Tetrahedron Vol. 35, pp. 1499 to 1508
Pergamon Press Ltd., 1979. Printed in Great Britain

CHIROPTICAL PROPERTIES OF 1-CARBAPENAM AND ORBITAL MIXING IN NONPLANAR AMIDES†

D. B. Boyd*
Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, IN 46206, U.S.A.

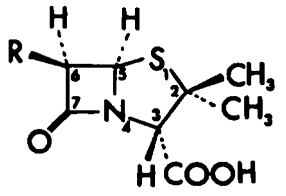
and

J. P. Riehl and F. S. Richardson
Department of Chemistry, University of Virginia, Charlottesville, VA 22901, U.S.A.

(*Received in USA 29 August 1978*)

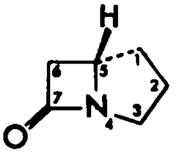
Abstract—Optical rotatory properties of β-lactam structures are calculated using semiempirical Extended Hückel and CNDO wavefunctions. Possible interpretations of CD and UV absorption data for a recently reported 5-epi-1-carbapenam, (5*S*)-1-azabicyclo-[3.2.0] heptan-7-one, are proposed. This compound lacks the sulfur of a penicillin nucleus, but still shows a Cotton effect at 231 nm. Analysis is aided by calculations on some monocyclic β-lactams, N-methyl-3-aminoazetidin-2-ones, where the Me carbon is incrementally bent out of the plane of the 4-membered ring. When N is pyramidal, the n and π orbitals of planar amides become mixed into two orbitals which correctly yield opposite signs for the Cotton effects at 231 nm and at just below 200 nm. A correspondence is proposed between the CD bands of 5-epi-1-carbapenam and those observed for another carbocyclic, nonplanar lactam, 4-azatricyclo[4.4.0.$0^{3,8}$] decan-5-one. The origin of the spectroscopically relevant orbitals of penams, penam sulfoxides, and other β-lactams is shown in a correlation diagram. In the spectral calculations, shortcomings of the semiempirical methods are encountered and discussed.

Recent theoretical studies[1,2] on penicillins 1 have suggested that the Cotton effect observed[2] near 203 nm can be associated with a transition involving orbitals mainly localized on the β-lactam amide. At longer wavelengths near 230 nm there is a positive CD band (which in some structures and solvents resolves into two overlapping, positive peaks[3]). The calculations[1,2] indicate two strong, optically active transitions near 230 nm involving charge transfer between and mixing of the sulfide and amide orbitals. Whereas these assignments are plausible and fit the available experimental data, alternate interpretations, as is often the case in complex amides, are conceivable. For instance, it has been suggested that the short wavelength Cotton effect should be a transition associated with sulfur, and the long wavelength one might be contributed to by another sulfide and the amide $n \rightarrow \pi^*$ transitions.[3] Other possible assignments have been summarized before.[1-3]



1

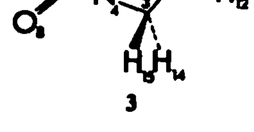
More recently, a novel molecule has been synthesized and studied spectroscopically[4] which helps to elucidate the assignments. The molecule is (5*S*)-1-azabicyclo[3.2.0]heptan-7-one 2, which will be recognized as a 5-epi-1-carbapenam (using the penam numbering system below).



2

Not only does this molecule lack the sulfur of penicillins, it also lacks the common 6-amino or 6-acylamino and other side-chains of penicillins. Hence it is an ideal model compound for determining the chiroptical properties of the β-lactam chromophore isolated in a bicyclic ring system analogous to that of penicillins. Further important information on the β-lactam chromophore has become available from a series of substituted monocyclic β-lactams related to penicillins which have recently been synthesized and studied spectropolarimetrically.[5]

In light of the continuing interest in the nature of the chiroptical properties of β-lactams, extensions of our earlier theoretical studies are described in this paper. Molecular orbital and rotatory strength calculations are presented for 1-carbapenam 3, which is the optical



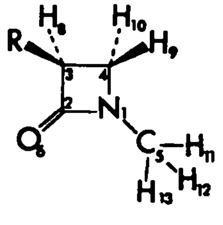
3

---

† Paper VIII of the series *Electronic Structures of Cephalosporins and Penicillins*. For previous papers, see Refs. 1 and 2.

isomer of 2 and has the same stereochemistry as natural penicillins. After taking into account the expected sign change in the CD bands, noteworthy agreement with the experimental Cotton effects is achieved. Evidence is found among the new theoretical, as well as experimental, data for preferring certain assignments over some of the alternate possibilities.

Calculations were also done on monocyclic β-lactams, N-methyl-3β-R-azetidin-2-ones 4, where R is NH_2 or NH_3^+. (In 4 the conventional azetidin-2-one number system is used). In penicillins and in 2 or 3, the exocyclic substituent on the β-lactam nitrogen is forced by the 5-membered ring to be out of the plane of the β-lactam ring. The effect of this nonplanarity on the β-lactam amide orbitals and on the chiroptical properties was studied by doing calculations on 4 with the Me group carbon in the plane or bent to various degrees out of the plane of the 4-membered ring. The C_3C_2–N_1C_5 dihedral angle ω in 4 is twisted to values less than 180° such that C_5 is on the β face of the molecule and *syn* to the 3β-R substituent. As expected, this pyramidalization has a pronounced effect on the CD spectra. Also, the orbitals of the amide are mixed as shown in a correlation diagram such that the usual terminology of n and π orbitals, while still convenient and commonly used, no longer accurately represents the shape of the orbitals. This mixing of the n and π orbitals is an important point that earlier papers have not made note of.



4

The analysis in this paper points out that application of semiempirical MO methods to spectral problems can be useful only if done prudently. Accurate *ab initio* calculations with configuration interaction (CI) on the ground and excited states of penams and the other rather large systems covered here would be lengthy, but should be a useful future step in the quantification of the electronic structure of these molecules.

EXPERIMENTAL

Atomic coordinates of 3 were determined using the MINDO/3 MO method.[6] A complete optimization of all geometrical variables, except bond lengths and angles to the H's, was carried out. Hydrogens were placed with standard[7] bond lengths and angles. The resulting molecular structure of 3 is in very satisfactory agreement with available geometrical data[8] for those β-lactam structures which have been determined by X-ray crystallography. The β-lactam ring of 3 is almost, but not exactly, planar; the 5-membered ring is roughly planar with a C_5C_1–C_2C_3 dihedral angle of −7°. The β-lactam nitrogen is pyramidal as indicated by the C_6C_7–N_4C_3 dihedral angle of 139°, and this agrees well with the 136° found in penicillins.[8,9] Atomic coordinates for the monocyclic β-lactam 4 are those described previously[9] and correspond to a blend of standard and MINDO/3-optimized geometrical data. The C_3C_2–N_1C_5 dihedral angle was varied from 180° (planar) to 135° (syn to 3β-R) in 15° increments.[9]

Molecular orbitals were computed by the Extended Hückel (EH) method[7,10] as before.[1,2] In addition, MO's were computed by the complete-neglect-of-differential-overlap/spectroscopic (CNDO/S) method.[11] The CNDO/S calculations were carried out with the Nishimoto-Mataga[12] approximation for the γ integrals, β_0's from Del Bene and Jaffé, and $\kappa = 0.585$.[11] CNDO/S with configuration interaction (3, 5, 20 and 50 configurations) gave $n \rightarrow \pi^*$ transition energies which were much too low. (Examples of what happens to the λ's are seen in the CNDO/S-CI calculations of Bláha and coworkers[13-15] and others[16-18]). Many nonstandard variants of the CNDO/S, as well as CNDO/2[19], parameterizations were tried, but the predicted spectral quantities were disappointing. Theoretically calculated, as well as Ohno, values for γ were tried in CNDO/S. CNDO/2, with or without CI, also gave nonsensical transition energies, especially for 4 with $R = NH_3^+$. Consequently, CNDO/S with standard parameters, but without CI, was tried, and the results, being satisfactory in some respects, are included in this paper.

Although a full CI treatment would in principle be preferable, some justification for leaving out CI comes from the limited extent that the pertinent excited state configurations (for some of the structures) mix with other configurations. Precedent for not using CI in CNDO/S calculations of optical properties comes from the work of Bouman.[17] However, it should be kept in mind that earlier studies on carbonyls have shown that increasing the number of configurations in CNDO/S-CI calculations can lead to erratic changes in the sign and magnitude of rotatory strengths and that the number of configurations must be well above 100 before some convergence in the predictions is seen in some cases.[17,18]

Spectral properties are computed from the EH and CNDO/S LCAO-MO coefficients for the high-lying filled and low-lying empty MO's along with the corresponding orbital energies (ϵ) in the virtual orbital approximation.[1,2] Whereas the EH transition energies is computed simply as a difference in orbital energies,[7] the CNDO/S transition energies are computed from $\Delta E = \epsilon_i - \epsilon_j - J_{ij} + 2K_{ij}$, where J_{ij} and K_{ij} are Coulomb and exchange integrals between MO's i and j.[11,20] The CNDO/S coefficients are deorthogonalized with an $S^{-1/2}$ transformation.[21] Then transition moment integrals are evaluated in the dipole velocity formalism including all one- and two-center terms as in earlier work.[1,2,22] Results include the transition energies expressed in terms of wavelength λ_a, reduced rotatory strength $[R_a]$, dipole strengths D_a, and oscillator strengths f_a. Equations for these are well known.[22] Also, oscillator strengths are calculated for some structures in the dipole length formalism.[1,7] Absorption and CD spectra are computed from the EH MO's assuming that all transition bands are Gaussian shaped and have the same half-width δ. Such spectra are calculated from $[R_a]$ (in units of a pure number[23]), D_a (in Debye[2]), λ_a (in nm), and $\delta = 20$ nm. The following summations are over the three lowest energy transitions. The extinction coefficients are in units of $1\ \text{mole}^{-1}\ \text{cm}^{-1}$.

$$\epsilon(\lambda) = 61.7 \sum_{a=1}^{3} \frac{D_a \lambda_a}{\delta} \exp[-(\lambda - \lambda_a)^2/\delta^2]$$

$$\Delta\epsilon(\lambda) = 0.0227 \sum_{a=1}^{3} \frac{[R_a]\lambda_a}{\delta} \exp[-(\lambda - \lambda_a)^2/\delta^2].$$

RESULTS AND DISCUSSION

We begin this section by presenting the calculated results on the chiroptical properties of 3 and 4. These results will be compared to available experimental CD and UV data for 2 and other lactams. Then we discuss the nature of the orbitals responsible for the transitions, and, in particular, we call attention to the mixing of the n and π levels in nonplanar amides.

Calculation of spectra. The calculational results for 1-carbapenam 3 are given in Table 1 and Fig. 1. Both EH and CNDO/S calculations give only two transitions which are strongly optically active in the UV region. Both methods also agree that the first transition has positive rotatory strength and the second is negative. The prediction of the first band to be positive agrees well

Table 1. Spectral properties for the low energy transitions calculated from EH and CNDO/S MO's for 1-carbapenam 3

Transition	λ(nm)	D_n	f_n^{a}	f_n^{b}	$[R_n]$
			EH		
1	232.2	6.92	0.1401	0.2447	194.90
2	201.0	4.96	0.1159	0.1754	-186.51
3	176.4	1.08	0.0288	0.0571	0.87
			CNDO/S		
1	217.9	4.12	0.0894	0.0946	155.12
2	209.0	4.21	0.0978	0.1460	-111.50

^{a}Calculated from dipole velocity integrals.
^{b}Calculated from directly evaluated dipole length integrals in the case of the EH MO's and dipole length integrals as approximated in Ref. 22 from dipole velocity integrals in the case of the CNDO/S MO's.

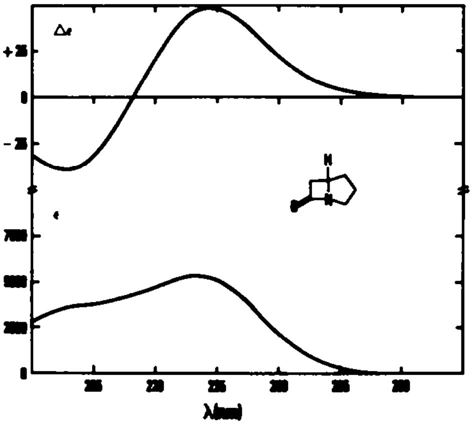


Fig. 1. CD (top) and UV (bottom) spectra of 1-carbapenam 3 predicted from EH MO's.

with the CD spectrum observed[4] for 2, which (being the mirror image of 3) displays a negative Cotton effect at 231 nm ($\Delta\epsilon = -3.8$). The predicted $\Delta\epsilon$(Fig. 1) is about an order of magnitude too large, but the EH MO's do well at predicting the first Cotton effect to be at 232 nm.

Both EH and CNDO/S predict the second Cotton effect of 3 to be negative (Table 1). Because of the difference in configurations at the asymmetric center in 2 and 3, one would anticipate that 2 should display a positive second Cotton effect. In fact, the CD spectrum of 2 was interpreted[4] as showing a weak positive shoulder at 212 nm. Also, the spectral curve[4] is heading toward a positive extremum somewhere below 200 nm. The experimental spectrum extended down to only 200 nm unfortunately, but visual inspection of the curve leads one to believe that the positive extremum is real. On the other hand, the nature of the intermediate shoulder was regarded[4] as not absolutely certain because of noise in the spectrum, sensitivity of the apparatus, and fairly rapid decomposition of 2 upon standing. Although the shape and position of the shoulder suggest that it could arise from a transition of positive rotatory strength, one could also imagine a combination of a weak, *negative* intermediate transition near 205 nm and a broad, somewhat stronger, *positive* transition around 195 nm which might also combine to fit the same experimental curve. Resolution of this question of the sign of the intermediate transition may not be feasible until the shape of the curve below 200 nm is known, and even then the question may be unsettled because of the nonuniqueness of fitting Gaussians to curves.[24] As explained later, we prefer to associate the positive extremum just below 200 nm with our calculated second Cotton effect. The predicted sign and wavelength (Table 1 and Fig. 1) are therefore not unreasonable. The nature of the intermediate transition is discussed later.

Regarding the absorption spectrum of 3, the two lowest energy transitions are predicted to be dominant as seen in Table 1 and Fig. 1. The relative size of the f values for each transition (Table 1) is maintained regardless of whether dipole velocity or dipole length integrals are used in their prediction. Experimentally, 2 has λ_{max} at 222 nm and $\epsilon = 1100$ in methanol.[4] The simulated UV spectrum in Fig. 1 shows a peak at about 230 nm with $\epsilon \sim 5000$, so modest agreement is achieved.

Consider next the monocyclic β-lactam results from the EH (Table 2) and CNDO/S (Table 3) MO's. The corresponding spectra from the EH MO's are given for the protonated (NH_3^+) and unprotonated (NH_2) models of 4 in Figs. 2 and 3, respectively. For the hypothetical, nonplanar monocyclic β-lactams there are no experimental CD or UV data for comparison. We do note that the CNDO/S and EH results for 4 with $R = NH_3^+$ and $\omega = 135°$ are very similar to those for 3 (Table 1). Also, we note that the first and second predicted transitions have opposite sign. Although quantitative differences between the two MO methods are anticipated, a problem exists in regard to the consistency of the signs of the rotatory strengths through the range of ω (see Tables 2 and 3). We have rechecked the calculations, so the problem may stem from one or both types of wavefunction simply not being good enough.

Monocyclic β-lactams are known to prefer an sp^2 nitrogen (although the energy required to bend the N-substituent out of coplanarity 15° or so degrees is quite small[9] as expected.[25]). Experimentally, the CD spectra of monocyclic β-lactams with $\omega = 0°$ can display a peak at 213–234 nm ($|\Delta\epsilon| < 11$) depending on the solvent and the position and nature of substituents.[5,26,27] Frequently, substituents on the β face cause the first Cotton effect to be negative, whereas substituents on the α face cause it to be positive.[27] Because the "coplanar" form of 4 has the 3-R substituent on the β face, one would expect the predicted first Cotton effect to be negative. The CNDO/S calculations on the two forms of 4 with $\omega = 180°$ in Table 3 are qualitatively correct in this regard. The second Cotton effect (near 205 nm) in monocyclic β-lactams is observed[5] to have a sign

Table 2. Spectral properties for the low energy transitions calculated from EH MO's for N-methyl-3β-R-azetidin-2-ones 4 with various C_3C_2–N_1C_{methyl} dihedral angles ω

Structure	Transition	λ(nm)	D_n	f_n	$[R_n]$
NH_2,180°	1	231.6	0.75	0.0152	10.31
	2	219.1	12.68	0.2720	-44.02
	3	193.5	0.89	0.0216	32.23
NH_2,165°	1	235.4	1.99	0.0397	71.86
	2	218.0	11.96	0.2363	-79.46
	3	194.4	0.84	0.0203	16.93
NH_2,150°	1	243.1	2.68	0.0519	94.78
	2	217.5	9.42	0.1971	-76.59
	3	196.5	0.86	0.0205	0.81
NH_2,135°	1	253.9	2.63	0.0487	100.44
	2	218.2	8.39	0.1593	-57.80
	3	200.0	0.93	0.0219	-15.36
NH_3^+,180°	1	219.2	12.82	0.2751	-9.43
	2	211.0	0.99	0.0221	3.49
	3	179.1	0.13	0.0033	-18.80
NH_3^+,165°	1	222.5	10.26	0.2169	144.71
	2	210.3	3.05	0.0681	-150.42
	3	179.5	0.41	0.0107	-14.44
NH_3^+,150°	1	229.9	7.62	0.1558	173.33
	2	209.5	4.56	0.1024	-175.41
	3	180.9	0.96	0.0251	-13.26
NH_3^+,135°	1	240.1	5.65	0.1106	169.70
	2	209.8	4.99	0.1069	-169.34
	3	183.4	1.80	0.0461	-20.81

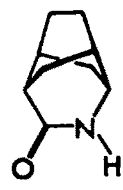
Table 3. Spectral properties for the low energy transitions calculated from CNDO/S MO's for N-methyl-3β-R-azetidin-2-ones 4 with various C_3C_2–N_1C_{methyl} dihedral angles ω

Structure	Transition	λ(nm)	D_n	f_n^a	f_n^b	[R]
NH_2,180°	1	249.1	0.83	0.0156	0.0075	-19.50
	2	170.7	5.46	0.1505	0.3294	18.96
NH_2,165°	1	222.9	2.40	0.0506	0.0570	110.04
	2	184.2	5.00	0.1276	0.2407	-79.46
NH_2,150°	1	210.0	3.74	0.0836	0.1257	-106.50
	2	191.0	3.68	0.0904	0.1459	112.26
NH_2,135°	1	230.7	2.44	0.0500	0.0654	-99.92
	2	171.9	3.68	0.1080	0.1976	87.00
NH_3^+,180°	1	276.1	0.48	0.0082	0.0013	-11.22
	2	179.2	5.46	0.1430	0.3222	1.48
NH_3^+,165°	1	268.4	1.00	0.0176	0.0390	58.72
	2	182.2	5.19	0.1338	0.2231	-35.94
NH_3^+,150°	1	246.6	2.30	0.0438	0.0103	108.30
	2	192.2	4.54	0.1110	0.2940	-69.22
NH_3^+,135°	1	218.9	3.28	0.0704	0.0842	126.86
	2	208.9	3.54	0.0894	0.1381	-91.32

[a] Calculated from dipole velocity integrals.
[b] Calculated from dipole length integrals as approximated in Ref. 22.

opposite to that of the first, and again the CNDO/S predictions (Table 3) are qualitatively satisfactory. The EH results (Figs. 2 and 3, Table 2) for the *planar* (ω = 180°) structures are unsatisfactory for reasons to be discussed later.

Comparison to another lactam. UV absorption data have recently been reported for an interesting cyclic, nonplanar lactam, (−)−(3*S*)−4-azatricyclo-[4.4.0.0^{3,8}] decan-5-one 5.[13] This molecule is known from X-ray studies[28] to have a CC-NC dihedral angle at the lactam C-N bond close to 15°. The corresponding dihedral angle is 2° in 3 and 0° in 4. The CC–NH dihedral angle at the lactam bond of 5 is observed[13] near 194° and calculated by CNDO/2 optimization[14] to be near 206°.



5

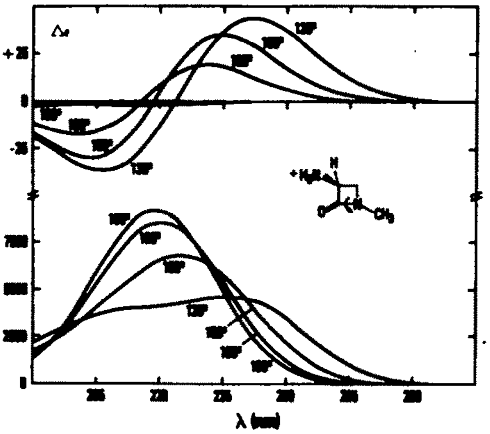


Fig. 2. CD (top) and UV (bottom) spectra of N-methyl-3β-NH_3^+-azetidin-2-one 4 predicted from EH MO's as a function of C_3C_{2}-N_1C_{methyl} dihedral angle ω.

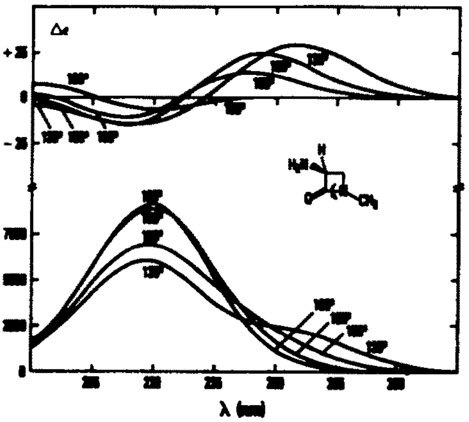


Fig. 3. CD (top) and UV (bottom) spectra of N-methyl-3β-NH_2-azetidin-2-one 4 predicted from EH MO's as a function of C_3C_{2}-N_1C_{methyl} dihedral angle ω.

Since this angle is analogous to dihedral angle ω in 4, the nitrogen is slightly pyramidal (but in the mirror image configuration compared to 3 and 4). UV results calculated for 4 with ω = 150° or 165° should be roughly comparable to the experimental UV data for 5. Bláha *et al.*[13] observed λ_{max} for 5 at 202 nm ($\epsilon = 3400$) in 3-methylpentane and at 204.5 nm ($\epsilon = 2600$) in cyclohexane. There is a shoulder visible at 226 nm ($\epsilon = 310$–330) in these solvents, but not in methanol.[13] These data agree modestly with the UV curves in Figs. 2 and 3 which have λ_{max} near 220 nm and a shoulder (in Fig. 3 for ω = 150°) near 242 nm, except that the transitions for 4 are red-shifted about 20 nm compared to 5.

The availability of CD data for 5 allows further comment on the nature of the higher energy Cotton effects mentioned earlier for 1-carbapenam. Experimentally,[4] the first Cotton effect of 2 has a sign opposite that of the extremum just below 200 nm. EH and CNDO/S wavefunctions clearly give opposite signs (Table 1) as expected for a pyramidal distortion.[15] Molecule 5 has a negative Cotton effect at 211–232 nm (depending on solvent) and a positive Cotton effect at 192–197 nm.[13] The signs are exactly what one would expect to see for a twisted lactam with the same configuration as that of 5-epi-1-carbapenam 2 and opposite to that of 3. Bláha, *et al.*,[13] made the interesting discovery that 5 also showed a weakly negative, intermediate shoulder at 210–215 nm in two nonhydrogen-bonding solvents. Thus the sign of the shoulder is the same as that of the first Cotton effect. Their conclusions[13] were reached with experimental data which extended down to below 190 nm and which were resolved with the aid of computer separation of the individual Gaussian bands.

We would like to propose that the first Cotton effect in 2 (at 231 nm) and in 5 (at 211–232 nm) are analogous transitions. Furthermore, the third Cotton effect of 5 (at 192–197) nm) corresponds to the positive extremum occurring just below 200 nm for 2. This correlation, as summarized in Table 4, suggests that the peak *calculated* at 198 nm for 3 (Fig. 1) should correspond to "Transition 3" of 2 rather than "Transition 2" (see Table 4).

The intermediate Cotton effect in 5 observed at 210-215 nm could be analogous to that in 2 at 212 nm, especially if the sign of the latter could be interpreted as negative. The nature of this Cotton effect in 2 is obscured by the fact that it is observed in methanol, whereas the intermediate band in 5 only shows up in aprotic solvents. Hence it is not yet absolutely clear whether the 212 nm transition actually arises from 2 or from a polymeric decomposition product.[4] The CD data for 5 (Table 4) do raise the question of what is the nature of the second Cotton effect.

The existence of an intermediate or so-called "mystery band" in amides is not new. For over 10 years, it has been known that in planar amides there exists a band (or bands) between the usual $n \rightarrow \pi^*$ and $\pi \rightarrow \pi^*$ bands.[29–37] However, there remain ambiguities about the origin of the intermediate band.

Bláha *et al.*, initially referred to the intermediate transition of 5 as $n \rightarrow \sigma^*$.[13] However, *ab initio* calculations[29–32] generally describe the second lowest excited state of formamide as a Rydberg state. Hence they switched to $n \rightarrow 3s$ as a tentative assignment. Even though a Rydberg excited state may exist at the appropriate wavelength, it

Table 4. Summary of EH calculated and experimental CD λ_{max}'s, in nm, and Δε, in l mole^{-1} cm^{-1}, for various twisted lactams

	3	2[a]	5[b]	5[c]
Transition	λ_{max} (−Δε)	λ_{max} (Δε)	λ_{max} (Δε)	λ_{max} (Δε)
1	232 (−48)	231 (−3.8)	220 (−11.7)	232 (−9.2)
2	−	212 (|Δε|≤1)	−	210 (−2.3)
3	198 (+38)	<200 (>+1)	197 (+7.7)	197 (+9.5)

[a] From Ref. 4 for methanol solvent.
[b] From Ref. 13 for methanol solvent.
[c] From Ref. 13 for cyclohexane solvent.

is not known for sure how much such a transition would contribute to the *solution phase* optical activity of 5 (or 2). In general, Rydberg states are observed in gas phase spectra, and it is usually believed that these CD bands will not have appreciable intensity in condensed phases.[30]

Gas phase studies[30] do show that Rydberg states contribute to optical activity. Calculational studies of Rydberg transitions in amides have included oscillator strength predictions,[29-32] but not rotatory strength predictions, as far as we know. (Our calculations, as well as the CNDO/S-CI calculations of Bláha, *et al.*,[13-15] give only two, not three, CD bands for the amide chromophore because they involve a basis set of only valence-shell orbitals.)

Among the various other possibilities[13] that can be envisioned for the second Cotton effect of 5 is that it arises from intermolecular association. The shoulder in the CD of 5 only showed up in cyclohexane and acetonitrile.[13] It was not observed in protic solvents. However, Bláha, *et al.*,[13] discounted the possibility of intermolecular association for their molecule because they observed concentration independence of their CD spectra and the presence of the band in acetonitrile as well as cyclohexane.

There have been solution phase CD studies which demonstrated that an intermediate band could be associated with dimerization of amides. For instance, 1, 7, 7-trimethyl-2-azabicyclo[2.2.1]heptan-3-one in hexane develops a new CD band intermediate between the $n \rightarrow \pi^*$ and $\pi \rightarrow \pi^*$ bands as the solution becomes more concentrated.[35] Similarly, substituted 2-pyrrolidones when concentrated are known to dimerize in hexane or cyclohexane, and a new band near 200 nm occurs.[34,37] Presumably the amide groups are H-bonded together. The sign of the new CD band is the same as that of the first Cotton effect (near 225 nm) and opposite that of the third Cotton effect (near 193 nm).[37] All of these three CD bands are of opposite sign compared to 5. The dimer-containing solution of the 3-methylpyrrolid-2-one also shows a fourth Cotton effect below 190 nm with the same sign as the first.[37]

The question of whether 2-pyrrolidones are indeed showing a dimerization-induced intermediate CD band is complicated by the fact that N-substituted 2-pyrrolidone[29] and other dialkylamides[33] also show an intermediate absorption band in the gas phase. In these molecules, hydrogen bonding is not possible. Also, association in the gas phase has been regarded by some[29,30] as remote, although in one study the appearance of new bands in gas phase absorption spectra was associated with hydrogen-bonded dimers.[36]

.One could imagine weak intermolecular association involving stacking of the polar amide carbonyl groups with antiparallel dipoles. The dipole moment of amides is fairly large and roughly along the $C^+\text{–}O^-$ axis.[29,31] Such stacking of the amide groups would be the main type of association that 2 could undergo since it is a dialkyl amide and is totally hydrocarbon except for the amide group. It would be interesting to determine whether this molecule dimerizes in nonpolar solvents. Self-association of 2 in methanol is probably not extensive. Likewise, it would be unusual if a Rydberg transition were showing up as the intermediate shoulder in this solvent.

At this point, the nature of the intermediate transition of 5 and 2 remains unclear. Further experiments would be desirable, as would *ab initio* calculations of optical rotatory properties of nonplanar amides and model dimeric amide structures. In the next section, attention will be concentrated on the two transitions of the β-lactams which are predictable by semiempirical calculations.

Molecular orbitals. This section on the MO's of 3 and 4 should be prefaced with the reminder that, although the discussion will be in terms of orbitals, translation to a description in terms of spectroscopic excited states is implicit. In other words, when we describe a transition as from some orbital n to another orbital, say π^*, the transition is from the singlet ground state (with configuration... n^2) to the singlet excited state described by the configuration... $n\pi^*$. (CI, if done, would mix smaller amounts of other configurations into the wavefunctions). The problem of using one-electron spin orbitals to describe two-orbital processes, such as electronic transitions, is well recognized.[38] However, the basic MO approach of using a single determinant of suitable orbitals to describe a many-electron wavefunction can work in some situations for certain properties. A link between orbital energies from EH calculations and those from *ab initio* calculations involving an "average state" of a molecule has recently been discovered.[39]

The EH MO's and orbital energies are given in Tables 5–9 for 1-carbapenam 3 and the unprotonated and protonated forms of the monocyclic β-lactams 4. Included in each table are the orbital energies and all the large (≥ 0.25) LCAO-MO coefficients, which reflect the general shape of the orbitals. Also included are mnemonics which are convenient labels, but which in no way should be regarded as accurate descriptions of the orbitals. The coefficients or electron density diagrams[2,7] should be consulted for a better description of the orbitals.

For all structures,† only one low-lying empty orbital is obtained from EH calculations which has an energy appropriate for transitions in the UV region. This orbital is the lowest empty MO (LEMO). For 3 the highest occupied MO (HOMO) and next to the highest occupied MO (NHOMO) are localized on the β-lactam amide, and the next lower orbitals are σ orbitals (Table 5). The same situation applies to the protonated forms of 4; MO's for two of the structures ($\omega = 180°$ and $135°$) are given as examples in Tables 8 and 9. For the unprotonated form of 4, the lone pair orbital on the amino group is at an energy such that it mixes strongly with the occupied amide orbitals. Hence in Tables 6 and 7 there are three high-lying occupied MO's with amide character. For sake of convenience, the higher energy MO resulting from this

---

†The nature of the MO's produced by the other semiempirical MO methods can be summarized here. According to CNDO/S, 3 and 4 have only one low-lying empty MO and two high-lying occupied MO's which can contribute to transitions in the region of interest. The NLEMO has σ^* character. The occupied orbitals for 3 and the protonated form of 4 are similar in shape and sequence to the EH orbitals. For the unprotonated form of 4 at $\omega = 180°$, the CNDO/S HOMO is the amide π orbital, whereas the next two occupied MO's are combinations of the amide n and NH_2 n orbitals. By MINDO/3, 3 and 4 have two low-lying empty MO's, one of which is the expected amide π^* and the second (lower energy) one is an N-C σ^* orbital. The situation for the occupied MINDO/3 MO's is also quite complex. Amide character is spread through three or four of the highest occupied MO's of 3 and 4. The two low-lying empty MINDO/3 MO's of 4 change only slightly in energy as a function of dihedral angle ω. The energies of the high-lying filled MO's show dependences on ω similar to those of the EH MO's.

Table 5. EH orbital energies and MO's of 1-carbapenam 3^a

MO^b	ε,eV	Large LCAO-MO Coefficients	Mnemonic
LEMO	−6.81	$-0.47(N_42p_y)+0.93(C_72p_y)-0.50(O_82p_y)$	amide π*
HOMO	−12.15	$+0.25(N_42p_z)-0.29(N_42p_x)+0.55(N_42p_y)$ $-0.26(O_82p_x)-0.30(O_82p_y)-0.27(C_62p_x)$	amide N n
NHOMO	−12.98	$+0.44(N_42p_y)-0.36(O_82p_z)+0.47(O_82p_x)$ $+0.38(C_62p_x)$	amide n
NNHOMO	−13.84	$-0.32(C_52p_y)+0.35(C_12p_y)-0.31(C_22p_y)$ $+0.26(C_32p_y)-0.29(H_{13}1s)+0.31(H_{17}1s)$	σ

^{a}The Cartesian coordinate system has N_4 at the origin, C_7 on the +z axis, and O_8 in the ++ quadrant of the xz plane.
^{b}LEMO is the acronym for lowest empty MO; HOMO for highest occupied MO; N for next; and NN next to the next.

Table 6. EH orbital energies and MO's of N–CH$_3$–3β–NH$_2$–azetidin-2-one with C$_3$C$_2$–N$_1$C$_5$ = 180°^{a}

MO	ε,eV	Large LCAO-MO Coefficients	Mnemonic
LEMO	−6.93	$-0.50(O_62p_y)+0.91(C_22p_y)-0.51(N_12p_y)$	amide π*
HOMO	−12.29	$-0.43(O_62p_z)+0.27(C_22p_z)-0.25(C_32p_x)$ $+0.36(N_72p_x)-0.55(N_72p_y)$	NH$_2$,O n
NHOMO	−12.59	$+0.42(O_62p_y)-0.78(N_12p_y)$	amide π
NNHOMO	−13.34	$+0.56(O_62p_x)-0.35(C_32p_z)-0.54(N_72p_y)$	NH$_2$,O n'

^{a}The Cartesian coordinate system used here and in Tables VII–IX has O_6 at the origin, C_2 on the +z axis, and N_1 in the ++ quadrant of the xz plane.

Table 7. EH orbital energies and MO's of N–CH$_3$–3β–NH$_2$–azetidin-2-one with C$_3$C$_2$–N$_1$C$_5$ = 135°

MO	ε,eV	Large LCAO-MO Coefficients	Mnemonic
LEMO	−7.14	$-0.51(O_62p_y)+0.91(C_22p_y)-0.44(N_12p_y)$	amide π*
HOMO	−12.02	$-0.36(O_62p_z)+0.26(C_22p_z)-0.36(N_12p_z)$ $-0.38(N_12p_y)-0.26(C_32p_x)+0.28(N_72p_x)$ $-0.43(N_72p_y)+0.25(H_81s)$	NH$_2$,O n-derived
NHOMO	−12.82	$-0.35(O_62p_y)+0.60(N_12p_y)-0.40(N_72p_y)$	amide π-derived
NNHOMO	−13.34	$+0.57(O_62p_x)-0.38(C_32p_z)-0.50(N_72p_y)$	NH$_2$,O n'

Table 8. EH orbital energies and MO's of N–CH$_3$–3β–NH$_3^+$–azetidin-2-one with C$_3$C$_2$–N$_1$C$_5$ = 180°

MO	ε,eV	Large LCAO-MO Coefficients	Mnemonic
LEMO	−6.94	$-0.50(O_62p_y)+0.91(C_22p_y)-0.51(N_12p_y)$	amide π*
HOMO	−12.59	$-0.42(O_62p_y)+0.79(N_12p_y)$	amide π
NHOMO	−12.81	$-0.68(O_62p_z)+0.33(C_22p_z)-0.28(N_12p_x)$ $+0.35(C_32p_z)-0.26(C_32p_x)$	amide n
NNHOMO	−13.86	$-0.32(O_62p_z)+0.27(C_42p_z)+0.40(C_42p_x)$ $-0.42(C_32p_z)-0.25(C_32p_x)$	C$_3$–C$_4$ σ

Table 9. EH orbital energies and MO's of N–CH$_3$–3β–NH$_3^+$–azetidin-2-one with C$_3$C$_2$–N$_1$C$_5$ = 135°

MO	ε,eV	Large LCAO Coefficients	Mnemonic
LEMO	−7.14	$+0.51(O_62p_y)-0.91(C_22p_y)+0.44(N_12p_y)$	amide π*
HOMO	−12.31	$-0.37(O_62p_z)+0.27(O_62p_y)-0.42(N_12p_x)$ $-0.56(N_12p_y)$	amide π-derived
NHOMO	−13.05	$+0.56(O_62p_x)-0.45(N_12p_y)-0.37(C_32p_z)$	amide n-derived
NNHOMO	−13.90	$+0.43(C_42p_x)-0.37(C_32p_z)-0.26(C_32p_x)$	C$_3$–C$_4$ σ

mixture is labeled "n'" and the lower one "n"". (As seen in Table 2, n' does *not* contribute much oscillator or rotatory strength to the region of interest.) Protonation of 4 has almost no effect on the LEMO; hence use of the label "amide π^*" is arelatively good description for this MO.

The shape and energy of filled EHMO's depend on the degree of pyramidization of the β-lactam nitrogen. Traced in Fig. 4 are the orbital energies of 4 as a function dihedral angle ω. Also shown in Fig. 4 are *ab initio* orbital energies for formamide.[30,32] Formamide, being nearly planar,[15,29-32,40] can have its high-lying filled MO's easily identified as being π or n. The *ab initio* calculations [29-32] place the occupied π orbital above the n orbital. (As has been pointed out before,[29,30] the *ab initio* orbital energies of formamide may not be used to predict ionization potentials because of a breakdown in Koopmans' theorem.[41] Likewise, the ordering of the filled orbitals cannot be used directly to predict excitation energies because of the contribution of Coulomb and exchange integrals). The EH MO's of 4 can be easily labeled when $\omega = 180°$, and the labels added to the curves in the correlation diagram of Fig. 4 apply to the structures with the N-Me carbon coplanar with the β-lactam ring. Note that the EH method places the π orbital above the n orbital in 4 when $R = NH_3^+$ and $\omega = 180°$. When $R = NH_2$, perturbational mixing of the amino and amide n orbitals splits them apart into n and n'. The top two occupied MO's diverge in energy as ω decreases from 180° to 135° regardless of whether $R = NH_3^+$ or NH_2.

As a β-lactam nitrogen becomes more pyramidal, the amide n and π orbitals mix with each other, so that the final orbitals acquire shapes similar to those shown in Ref. 2 for a penam. The traditional picture of n and π orbitals of a planar amide has the axis of the 2p-like lobes on oxygen *in* the O–C–N plane in the case of the n orbital and *perpendicular* to the O–C–N plane in the π orbital.[31,42,43] Similar directionality is apparent from the MO coefficients for the $\omega = 180°$ conformers of 4 in Tables 6 and 8. The picture is altered when the amide moiety is nonplanar. The top two occupied orbitals plotted in Fig. 4 for 4 at 135° have lobes on oxygen which are tipped with respect to the O–C–N plane. Also the orbital lobes on nitrogen change significantly as its hybridization changes from sp^2 toward sp^3. Because of the mixing of the orbitals, it is not altogether accurate to refer to $n \rightarrow \pi^*$ and $\pi \rightarrow \pi^*$ transitions in *nonplanar* β-lactams, although this terminology may be adequate for small deformations. CNDO/S calculations done with configuration interaction demonstrate that as the nitrogen becomes more pyramidal, the excited states become less configurationally pure.

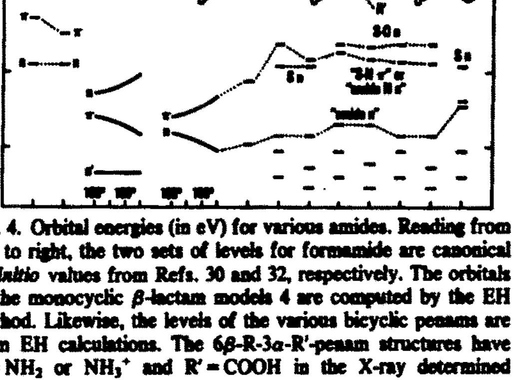


Fig. 4. Orbital energies (in eV) for various amides. Reading from left to right, the two sets of levels for formamide are canonical *ab initio* values from Refs. 30 and 32, respectively. The orbitals of the monocyclic β-lactam models 4 are computed by the EH method. Likewise, the levels of the various bicyclic penams are from EH calculations. The 6β-R-3α-R'-penam structures have $R = NH_2$ or NH_3^+ and R' = COOH in the X-ray determined position described in Refs. 1 and 2. Included are the S(β) and R(α)-sulfoxides of penam as calculated in Ref. 2. The cepham levels are EH values as reported in Ref. 45.

The orbitals of the 1-carbapenam 3 correspond closely to the orbitals of protonated 4 when $\omega = 135°$ as seen in Fig. 4 and in Table 5 and 9. The two occupied orbitals of 3 have been given the mnemonics "amide N n" and "amide n" in Table 5. These labels are chosen for consistency with earlier notations.[1,2] The "amide N n" label reflects the fact that about 40% of the electron population in the HOMO is in the nitrogen orbitals. However, these mnemonics can be misleading because of the conformational mixing described above. In retrospect, the labels used before were not the best choices. Perhaps "π-derived" and "n-derived" as in Tables 7 and 9 would have been better labels to describe the two occupied orbitals localized in *nonplanar* β-lactams.

Turning now to the assignment of the CD transitions as suggested by the correlation diagram (Fig. 4), it becomes apparent that EH calculations in the virtual orbital approximation gives the $\pi\pi^*$ state below the $n\pi^*$ state for the *planar, protonated* forms of 4. This is obviously incorrect in light of the *ab initio* calculations and the usual experimental interpretations of the amide chromophore. The problem with the EH predictions is not in the ordering of the MO's because CNDO/S and *ab initio* (Fig. 4) calculations give the same sequence. Rather, the discrepancy arises because the virtual orbital approximation in the EH framework neglects the contributions from the Coulomb and exchange integrals to the excitation energy. The CNDO/S predictions (as in Table 3) do include these contributions. Hence the CNDO/S results for the monocyclic β-lactams with $\omega = 180°$ mentioned above give the $n \rightarrow \pi^*$ transition at longer wavelengths than the $\pi \rightarrow \pi^*$ transition as expected.

In spite of the problem in the EH framework for some of the planar or nearly planar β-lactam structures, the EH MO's give what appear to be correct predictions of chiroptical properties for the "pyramidal" β-lactam structures. In penams[1,2] the mixing of the n and π orbitals may be great enough so that the orbital shapes are apparently fairly well represented by the EH wavefunctions.

The mixing of the orbitals due to nonplanarity of the β-lactam nitrogen can be expressed in terms of perturbation theory.[44] Hence in essence, $\mathbf{n} = n + c\pi$, and $\boldsymbol{\pi} = \pi - cn$, where boldface orbitals are the "n-derived" and "π-derived" orbitals, c is a mixing coefficient, and n and π are the orbitals of a planar amide. Orbital mixing can be described quite well by the EH method. The divergence of the energies of the HOMO and NHOMO of 4 as a function of ω in Fig. 4 is consistent with perturbational mixing.

Guided by the semiempirical calculations on the nature of the orbitals, as well as consideration of available experimental and other theoretical data, we are led to the following proposition and conclusion. The 231-nm Cotton effect of 2 involves an excited state related to the $\mathbf{n}\boldsymbol{\pi}^*$

configuration and which is mixed to some extent with the $\pi\pi^*$ and (to a lesser extent) other configurations. The Cotton effect of opposite sign at just below 200 nm is probably related mainly to the $\pi\pi^*$ configuration, but which is also mixed with other configurations by pyramidalization of nitrogen. The assignments we are putting forward can be summarized in terms of the wavefunctions of the two excited states which to a first approximation are:

$$\Psi(231) = c_1\psi(\ldots n\pi^*) + c_2\psi(\ldots \pi\pi^*)$$

$$\Psi(197) = c_2\psi(\ldots n\pi^*) - c_1\psi(\ldots \pi\pi^*),$$

where c_1 and c_2 are coefficients for the single determinantal wavefunctions on the right. We anticipate that *ab initio* calculations will in the future show that multiconfiguration wavefunctions composed of perturbationally mixed MO's are needed to describe the excited states of 1-carbapenam and other bicyclic β-lactams.

Relation to electronic structure of other β-lactams. In the remainder of this article, the orbitals and assignments reported earlier[1,2,7,45] for penams, penam sulfoxides, and cephams will be discussed in light of the new results on the 1-carbapenam and the monocyclic β-lactams. The EH orbital energies for these other species are shown in Fig. 4. The main point to make is that the origin of the two filled orbitals localized on the β-lactam amide group is now better understood. In particular, the nonplanarity of the β-lactam nitrogen in the bicyclic structures mixes the n and π orbitals. Then one or both of these mixed orbitals can mix with the orbitals of the other functionalities, such as sulfur or an NH_2 group.

The energy and shape of the virtual amide π^* orbital carries through pretty much intact for all structures in Fig. 4. The π-derived orbital in 1-carbapenam 3 (*i.e.*, the orbital labeled "amide N n" in Table 5) is similar to the HOMO of the two penam structures (Fig. 4). In the penam sulfoxides, this orbital character occurs in the NHOMO. (The NHOMO of the penams is the sulfur lone pair, and the HOMO of the sulfoxides is an orbital identified[2] as "S-O n".) The HOMO of the penams and the NHOMO of the S(or β) sulfoxide is labeled "S-N π" because the lone pair orbital lobes on S and N extend below the molecular plane and overlap in roughly π fashion.[2,7] In the R(or α) sulfoxides, such overlap is essentially eliminated, and the "amide N n" label comes closer to describing the shape of the orbital. For the cepham, some of the orbitals have delocalized character so it is not possible to simply correlate them with those of the other structures. The NHOMO of 3 (Fig. 4) correlates with the NNHOMO of the penams and penam sulfoxides.

Regarding the various other assignments that have been proposed for the penam chromophores, it now appears that the characteristic Cotton effect near 230 nm cannot be due *exclusively* to either a β-lactam amide transition or a sulfide transition. Rather, there seem to be two transitions involved as suggested previously.[1,2] One of these transitions, the one present in 1-carbapenam, involves the conformationally modified $n\pi^*$ excited state that we have been discussing. The second of these is associated with the sulfur, possibly involving charge transfer to the amide group.[1,2] The 203-nm CD band of penams cannot be due to a traditional $n\pi^*$ excited state. Instead, it appears to arise from the conformationally modified $\pi\pi^*$ β-lactam amide excited state. Although this band occurs at wavelengths similar to those for Rydberg and/or dimer-induced transitions, the aqueous solution CD spectra of penams are probably not affected appreciably by these. The presently available evidence does not allow assessment of the contribution, if any, of the sulfur chromophore to penam's 203-nm band. A theoretical or experimental study of the chiroptical properties of model structures, such as 2-thia [3.2.0] heptane and its sulfoxide, may be helpful in this regard.

The assignment for the positive CD band near 185 nm of 6-aminopenicillanic acid[2] needs revision. The band is quite sensitive to pH, but always positive. The band undergoes its biggest change upon protonation of the amino group. Although no calculations were done on it because of its high energy, the band was thought to be due to carbonyl $\pi \rightarrow \pi^*$ transitions.[2] A more likely assignment for the 185-nm band is charge transfer from the β-lactam amide localized orbitals to the amino group orbitals. A similar assignment has been advanced for 3-ammonium-pyrrolidin-2-one.[46] This excited state being of high energy would no doubt be quite complex, especially when described by an accurate wavefunction.

Acknowledgements—We thank H. Vanderhaeghe for correspondence and preprints, and T. D. Bouman, M. M. Marsh and A. H. Hunt for discussions.

REFERENCES

[1] D. B. Boyd, C. -Y. Yeh and F. S. Richardson, *J. Am. Chem. Soc.* 98, 6100 (1976).

[2] F. S. Richardson, C. -Y. Yeh, T. C. Troxell and D. B. Boyd, *Tetrahedron* 33, 711 (1977).

[3] R. Busson, E. Roets and H. Vanderhaeghe, *Recent Advances in the Chemistry of β-Lactam Antibiotics* (Edited by J. Elks) p. 304. Chemical Society, London, Special Publication No. 28 (1977).

[4] R. Busson and H. Vanderhaeghe, *J. Org. Chem.* 43, 4438 (1978).

[5] R. Busson, E. Roets and H. Vanderhaeghe, *Ibid.* 43, 4434 (1978).

[6] R. C. Bingham, M. J. S. Dewar and D. H. Lo, *J. Am. Chem. Soc.* 97, 1285 (1975).

[7] D. B. Boyd, *Ibid.* 94, 6513 (1972).

[8] D. B. Boyd, *J. Chem. Educ.* 53, 483 (1976).

[9] D. B. Boyd, *Int. J. Quantum Chem., Quantum Biol. Symp. No.* 4, 161 (1977).

[10] D. B. Boyd and W. N. Lipscomb, *J. Theor. Biol.* 25, 403 (1969).

[11] J. Del Bene and H. H. Jaffé, *J. Chem. Phys.* 48, 1807 (1968); H. H. Jaffé, *Acc. Chem. Res.* 2, 136 (1969); R. L. Ellis, G. Kuehnlenz and H. H. Jaffé, *Theor. Chim. Acta* 26, 131 (1972).

[12] K. Nishimoto and N. Mataga, *Z. Phys. Chem.* (Frankfurt am Main) 12, 335 (1957).

[13] I. Frič, P. Maloň, M. Tichý and K. Bláha, *Coll. Czech. Chem. Commun.* 42, 678 (1977). See, also, M. Tichý, E. Dušková and K. Bláha, *Tetrahedron Letters*, 237 (1974).

[14] P. Maloň and K. Bláha, *Coll. Czech. Chem. Commun.* 42, 687 (1977).

[15] P. Maloň, S. Bystrický and K. Bláha, *Ibid.* 43, 781 (1978).

[16] C. -Y. Yeh and F. S. Richardson, *Theor. Chim. Acta* 39, 197 (1975).

[17] T. D. Bouman and D. A. Lightner, *J. Am. Chem. Soc.* 98, 3145 (1976); T. D. Bouman, *J. Chem. Soc.*, Chem. Commun. 665 (1976).

[18] A. P. Volosov and V. A. Zubkov, *Theor. Chim. Acta* 44, 375 (1977).

[19] J. A. Pople and G. A. Segal, *J. Chem. Phys.* 44, 3289 (1966).

[20] C. C. J. Roothaan, *Rev. Mod. Phys.* 23, 69 (1951).

[21] P. -O. Löwdin, *J. Chem. Phys.* 18, 365 (1950); see also, D. B. Boyd, *J. Am. Chem. Soc.* 94, 64 (1972); Ref. 22; and A. Rauk, J. O. Jarvie, H. Ichimura, and J. M. Barriel, *J. Am. Chem. Soc.* 97, 5656 (1975).

[22] F. S. Richardson and N. Cox, *J. Chem. Soc.*, Perkin II, 1240

(1975); F. S. Richardson and W. Pitts, *Ibid.* Perkin II, 1276 (1975); H. Kreigh and F. S. Richardson, *Ibid.* Perkin II, 1674 (1976); G. Hilmes, C. -Y. Yeh and F. S. Richardson, *J. Phys. Chem.* 80, 1798 (1976); H. Dickerson and F. S. Richardson, *Ibid.* 80, 2686 (1976); S. Ferber and F. S. Richardson, *Tetrahedron* 33, 1037, 1095 (1977).

[23] F. S. Richardson, D. D. Shillady, and J. E. Bloor, *J. Phys. Chem.* 75, 2466 (1971), and Ref. 22 describe the units for reduced rotatory strength. N.B. the units used in Refs. 1 and 2 are the same as those used in these papers and in the present paper. The units were not described properly in Refs. 1 and 2, although they were used properly in the calculations. See also, A. Moscowitz, *Optical Rotatory Dispersion*, (Edited by C. Djerassi), p. 170, McGraw-Hill, New York, (1960), for the standard definition of reduced rotatory strength which is used in our calculations.

[24] I. Tinoco, Jr. and C. R. Cantor, *Methods in Biochemical Analysis* (Edited by D. Glick) Vol. 18, p. 81. Wiley, New York (1970).

[25] D. B. Boyd, R. B. Hermann, D. E. Presti and M. M. Marsh, *J. Med. Chem.* 18, 408 (1975).

[26] H. Rehling and H. Jensen, *Tetrahedron Letters*, 2793 (1972).

[27] H. Ogura, H. Takayanagi, K. Kubo and K. Furuhata, *J. Am. Chem. Soc.* 95, 8056 (1973); H. Ogura, K. Takeda and H. Takahashi, *Chem. Pharm. Bull.* 23, 2469 (1975).

[28] S. R. Ramakumar, K. Venkatesan and H. P. Weber, *Helv. Chim. Acta* 60, 1691 (1977); see also, K. Bláha, P. Maloň, M. Tichý, I. Frič, R. Usha, S. Ramakumar and K. Venkatesan, *Coll. Czech. Chem. Commun.* 43, 3241 (1978).

[29] H. Basch, M. B. Robin and N. A. Kuebler, *J. Chem. Phys.* 47, 1201 (1967).

[30] H. Basch, M. B. Robin and N. A. Kuebler, *Ibid.* 49, 5007 (1968).

[31] M. A. Robb and I. G. Csizmadia, *Theor. Chim Acta* 10, 269 (1968); *J. Chem. Phys.* 50, 1819 (1969).

[32] L. Z. Stenkamp and E. R. Davidson, *Theor. Chim. Acta* 44, 405 (1977); see also, L. E. Nitzsche and E. R. Davidson, *J. Chem. Phys.* 68, 3103 (1978); *J. Am. Chem. Soc.* 100, 7201 (1978).

[33] D. G. Barnes and W. Rhodes, *J. Chem. Phys.* 48, 817 (1968).

[34] D. W. Urry, *J. Phys. Chem.* 72, 3035 (1968); *Ann. Rev. Phys. Chem.* 19, 477 (1968).

[35] M. Goodman, C. Toniolo and J. Falcetta, *J. Am. Chem. Soc.* 91, 1816 (1969).

[36] K. Kaya and S. Nagakura, *Theor. Chim. Acta* 7, 117, 124 (1967).

[37] N. J. Greenfield and G. D. Fasman, *J. Am. Chem. Soc.* 92, 177 (1970).

[38] K. Wittel and S. P. McGlynn, *Chem. Rev.* 77, 745 (1977).

[39] P. K. Mehrotra and R. Hoffmann, *Theor. Chim. Acta* 48, 301 (1978).

[40] D. H. Christensen, R. N. Kortzeborn, B. Bak and J. J. Led, *J. Chem. Phys.* 53, 3192 (1970); M. Perricaudet and A. Pullman, *Int. J. Peptide Protein Res.* 5, 99 (1973); A. M. Armbruster and A. Pullman, *FEBS Lett.* 49, 18 (1974); R. F. Nalewajski, *J. Am. Chem. Soc.* 100, 41 (1978); and refs cited.

[41] T. Koopmans, *Physica* 1, 104 (1933). Oddly, there are as many literature citations giving 1934 as the year of publication for this famous paper as there are those giving 1933. See, also, *Chem. Abstr.* 28, 2606 (1934).

[42] W. L. Jorgensen and L. Salem, *Organic Chemist's Book of Orbitals.* Academic Press, New York (1973).

[43] R. E. Geiger and G. H. Wagniere, *Helv. Chim. Acta* 58, 738 (1975).

[44] R. Hoffmann, *Acc. Chem. Res.* 4, 1 (1971); L. Libit and R. Hoffmann, *J. Am. Chem. Soc.* 96, 1370 (1974).

[45] D. B. Boyd, *J. Med. Chem.* 16, 1195 (1973); *Int. J. Quantum Chem., Quantum Biol. Symp. No.* 1, 13 (1974).

[46] F. S. Richardson and W. Pitts, *Biopolymers* 13, 703 (1974); F. S. Richardson, R. Strickland and D. D. Shillady, *J. Phys. Chem.* 77, 248 (1973).