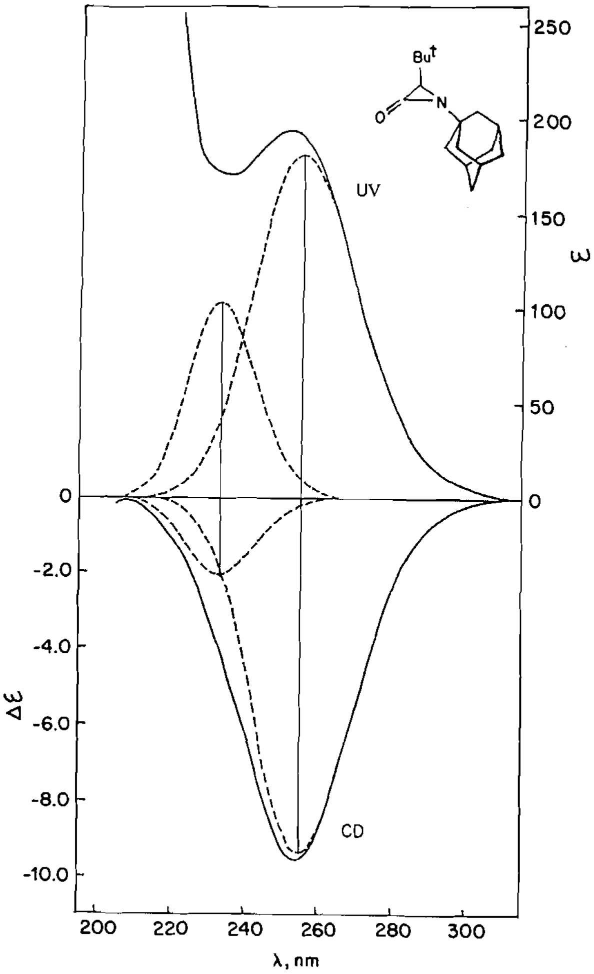


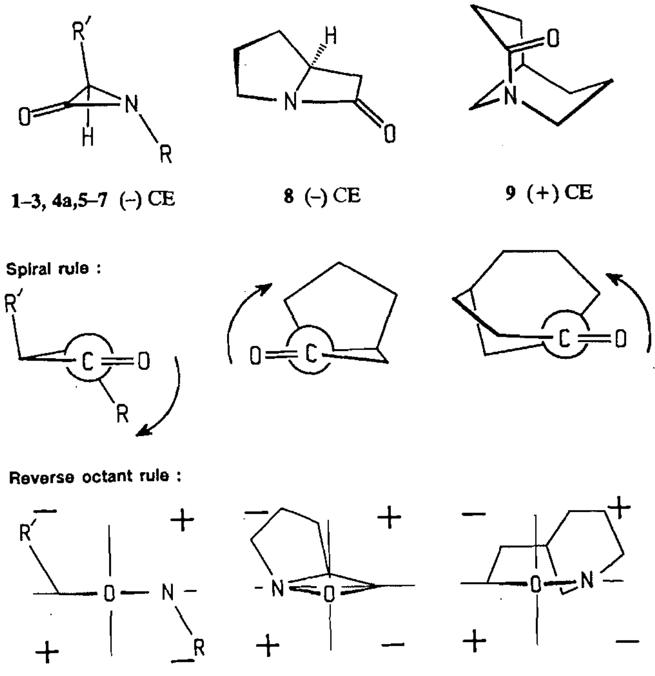
FIG. 4. The CD and UV spectra of aziridinone **7** in heptane and their Gaussian components (---).

the evident bathochromic shift (20–30 nm) of the first CE of aziridinones in comparison with usual planar amides as in the case of *N*-acylaziridines (5*a*) is caused mainly by lowering of the π_{CO}* orbital energy, owing to a weakening of the amide conjugation.

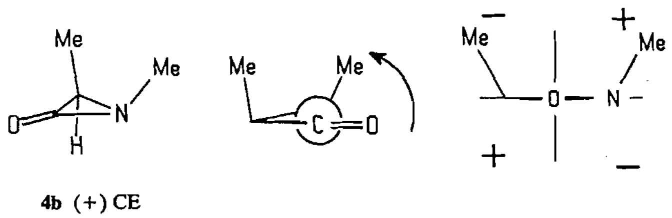
Unlike the first excited state, the second one is formed almost exclusively by electron transition from MO 23 (HOMO) which has a considerable contribution of the nitrogen lone electron pair (Fig. 2). As a whole, this orbital is similar to the n_N orbital of *N*-formylaziridine (5*a*), from which the second electronic transition is to the 3*s* orbital in this compound. The evident hypsochromic shift of the observed dichroic absorption band in the CD spectra of aziridinones **6** and **7** in MeOH in comparison with the spectra in *n*-heptane and gaseous phase (Table 1, Fig. 3) is consistent both with the participation of the heteroatom lone electron pairs in the first and second electronic transition, and with the Rydberg nature of the second. Thus, a complete analogy in the orbital origin of the lower electronic transitions is observed between 1,3-*trans*-aziridinones and *N*-acylaziridines. The same conclusion is obtained for *cis*-aziridinones **4***b*.

The quasi-symmetry of aziridinones, i.e., quasi-C_s of the *cis* isomer **4***b* and quasi-C_2 of *trans*-aziridinones **1–3**, **4***a*, and **5–7**, makes them suitable models for testing the chiral rules. It is the spiral rule (3*a*, 5) and reverse octant rule (ROR) (5*b*), which connect the first CE sign with the stereochemistry of a molecule containing the nonplanar amide chromophore. According to the first rule, the positive CE corresponds to the negative torsion O=C—N—C angle and vice versa; on the second rule, the CE sign can be predicted as in the case of the usual carbonyl chromophore (14), but with the reverse octant signs (5*b*). It is necessary to note the same $n_O \rightarrow \pi_{CO}$* orbital origin of the nonplanar amide and carbonyl chromophores. The interchangeability of the rules follows from the examination of the stereochemistry and chiroptical properties of *N*-acyl- and *N*-nitrosoaziridines, and cyclopropylketones (5*b*).

At first glance one can come to the same conclusion in the cases of (3*R*)-*trans*-aziridinones **3**, **4***a*, and **5–7**, azetidinone **8**, and azabicyclooctanone **9** (in the boat–chair conformation) as shown in Scheme 3. However, an attempt to apply the ROR to (3*R*)-*cis*-aziridinone **4***b* evidently indicates a limitation of the rule, because the methyl groups at the N and C3 atoms are found in oppositely signed octants and perturbations of the groups should compensate each other, resulting in a reduced rotational strength. Nevertheless according to the calculation, the value of the rotational strength of the $n_O \rightarrow \pi_{CO}$* transition of (3*R*)-*cis*-aziridinone **4***b* is even larger in absolute magnitude than that calculated for the (3*R*)-*trans*-isomer **4***a* (Table 2). In contrast to the ROR, the spiral rule correctly connects the first CE sign with the intrinsic chirality of the chromophore in (3*R*)-*cis*-aziridinone **4***b* (Scheme 4). On the other hand, the ROR well works in the cases of azabicyclooctanone **9** (in the chair–chair conformation) and quinuclidone **10** (Scheme 5).



SCHEME 3



SCHEME 4

TABLE 2. Calculated properties of aziridinones **1**–**5**[a]

Property	**1**	**2**	**3**	**4***a*	**4***b*	**5**
E_{SCF}, hartree	−206.732 327	−245.765 652	−245.773 873	−284.806 762	−284.804 902	−401.912 249
MO energies (IP[b]), eV						
HOMO[c]	−11.1(10.0)	−10.7(9.6)	−10.8(9.73)	−10.5(9.4)	−10.4(9.4)	−10.4(9.7)
HOMO-1[c]	−12.6(11.6)	−12.0(10.8)	−12.4(11.4)	−11.8(10.7)	−11.6(10.5)	−11.7(11.1)
μ, debye	3.77	3.99	3.89	4.05	4.23	3.96
$S_0 \to S_1$ ($n_O \to \pi_{CO}{}^*$)						
ΔE, eV	6.02	6.25	6.02	6.15	6.31	6.48
$[R]^r$	−30.9	−35.0	−22.2	−22.3	37.0	−38.2
$[R]^v$	−11.1	−12.8	−2.5	−4.1	14.8	−21.4
f	0.0010	0.0024	0.0004	0.0011	0.0043	0.0041
$S_0 \to S_2$ ($n_N \to 3s$)						
ΔE, eV	7.89	7.98	7.87	7.97	7.82	8.12
$[R]^r$	41.0	−31.5	15.1	−24.83	−3.9	−42.6
$[R]^v$	29.9	−21.2	9.8	−16.7	−2.5	−29.2
f	0.0235	0.0220	0.0127	0.0061	0.0203	0.0200
$S_0 \to S_3$ ($n_N \to 3p$)						
ΔE, eV	8.59	8.56	8.57	8.68	8.63	8.75
$[R]^r$	−11.0	−6.7	6.6	−2.87	−24.0	3.1
$[R]^v$	−11.3	−4.6	2.0	−1.8	−13.3	2.1
f	0.0036	0.0086	0.0069	0.0122	0.0045	0.0148

[a] Geometries are optimized with 6-31+G* basis set (see Fig. 1).
[b] By the method of Ref. 19.
[c] See Fig. 2.

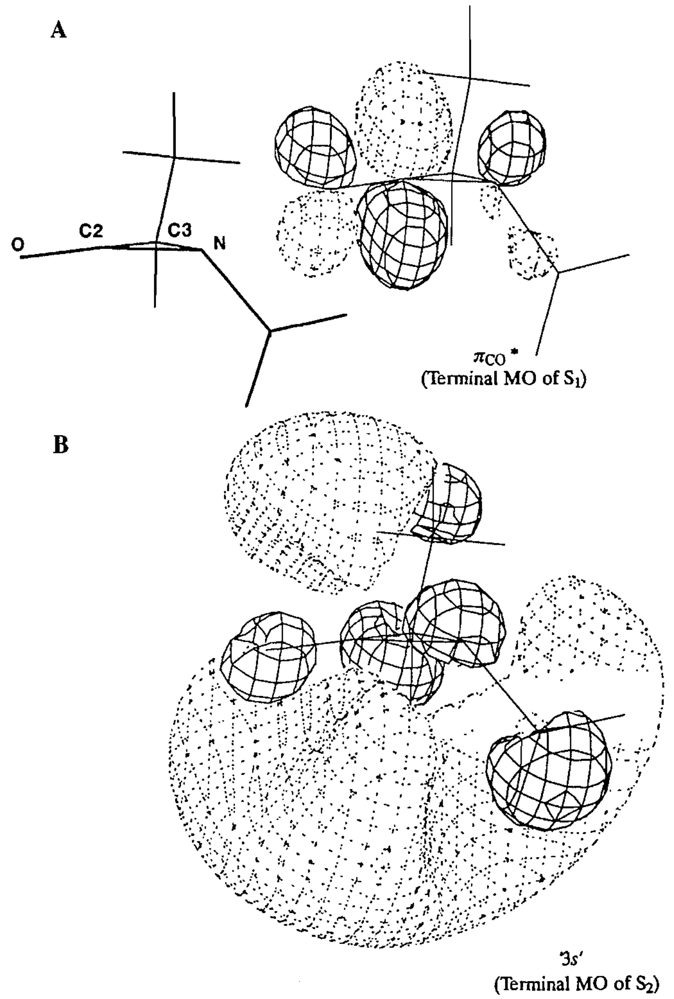
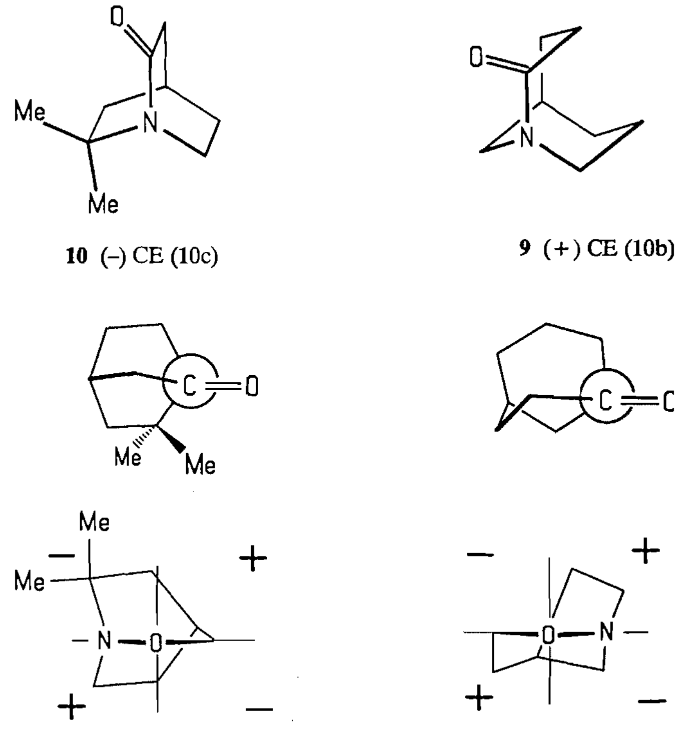


FIG. 5. The terminal orbitals of the lowest excited singlet states of aziridinone **4***a*. (A) First excited singlet state, contour value 0.075; (B) Rydberg orbital of next singlet state, contour value 0.025.



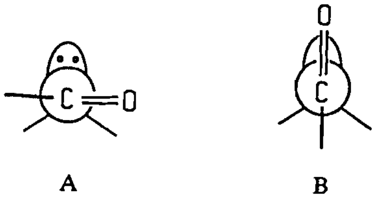
SCHEME 5

These compounds have a conformation around the N—C(O) bond, which is close to symmetrical antiperiplanar, and it is difficult to determine the sign of the torsion O═C—N—C angle for them.

Conclusions

1,3-Dialkylaziridinones (α-lactams), as do earlier investigated *N*-acylaziridines (**5***a*), possess the stereochemically labile intrinsically chiral amide group. Inversion of the configuration of this group is carried out by pyramidal inversion of the nitrogen under the control of a carbon chiral centre. The chiroptical properties of the nonplanar amide chromophore connected with the first electronic transition are independent from whatever influence causes the chromophore to become nonplanar. 1,3-Dialkylaziridinones and *N*-acylaziridines, for which nonplanarity of the amide chromophore is caused by insertion of the nitrogen atom into a strained three-membered ring, have the same features of the CD spectra as bicyclic amides (3*a*). All the compounds are different from virtually planar amides by the position of the long-wavelength absorption and high intensity of the first CE, the sign of which is determined only by the intrinsic chirality of the chromophore. In fact, the chromophore chirality is determined by the carbon chiral centres (thermodynamic control of the isomers populations) or by the chirality of a bicyclic molecule. Thus, there is the possibility of determination of the absolute stereochemistry of nonplanar amides on the basis of the first CE sign.

Both the chiral rules discussed above, which aim to connect the first CE sign with the absolute stereochemistry of the nonplanar amide, are empirical in character. Nevertheless, the spiral rule more correctly reflects the spiral nature of the nonplanar amide chromophore and may be used for all occurrences. In practice, this rule is preferred for compounds with a pronounced helicity of the chromophore, i.e., with the *syn*-clinal conformation (A, Scheme 6) around the N—C(O) bond. On the other hand, the ROR rule is more reliable for amides with a configuration that is close to antiperiplanar (B, Scheme 6):



SCHEME 6

Methods

Experimental

The CD spectra were measured on a JASCO J-500A spectropolarimeter with DP-500N dataprocessor, the UV spectra were measured on a Specord UV VIS spectrophotometer, the NMR spectra were measured on a Bruker WM-400 spectrometer (^{1}H, 400.13 MHz; ^{13}C, 100.62 MHz, in $CDCl_3$ from TMS), and optical rotation angles were determined on Autopol III and Polamat A polarimeters.

Amides of (S)-2-bromo-3,3-dimethylbutyric acid

A solution of (*S*)-2-bromo-3,3-dimethylbutyric acid (3.12 g, 16 mmol) (was prepared from L-*tert*-leucine according to ref. 15) and $SOCl_2$ (3.81 g, 32 mmol) in CH_2Cl_2 (15 mL) was refluxed for 7 h. After removal of the solvent in vacuo, the residual clear liquid (3.1 g) was dissolved in CH_2Cl_2 (20 mL) and added to a solution of *tert*-alkylamine (32 mmol) in CH_2Cl_2 (50 mL) with cooling (0°C) and stirring. After 2 h at 20°C, the reaction mixture was washed with 10% aqueous HCl (2 × 30 mL), water, and saturated aqueous $NaHCO_3$ (2 × 30 mL), and then dried ($CaCl_2$). After removal of the solvent, the residue was recrystallized from *n*-hexane–CH_2Cl_2.

*(S)-*N-tert*-Butyl-2-bromo-3,3-dimethylbutyramide*: yield 82%; mp 164–165°C (lit. (11*a*) mp 156–157°C racemate); $[\alpha]_D{}^{20}$ −36.6° (*c* 2.5, $CHCl_3$). ^{1}H NMR δ: 1.14 (9H, Bu^tC), 1.37 (9H, Bu^tN), 4.00 (1H, CH), 5.86 (1H, br s, NH).

*(S)-*N-*(1′-Adamantyl)-2-bromo-3,3-dimethylbutyramide*: yield 86%; mp 196–197°C (lit. (11*b*) mp 173–174°C racemate); $[\alpha]_D{}^{20}$ −32.1° (*c* 3.2, $CHCl_3$). ^{1}H NMR δ (*J*, Hz): 1.14 (9H, Bu^tC), 1.68 (6H, t, Ad, δ-CH_2, ^3J = 3.0), 2.01 (6H, d, Ad, β-CH_2, ^3J = 2.9), 2.06 (3H, br m, Ad, γ-CH), 3.97 (1H, CH), 6.22 (1H, br s, NH).

Aziridinones 6 and 7

Potassium *tert*-butoxide (0.74 g, 6.6 mmol) was added to a solution of (*S*)-amide (6 mmol) in absolute ether (100 mL) with cooling (−20°C) and stirring. After 15 min at 20°C, the precipitate was filtered off and the filtrate was evaporated in vacuo. The product was extracted from the residue with pentane. After removal of pentane, the residue was twice distilled in vacuo (aziridinone **6**) or twice recrystallized from *n*-hexane at −3°C (aziridinone **7**). Optical purities of the aziridinones, ≈86% for **6** and ≈88% for **7**, were determined according to Ref. 6*d* from the ^{1}H NMR spectra in $CDCl_3$–CCl_4 (1:4) in the presence of two equivalents of (*R*)-1-(9-anthryl)-2,2,2-trifluoroethanol by integration of the methine proton signals.

*(3*R*)-1,3-Di-*tert*-butylaziridinone* **6**: yield 43%; bp 29–32°C (0.2 Torr; 1 Torr = 133.3 Pa); $[\alpha]_D{}^{20}$ −253.8° (*c* 0.9, heptane) (lit. (6*c*)) bp 60°C (0.5 Torr), $[\alpha]_D{}^{20}$ −267.3° (*c* 1.25, hexane)). ^{1}H NMR δ: 0.99 (9H, Bu^tC), 1.29 (9H, Bu^tN), 2.74 (1H, CH). ^{13}C NMR δ (*J*, Hz): 26.95 (qm, $(CH_3)_3$CC, ^1J = 125.5, ^3J = 4.9, 2.8), 27.58 (qm, $(CH_3)_3$CN, ^1J = 126.2, ^3J = 4.2), 31.14 (m, Me_3CC, ^2J = 4.2), 54.09 (dm, *C*H, ^1J = 195.5, ^3J = 5.6), 55.98 (m, Me_3CN, ^2J = 4.2), 160.99 (d, *C*O, ^2J = 3.2).

*(3*R*)-1-(1′-Adamantyl)-3-*tert*-butylaziridinone* **7**: yield 58%; mp 75–76°C (lit. (11*b*) mp 79°C racemate); $[\alpha]_D{}^{20}$ −206.9 (*c* 1.0, heptane). ^{1}H NMR δ: 0.99 (9H, Bu^tC), 1.68 (6H, br t, Ad, δ-CH_2), 1.85 (6H, br q, Ad, β-CH_2), 2.14 (3H, br m, Ad, γ-CH), 2.83 (CH). ^{13}C NMR δ (*J*, Hz): 27.05 (q, $(CH_3)_3$C, ^1J = 126.2), 29.16 (d, Ad, γ-*C*H, ^1J = 133.2), 31.15 (Me_3C), 35.81 (t, Ad, δ-*C*H_2, ^1J = 127.6), 40.91 (t, Ad, β-*C*H_2, ^1J = 127.6), 53.30 (dm, *C*H, ^1J = 160.9, ^3J = 5.6), 56.29 (Ad, α-C), 160.88 (d, *C*O, ^2J = 3.1).

Theoretical

The geometries of (1*S*)-aziridinone **1**, (1*S*)-1-methylaziridinone **2**, (1*S*,3*R*)-3-methylaziridinone **3**, (1*S*,3*R*)-1,3-dimethylaziridinone **4***a*, its *cis*-diastereomer (1*R*,3*R*)-1,3-dimethylaziridinone **4***b*, and (1*S*,3*R*)-3-*tert*-butyl-1-methylaziridinone **5** were fully optimized by Hartree–Fock SCF calculations at the 6–31+G* level (16) by using the GAUSSIAN 90 (17) or 92 (18) system of programs. In the case of the (3*R*)-1,3-dimethylaziridinones **4***a* and **4***b*, the transition structure for pyramidal inversion at N, **4-TS**, was also located. The transition properties were determined with the same basis set. The diffuse *s* and *p* functions in this basis set permit a better description of the lowest few valence states and the identification of Rydberg states. Ionization potentials are calculated using a many body perturbation theory correction to Koopmans' theorem based on the work of Pickup and Goscinski (19). The frontier orbitals are displayed as modified Jorgensen–Salem plots (20).

The method used to calculate oscillator and optical rotatory strengths is the same as was used previously (5, 21, 22) and has been described in detail elsewhere (23). Partially correlated wave functions for the ground and excited states are determined to first order in Rayleigh–Schrödinger perturbation theory,

$$[1] \quad \Psi_n = \Psi_n^0 - \Sigma_j a_{nj} \Phi_j^0$$

where

$$[2] \quad a_{nj} = \langle \Psi_n^0 | H | \Phi_j^0 \rangle (\langle \Phi_j^0 | H | \Phi_j^0 \rangle - \langle \Psi_n^0 | H | \Psi_n^0 \rangle)$$

H is the exact Hamiltonian, Φ_j^0 is a singlet singly or more highly excited configuration derived from the Hartree–Fock determinant, Φ_{HF}, and Ψ_n^0 is a linear combination of strongly interacting Φ_l^0 $(l \neq j)$ selected from at most singly excited configurations. Thus, for the ground state, $\Psi_0^0 = \Phi_{HF}$. All configurations for which the interaction coefficient a_{nj} (eq. [2]) was greater than 0.05 were included in the zero-order part of the CI wave function. For reasons of expediency, the CI calculation was restricted to a window of 14 occupied orbitals and 48 unoccupied orbitals for each system.

Electric dipole transition moments in the length $\langle r \rangle_{0n}$ and velocity $\langle v \rangle_{0n}$ formalism and magnetic dipole transition moments $\langle m \rangle_{0n}$ are explicitly evaluated from

$$[3] \quad \langle r\rangle_{0n} = \Psi_0|\mu|\Psi_n\rangle$$

$$[4] \quad \langle v\rangle_{0n} = \langle\Psi_0|\nabla|\Psi_n\rangle/(E_n - E_0)$$

$$[5] \quad \langle m\rangle_{n0} = -i\langle\Psi_n|m|\Psi_0\rangle$$

where the dipole, gradient, and magnetic moment operators, μ, ∇, and m, have their usual definitions and

$$[6] \quad E_n = \langle\Psi_n|H|\Psi_n\rangle$$

Oscillator strengths f_{0n} are calculated by the mixed formalism

$$[7] \quad f_{0n} = \frac{2}{3}\langle\Psi_0|v|\Psi_n\rangle \cdot \langle r\rangle_{n0}$$

Optical rotatory strengths are evaluated as

$$[8] \quad [R_{0n}]^r = \langle r\rangle_{0n} \cdot \langle m\rangle_{n0}$$

and in the origin independent form

$$[9] \quad [R_{0n}]^v = \langle v\rangle_{0n} \cdot \langle m\rangle_{n0}$$

The extent of agreement between eqs. [8] and [9] serves as a measure of the quality of the wave function and the reliability of the calculated rotational strengths for the particular states.

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