Electronic Structures of Cephalosporin and Penicillin Moieties

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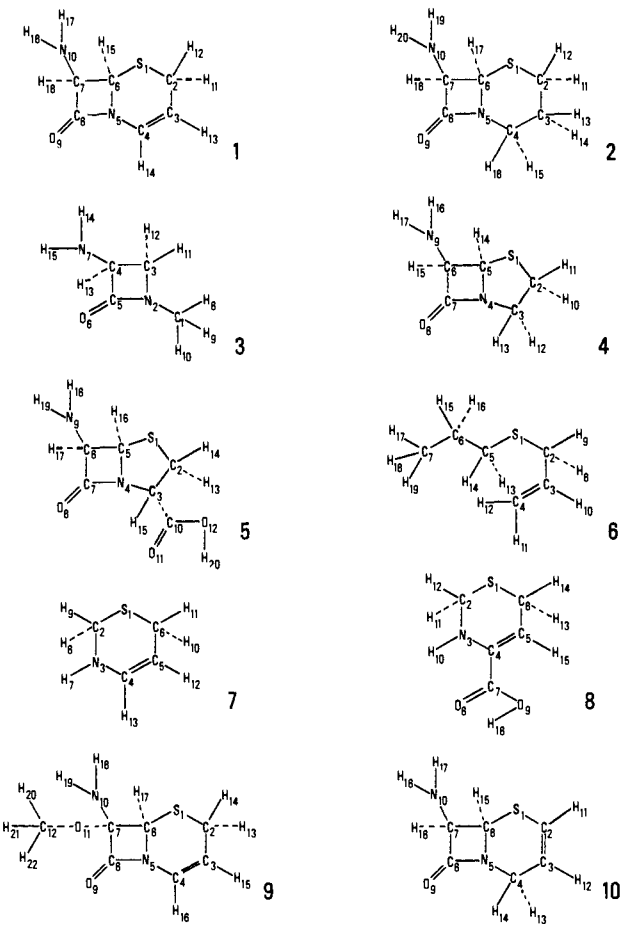
Abstract: The electronic energy levels and charge distributions of the cephem and penam nuclei and their analogs are obtained by extended Hückel molecular orbital calculations. Oscillator strengths for the uv transitions are computed from rigorously evaluated dipole length integrals, and excitation energies are obtained in the virtual orbital approximation. Qualitative agreement with experimental spectral properties across a range of related molecules indicates an adequacy of the theory to describe the general nature of the chromophores involved, even though quantitative agreement is expectedly mediocre. In agreement with deductions from experimental data, the 260-nm band of the 3-cephems is due to the excitation of an electron from an enamine π MO to one with both C=O π^* and C=C π^* character, and the 230-nm band arises from a transition from an amide lone-pair MO to the C=O, C=C π^* MO. In the β-lactams where no chromophore mixes strongly with the MO's localized on the β-lactam ring, the principal transition is of amide n $\rightarrow$ π^* character.

Cephalosporins and penicillins constitute an important class of therapeutically useful antibiotics. The molecular nuclei of these compounds, namely, a β-lactam ring fused to a dihydrothiazine or thiazolidine ring, have been shown to be responsible for the biological activity of these compounds, although, of course, the variety of side chains present may enhance or mitigate the activity.[1] In this paper the electronic structures of these molecular nuclei are explored by quantum mechanical calculations. In particular, the uv spectral transitions are studied in order to make assignments and to gain a description of the chromophores. If the calculations are reasonably successful in correlating with experimental data, and we will see that they are, then the computed molecular orbitals may be regarded as a correspondingly reliable description of the electronic structures. Utilizing the proposed[2] mechanism of action of these antibiotics and the knowledge of the electronic structure, it should be possible to rationally devise modifications of the cephalosporins and penicillins which will enhance their biological activity.[3]

Our initial goal then is to learn about the electronic structures of the cephalosporin and penicillin nuclei by a comparison of experimental and theoretical findings on the spectra of these moieties. The approach will be to investigate the model compounds depicted schematically below which are appropriate for the analysis of the chromophores of the cephem and penam nuclei. Experimental uv and CD spectral data are not available for these models, but by abstracting information from the most appropriate compounds which have been observed spectroscopically, it will be possible to make qualitative comparisons between theory and experiment.



Model **1**, 7-amino-3-cephem, is, of course, the fundamental nucleus of the biologically active cephalosporins. A detailed analysis of 3-cephem spectra has recently been published,[4] and it is of primary concern to study this species. Model **2**, 7-aminocepham, lacks the carbon–carbon double bond of **1**, but still contains the β-lactam and sulfide chromophores. The β-lactam chromophore is also investigated in the simple β-lactam model compound **3** and in the decarboxylated, **4**, and carboxylated, **5**, penams. Calculations on the known compound 6-aminopenicillanic acid (6-APA), which is **5** with geminal dimethyl substituents on C_2, are not included because the methyl groups are expected to have only a small perturbing effect and would lengthen the calculations considerably. The β,γ-unsaturated sulfide portion of **1** is modeled by compound **6**, propylallyl sulfide. A closer analog of **1** is the dihydrothiazine ring without, **7**, and with, **8**, the carboxyl group. Calculations on the dihydrothiazine ring systems can elucidate the combined effects of the enamine and sulfide chromo-

(1) C. Hansch and A. R. Steward, *J. Med. Chem.*, 7, 691 (1964); C. Hansch and E. W. Deutsch, *ibid.*, 8, 705 (1965); G. L. Biagi, M. C. Guerra, A. M. Barbaro, and M. F. Gamba, *ibid.*, 13, 511 (1970).

(2) D. J. Tipper and J. L. Strominger, *J. Biol. Chem.*, 243, 3169 (1968); B. Lee, *J. Mol. Biol.*, 61, 463 (1971); R. Hartmann, J.-V. Höltje, and U. Schwarz, *Nature (London)*, 235, 426 (1972).

(3) R. B. Hermann, to be published.

(4) R. Nagarajan and D. O. Spry, *J. Amer. Chem. Soc.*, 93, 2310 (1971).

phores. Comparison of **7** and **8** allows some assessment of the effect of the carboxyl group. The 3-acetoxymethyl-4-carboxyl form of **1** (giving 7-aminocephalosporanic acid, 7-ACA) was not calculated, again because of the computer times involved and because the smaller analogs should suffice. Experimentally, the effect of 7-methoxylation of a 3-cephem is known,[5] so calculations are included on **9** which will be compared to **1**. Finally, 7-amino-2-cephem, **10**, is studied both because it is an interesting α,β-unsaturated sulfide and because it affords an example of a cephem nucleus without antibiotic activity. The relevant uv and CD spectral data for all the model compounds will be given later along with the presentation of the calculational results.

Methodology

The extended Hückel (EH) method[6] of molecular orbital theory is especially well suited for the compounds of interest here because their nonplanarity necessitates the simultaneous treatment of all valence electrons. Moreover, the fact that the secular equation for each molecule needs to be solved only once (as contrasted with several times in an iterative, self-consistent MO method) means that the wave functions are rapidly evaluated on a computer. The main question to ask in regard to selection of the EH method is whether such a simple method is adequate to describe the ground and excited state wave functions. There are an increasing number of indications[7-9] that the EH method is adequate for making spectral assignments, if judiciously applied to compounds spanning a sufficiently narrow domain of chemical types. Hence we proceeded cautiously, not expecting quantitative agreement with experimental spectra, but aiming at obtaining qualitatively useful results.

One type of data entering into the calculation of an EH wave function includes the orbital exponents and the negative of the valence state ionization potentials (VSIP's). These were taken at the commonly accepted values for carbon, nitrogen, and hydrogen.[6] Several sets[10,11] of sulfur parameters were tested before settling on the following VSIP's[11]: 20.0 (S 3s), 13.3 (S 3p), 4.0 eV (S 3d). The energy assigned the S 3d orbitals is such that they are not highly occupied in divalent sulfur compounds (total occupation number of d orbitals is considerably less than 0.1), but such that the MO's formed of d orbitals are accessible by uv excitations. Exponents for sulfur atomic orbitals are the best atom values,[12] except for the S 3d exponent which is taken as 1.708, the optimized value in a molecular environment.[13] This exponent for the 3d Slater-type basis functions is in line with a proposed rule[14] on the size of the d orbitals of second-row atoms. Our sulfur parameters provided the most reasonable charge distribution (in terms of net atomic charges) and excitation energies for not only the compounds treated here, but also for other compounds of divalent sulfur.[15] Turning to the oxygen orbital parameters, we again tried several sets.[6,16] A set consisting of Slater exponents and VSIP's of 29.0 (O 2s) and 14.5 eV (O 2p) proved to give the least excessive charge separations. These VSIP's are based on an extrapolation of quadratic functions fitted, respectively, to the 2s and 2p VSIP's of boron,[17] carbon,[6] and nitrogen.[6] The values are considerably less negative than those used by previous authors. As is recognized, a common fault of the EH method is to give exaggerated charge separations, so that our set of orbital parameters compensates in the right direction. In addition, our standard usage[6,18,19] of a Wolfsberg-Helmholz constant of 2.0 also diminishes charge separations somewhat.

The second type of data entering into EH calculations is the geometry of the molecules specified in terms of atomic coordinates. The tabulation of coordinates for all atoms in compounds **1**–**10** would be too voluminous to include here, and hence we settle for the following descriptions. The crystal-structure determination[20a,b] of cephaloridine·HCl·H_2O is the best available source of the nonhydrogenic atomic positions of **1**. The preferred conformation of **6** is not known experimentally, so in order to be useful in the analysis of the spectra of **1**, the geometry of **6** is based on the SCC=C portion of **1** with the addition of a staggered propyl side chain oriented not to sterically interfere with the allyl portion of the molecule. Similarly, the geometry of **9** is derived from that of **1** with atoms added at standard bond lengths and angles as described below. Two conformations of **7** and **8** were investigated: one, a distorted half-chair, taken directly from the dihydrothiazine coordinates of **1**, and the other, a boat conformation,[21] based on Dreiding models. The positions of the nonhydrogenic atoms of **10** were obtained from the sole X-ray determined structure of a 2-cephem, phenoxymethyl-Δ^2-desacetoxyl cephalosporin.[20a,c] Since it was expected that the hybridization at the β-lactam nitrogen of **2** and **3** would be nearly planar as in **10**, the atomic coordinates of **2** and **3** were taken from **10** with the additional assumption that the tetrahydrothiazine ring in **2** exists in a chair conformation. The **4** and **5** penam geometries were taken from the refined crystal structure of potassium benzylpenicillin.[22] Hy-

(5) R. Nagarajan, L. D. Boeck, M. Gorman, R. L. Hamill, C. E. Higgens, M. M. Hoehn, W. M. Stark, and J. G. Whitney, *J. Amer. Chem. Soc.*, **93**, 2308 (1971). See, also, E. H. Flynn, "Cephalosporins and Penicillins: Chemistry and Biology," Academic Press, New York, N. Y., 1972.

(6) D. B. Boyd and W. N. Lipscomb, *J. Theor. Biol.*, **25**, 403 (1969), and references therein.

(7) R. Hoffmann, *Tetrahedron*, **22**, 539 (1966); *Accounts Chem. Res.*, **4**, 1 (1971).

(8) L. Burnelle and M. J. Kranepool, *J. Mol. Spectrosc.*, **37**, 383 (1971).

(9) D. L. Coffen, J. Q. Chambers, D. R. Williams, P. E. Garrett, and N. D. Canfield, *J. Amer. Chem. Soc.*, **93**, 2258 (1971).

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(11) R. Gleiter and R. Hoffmann, *Tetrahedron*, **24**, 5899 (1968).

(12) E. Clementi and D. L. Raimondi, *J. Chem. Phys.*, **38**, 2686 (1963).

(13) F. P. Boer and W. N. Lipscomb, *ibid.*, **50**, 989 (1969).

(14) D. B. Boyd, *ibid.*, **52**, 4846 (1970).

(15) D. B. Boyd, *J. Amer. Chem. Soc.*, in press.

(16) R. Hoffmann, G. D. Zeiss, and G. W. Van Dine, *ibid.*, **90**, 1485 (1968).

(17) R. Hoffmann, *J. Chem. Phys.*, **40**, 2474 (1964).

(18) R. A. Archer, D. B. Boyd, P. V. Demarco, I. J. Tyminski, and N. L. Allinger, *J. Amer. Chem. Soc.*, **92**, 5200 (1970).

(19) D. B. Boyd and R. Hoffmann, *ibid.*, **93**, 1064 (1971).

(20) (a) R. M. Sweet and L. F. Dahl, *ibid.*, **92**, 5489 (1970). (b) Our coordinate system for **1** has N_5 at the origin, C_6 on the $+z$ axis, C_3 in the xz plane, and the α face of the molecule projecting in the $+y$ direction. (c) Coordinates for **10** were put in a right-handed Cartesian system (as used for the other molecules) with an arrangement analogous to that described for **1**.

(21) The coordinate system for the boat forms of **7** and **8** is such that N_3 is at the origin, C_2 is on the $+z$ axis, S_1 is in the xz plane, and C_4 and C_5 project toward the β face of the molecule in the $-y$ direction.

(22) G. J. Pitt, *Acta Crystallogr.*, **5**, 770 (1952); D. Crowfoot, C. W. Bunn, B. W. Rogers-Low, and A. Turner-Jones in "The Chemistry of Penicillin," H. T. Clarke, J. R. Johnson, and R. Robinson, Ed., Prince-

drogens and other atoms necessary to complete structures **1–10** were added with the following bond lengths, 1.10 (C–H), 1.00 (N–H), 0.95 (O–H), 1.54 (C–C), and 1.43 Å (C–O), and the following bond angles, 109.4712° at nitrogens and saturated carbons, 120° at other carbons, 105° for C–O–H, and 110° for C–O–C. In cases where several conformers or rotamers were studied, structural details are described further in the Results.

Once the EH MO's are obtained, then the excitation energies and oscillator strengths may be computed. To reduce the computations to manageable proportions, it is common to employ the necessarily crude virtual orbital approximation. In this approximation a singlet–singlet excitation is assumed to occur by the promotion of an electron from one of the ground-state filled MO's to one of the previously empty virtual orbitals (which also come from the solution of the secular equation). Thus, the excitation energy is the gap between the MO eigenvalues, $\Delta E = \epsilon_m - \epsilon_n$, and the oscillator strength is evaluated from the transition moment integral between MO's ψ_m and ψ_n. When an electron is excited from ψ_m to ψ_n in an N-electron molecule, the transition moment integral (in atomic units and using the dipole length formalism) between the ground and excited state singlet wave functions is

$$\mathbf{R}^{mn} = \Big\langle (N!)^{-1/2}\sum_r (-1)^r P_r[\psi_1(1)\alpha(1)\ldots \psi_m(j)\alpha(j)\psi_m(j+1)\beta(j+1)\ldots \psi_{N/2}(N)\beta(N)]\Big|\sum_{i=1}^{N}\mathbf{r}_i\Big|\frac{1}{\sqrt{2}}\Big\{(N!)^{-1/2}\sum_r (-1)^r P_r[\psi_1(1)\alpha(1)\ldots \psi_n(j)\alpha(j)\psi_m(j+1)\beta(j+1)\ldots\psi_{N/2}(N)\beta(N)] - (N!)^{-1/2}\sum_r (-1)^r P_r[\psi_1(1)\alpha(1)\ldots \psi_n(j)\beta(j)\psi_m(j+1)\alpha(j+1)\ldots\psi_{N/2}(N)\beta(N)]\Big\}\Big\rangle$$

Here P_r is the usual electron permutation operator[23] with the index r going over all permutations of the N electrons among the one-electron orbitals, which are given as a product of a MO and a spin function, α or β. With the aid of the orthonormality of the MO's, the above expression reduces to $\mathbf{R}^{mn} = \sqrt{2}\langle\psi_m|\mathbf{r}|\psi_n\rangle$. Since the MO's are expressed as linear combinations of atomic orbitals, $\psi_m = \Sigma_p C_{pm}\chi_p$, we evaluate $\mathbf{R}^{mn} = \sqrt{2}\Sigma_p\Sigma_q C_{pm}C_{qn}\langle\chi_p|\mathbf{r}|\chi_p\rangle$, where the procedure for the exact evaluation of the dipole moment integrals over the Slater-type basis functions, χ_p, has been discussed.[24,25] If the transition moment integral is in atomic units and the excitation energy, ΔE, in electron volts, then the oscillator strength, which is proportional to the area under a uv absorption band, is given[26] by $f = 0.0245\Delta E|\mathbf{R}^{mn}|^2$. For molecules of interest here, symmetry is of little use in deciding on the allowedness of a transition, and, consequently, $\mathbf{R}^{mn}$ is evaluated exactly with all one- and two-center integrals.

No attempt is made to compute optical rotatory strengths because of the inadequacy of EH wave functions found in previous studies.[27] Nevertheless, experimental CD data can be useful to our analysis. Frequently, bands occurring in the uv region can be identified in CD spectra because of their optical activity.

Results and Discussion

7-Amino-3-cephem. The 3-cephem moiety is observed experimentally to have two well-defined transitions in the uv region: a strong band (extinction coefficient 7000–10,000) near 260 nm which is seen in both uv and CD spectra, and a weaker band (extinction coefficient <6000) at about 230 nm, which is not seen in all uv spectra of cephalosporins, but is discernible in the CD. By a comparison of many different cephalosporins, it has been proposed[4] that the 260-nm band is due to a $\pi \rightarrow \pi^*$ transition of the C=C bond, and the 230-nm band originates from the $n \rightarrow \pi^*$ transition of the β-lactam carbonyl group. The possible effects of other functional groups on these primary chromophores of 3-cephems have been discussed in detail.[4]

Computationally, only two relatively intense transitions are predicted to occur in the uv region: one at 297 nm ($f = 0.36$), which is the lowest energy excitation, and one at 245 nm ($f = 0.17$), which is third lowest. Although these predicted λ_{max} values are obviously red-shifted from the above experimental values, there are several indications that the calculations are mimicking experiment. First, two strong transitions are obtained with the longer wavelength, one being of greater intensity. Second, examination of the character of the relevant MO's, as described below, led to the prediction that reduction of the double bond of the dihydrothiazine ring should eliminate the long-wavelength band. This was indeed corroborated by experiments.[4] Third, the theoretical description of the 3-cephem chromophore is completely consistent with that experimentally deduced.[4]

Consider now the nature of the high-lying filled MO's and the low-lying empty ones. MO theory, by its very nature, gives a delocalized description to each MO. But in order to attach a convenient label to each MO, one may examine the largest of the LCAO expansion coefficients and deduce the main character of each MO. The data for **1** are given in Table I. Whereas the exact values of the coefficients and eigenvalues are dependent upon the parameters entering the calculations, the character and energies of the MO levels were found to be fairly consistent over the range of parameters tested. In Table I the next to the next lowest empty (NNLE) MO is of mainly enamine π^* character. The NLEMO consists of empty 3d atomic orbitals. The LEMO is a mixture of a π^* orbital localized on the C=C functionality and a π^* orbital localized on the amide C=O group. In effect, the LEMO is the less antibonding combination of two localized, antibonding orbitals. The highest occupied (HO) MO is of enamine π character with some S 3p atomic orbital mixed in. The next highest occupied (NHO) MO is a lone pair orbital on sulfur. Finally, the NNHOMO has the form of an

ton University Press, Princeton, N. J., 1949, p 310. The coordinate system for models **4** and **5** is defined by N_4 being at the origin, C_6 being on the $+z$ axis, C_2 being in the xz plane, and the α face of the molecule projecting in the $+y$ direction.

(23) A. Messiah, "Quantum Mechanics," Vol. 2, Wiley, New York, N. Y., 1962, p 599.

(24) D. B. Boyd in "Purines: Theory and Experiment," E. D. Bergmann and B. Pullman, Ed., Academic Press, New York, N. Y., 1972.

(25) D. B. Boyd, *J. Amer. Chem. Soc.*, **94**, 64 (1972).

(26) G. Herzberg, "Molecular Spectra and Molecular Structure," Vol. 3, D. Van Nostrand Co., Princeton, N. J., 1967, p 417.

(27) R. R. Gould and R. Hoffmann, *J. Amer. Chem. Soc.*, **92**, 1813 (1970).

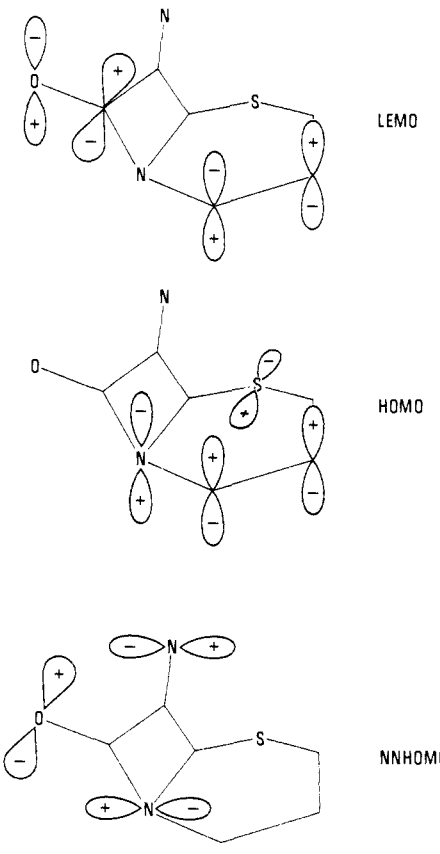


Figure 1. Schematic rendering of the principal shapes of the LEMO (C=C π^* and C=O π^*), HOMO (enamine π), and NNHOMO (amide n) of 7-amino-3-cephem.

Table I. Calculated Eigenvalues and MO's of **1**

MO	ϵ, eV	Large LCAO-MO coefficients[a]
NNLEMO	−5.82	$-0.51(C_3\ 2p_y) + 0.69(C_4\ 2p_y) - 0.48(N_5\ 2p_y) + 0.44(C_8\ 2p_y)$
NLEMO	−6.16	$+0.50(S_1\ 3p_x) + 0.48(S_1\ 3d_{xz}) - 0.53(S_1\ 3d_{xy})$
LEMO	−7.51	$-0.44(C_3\ 2p_y) + 0.44(C_4\ 2p_y) + 0.48(C_8\ 2p_z) - 0.60(C_8\ 2p_y) + 0.33(O_9\ 2p_y)$
HOMO	−11.69	$-0.33(S_1\ 3p_z) - 0.40(C_3\ 2p_y) - 0.29(C_4\ 2p_y) + 0.44(N_5\ 2p_y)$
NHOMO	−12.11	$+0.58(S_1\ 3p_z) + 0.54(S_1\ 3p_y)$
NNHOMO	−12.56	$-0.28(N_5\ 2p_z) + 0.35(O_9\ 2p_z) - 0.27(O_9\ 2p_y) + 0.39(N_{10}\ 2p_z)$

[a] Each MO, ψ_m, is a linear combination of AO's, χ_p, which are abbreviated as, *e.g.*, $C_3\ 2p_y$ for the $2p_y$ AO on C-3. See ref 6, 7, and 13 for similar notation.

amide lone pair orbital on the carbonyl oxygen and β-lactam nitrogen, but also it has some amino nitrogen character mixed in.

As can be derived from the data of Table I, there are eight possible excitations giving rise to transitions above 190 nm. The calculation of the oscillator strengths permitted the selection of those MO's involved in the two major transitions of the 3-cephem moiety mentioned before. The most intense band, which we associate with the experimental 260-nm transition, arises from an excitation of an electron from the HOMO to the LEMO. The second most intense band, which we associate with the experimenal 230-nm transition, involves an electron jumping between the NNHOMO and the LEMO. Thus, it is seen from the MO descriptions given above and sketched in Figure 1 that these MO's are in harmony with the proposed[4] nature of the 3-cephem chromophores. Furthermore, the extent of mixing of the various functional groups into the primary chromophores of the 3-cephem moiety can be seen in Table I. Other transitions, especially those involving the sulfur lone pair orbital (NHOMO) or the S 3d orbitals (NLEMO), are relatively weak as will be discussed later. The third strongest calculated transition has an oscillator strength of 0.11 and involves a HOMO → NNLEMO excitation at 211 nm. However, the lack of precise experimental data has not permitted the reliability of this prediction to be tested.

7-Aminocepham. The qualitative agreement obtained above for the two strongest transitions of the 3-cephem moiety gives us some confidence in analyzing further cephem analogs, and so we next consider the situation where the C=C bond is reduced. A cepham with an amide group at the 7 position and a carboxylate group at the 4 position has been found[4] to exhibit positive Cotton effects at about 220 and 200 nm. It is not clear whether one or the other of these transitions is due to end group absorption or to the cepham moiety itself, inasmuch as both fall in a range characteristic of the n → π^* peptide chromophore.[28] Calculations on **2** give one strong (f = 0.39) transition at 216 nm and a much weaker one (f = 0.12) at 219 nm. The former involves excitation between the following MO's

LEMO (ϵ = −6.75 eV): $+0.42(N_5\ 2p_y) + 0.45(C_8\ 2p_z) - 0.73(C_8\ 2p_y) + 0.37(O_9\ 2p_y)$

NNHOMO (ϵ = −12.49 eV): $+0.40(N_5\ 2p_z) - 0.39(N_5\ 2p_y) + 0.39(O_9\ 2p_y)$

These MO's are clearly identifiable as β-lactam amide π^* and n orbitals, respectively. Thus the calculations give an n → π^* transition in the appropriate energy range for amides. The weaker computed transition involves the LEMO and NHOMO, the latter being a mixture of lone pairs on sulfur and both nitrogens.

Penams and the β-Lactam Moiety. To further investigate the β-lactam chromophore, consider model compounds **3**, **4**, and **5**. As with the cephams, the β-lactam functionality does not absorb strongly enough to give a well-defined uv spectrum. However, CD studies[29] reveal an n → π^* transition of β-lactams near 210 nm. Calculations on **3**, **4**, and **5** predict only one strong transition: at 205 nm (f = 0.48) in **3**, at 195 nm (f = 0.24) in **4**, and at 199 nm (f = 0.17) in **5**. The spectrum of **5** was studied as a function of rotation of the carboxyl group about the C-C bond. A small rotational barrier, typical of sixfold barriers, was found. The most stable rotamer has the carboxyl group coplanar with N_4. However, the rotation had no significant effect on the above excitation energy or oscillator strength of **5**. The forms of a few of the occupied and empty MO's of **5** are given in Table II. The strong transition occurring in compounds **3**, **4**, and **5** is due to the expected amide n → π^* chromophore. Thus, the calculations are successful in indicating the proper qualitative nature of the orbitals involved and, in this

(28) P. Crabbé, "Optical Rotatory Dispersion and Circular Dichroism in Organic Chemistry," Holden-Day, San Francisco, Calif., 1965.

(29) L. Neelakantan and D. W. Urry, Abstracts of the 158th National Meeting of the American Chemical Society, New York, N. Y., Sept 1969, BIOL 176.

Table II. Calculated Eigenvalues and MO's of **5**[a]

MO	ϵ, eV	Large LCAO–MO coefficients
NNLEMO	−6.13	$+0.40(S_1\ 3p_x) - 0.43(S_1\ 3d_{z^2}) + 0.42(S_1\ 3d_{xz}) - 0.30(C_2\ 2p_z) - 0.33(C_{10}\ 2p_x)$
NLEMO	−6.62	$-0.32(N_4\ 2p_x) + 0.82(C_7\ 2p_x) - 0.32(C_7\ 2p_y) - 0.46(O_8\ 2p_x)$
LEMO	−6.91	$-0.37(C_{10}\ 2p_x) - 0.76(C_{10}\ 2p_x) + 0.41(O_{11}\ 2p_x) + 0.37(O_{12}\ 2p_x)$
HOMO	−11.69	$-0.46(S_1\ 3p_y) - 0.42(N_4\ 2p_y) + 0.28(C_5\ 2p_y) + 0.27(N_9\ 2p_x)$
NHOMO	−11.92	$-0.73(S_1\ 3p_y) - 0.27(C_6\ 2p_z)$
NNHOMO	−12.85	$+0.38(N_4\ 2p_x) - 0.27(C_6\ 2p_z) - 0.38(O_8\ 2p_z) + 0.29(O_8\ 2p_y) + 0.31(O_{11}\ 2p_y)$

[a] The carboxyl group for these data is in the conformation found in the crystal (ref 22).

case also, happen to give a reasonable excitation energy. The shapes of the NNHOMO (n) and NLEMO (π^*) of **5** are sketched in Figure 2. The NNLEMO (empty S 3d orbitals), the LEMO (a carboxyl π^* orbital), HOMO (an S_1–N_4 transannular π orbital), and NHOMO (a sulfur lone pair) of **5** give rise to only weak transitions, the strongest one predicted to be HOMO → NLEMO at 245 nm with $f = 0.07$. One final comment about the β-lactam chromophore is that addition of the thiazolidine ring and carboxyl group to the β-lactam ring (in going from **3** to **4** to **5**) does not affect λ_{max} greatly, but the intensity is greatly diminished. This effect may reflect the perturbation of the lone-pair density of the β-lactam nitrogen by the additional atoms.

Propylallyl Sulfide. Another analog of the 3-cephem nucleus is provided by the β,γ-unsaturated sulfide **6**. The experimental absorption maximum of propylallyl sulfide[30] is below 240 nm and probably near the 221-nm band found for diallyl sulfide.[31] The calculations give a single strong transition of ($f = 0.43$) at 215 nm involving the NHOMO (C=C π character) and the LEMO (C=C π^*). The apparent agreement with experiment may mean that the assumed conformation is a good choice, although the $\pi \rightarrow \pi^*$ chromophore should not be drastically influenced by the rest of the molecule. It may be expected that hyperconjugation will mix some sulfur character into these MO's, and, indeed, the NHOMO does have a small amount: $+0.10(S_1\ 3p_y) - 0.16(C_2\ 2p_y) - 0.20(H_8\ 1s) + 0.17(H_9\ 1s) + 0.40(C_3\ 2p_y) + 0.60(C_4\ 2p_y)$. The sulfur orbitals enter mainly in the HOMO which has lone-pair character.

Dihydrothiazines. Ethyl 3,6-dihydro-2,5-dimethyl-2*H*-1,3-thiazine-4-carboxylate is observed[32] to have a weak uv absorption maximum (extinction coefficient 3100) at 285 nm. This transition may be related to the 260-nm band of 3-cephems, and, if so, then removal of the β-lactam ring has produced a bathochromic shift of about 25 nm. Calculations were first done on the dihydrothiazine ring **7** in a half-chair conformation derived from **1**. What was obtained were two closely spaced lines at 234 ($f = 0.16$) and 232 nm ($f = 0.41$), which are blue-shifted, rather than red-shifted, with respect to the corresponding calculated transition of 297 nm in **1**. This gross disagreement between theory and experiment suggested that the dihydrothiazine ring

(30) H. P. Koch, *J. Chem. Soc.*, 387 (1949).
(31) E. A. Fehnel and M. Carmack, *J. Amer. Chem. Soc.*, 71, 2889 (1949).
(32) D. M. Green, A. G. Long, P. J. May, and A. F. Turner, *J. Chem. Soc.*, 766 (1964).

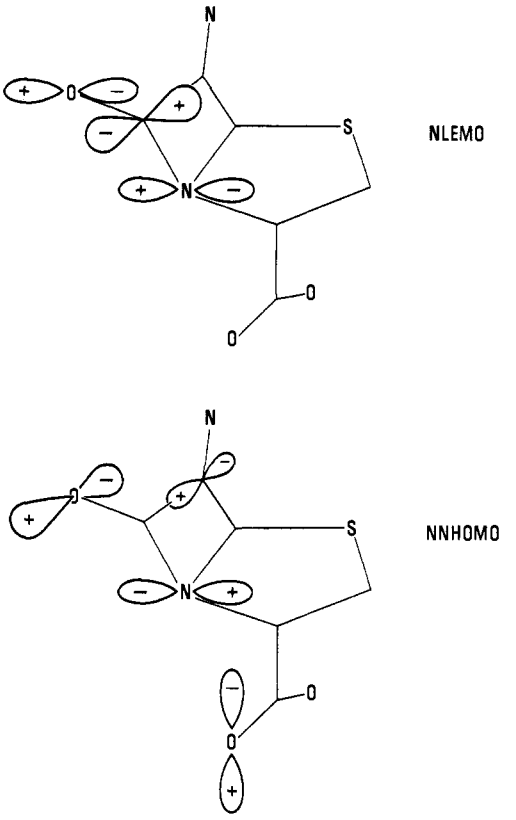
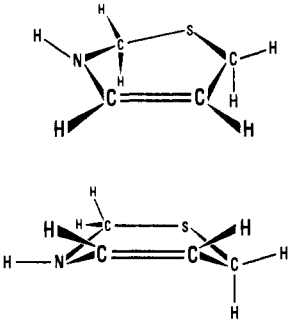


Figure 2. Nature of the MO's involved in the n → π^* transition of β-lactam compounds. The model compound is **5** with the carboxyl group positioned as in the crystal (see Table II).

undergoes a conformational change when the β-lactam ring is removed. Dreiding models support this view that there is a conformational change. Calculations on a sterically preferred boat conformer give rise to a single, strong transition in the uv region at 299 nm



($f = 0.21$). Now the excitation is red-shifted, although only slightly from the corresponding calculated band in **1**. Also in agreement with experiment is the result that the intensity of this band is weaker in **7** ($f = 0.21$) than in **1** ($f = 0.36$). We accept the improved agreement with experiment as support for the preference of a boat conformation for **7**. Associating the calculated 299-nm line with the observed 285-nm band, it may be concluded that it arises from an excitation from the HOMO to the LEMO. These MO's are constituted mainly of the following linear combinations of basis functions

LEMO ($\epsilon = -7.04$ eV):

$$+0.38(C_5\ 2p_z) - 0.56\ (C_5\ 2p_y) - 0.67(C_4\ 2p_z) + 0.41(C_4\ 2p_y)$$

HOMO ($\epsilon = -11.19$ eV):

$$+0.47(N_3\ 2p_x) - 0.56(C_5\ 2p_z) + 0.29(C_4\ 2p_z) - 0.27(C_4\ 2p_x)$$

Because of the choice of coordinate system[21] it may not be immediately obvious that the LEMO is simply a C=C π^* orbital, and the HOMO has the form of an enamine π system, *i.e.*, the 2p orbital of nitrogen mixed in with the C=C π bond.

It has been found[4] that the 3-carboxyl group of cephalosporins contributes a red shift of only about 10 nm. This implies that the plane of the carboxyl group is twisted from that of the C=C bond, thereby minimizing resonance between the functionalities. Also, it suggests that our lack of inclusion of the carboxyl group in model compound **1** should not be serious. Calculations on compound **8** permit the effect of the carboxyl group to be assessed. Using a boat conformation for the ring in **8**, the computations predict a preference for the coplanarity of the carboxyl and N_3–C_4=C_5 systems, but no preference exists as to whether the C_7=O_8 bond is cis or trans to the C=C bond. The rotational barrier about the C_4–C_7 bond is 3.5 kcal/mol using $^1/_2\Sigma_{i=1}^{N}\epsilon_i$ for comparison.[33] In the coplanar rotamer, an abnormally long wavelength of 466 nm ($f = 0.22$) is computed for the transition between the HOMO (enamine π) and the LEMO (a π^* orbital spanning the C=CC=O system). Rotating the carboxyl group 90° destroys the resonance between the π systems, and rather weak absorptions occur at 304 ($f = 0.08$) and 287 nm ($f = 0.13$). The former involves the HOMO (enamine π) and the LEMO (carboxyl π^*), and the latter the HOMO and the NLEMO (C=C π^*). Since λ_{max} values of 304 and 287 nm are in better agreement with the experimental value of 285 nm than is the 466-nm value, it may be concluded that the carboxyl group is twisted from planarity in ethyl 3,6-dihydro-2,5-dimethyl-2*H*-1,3-thiazine-4-carboxylate because of steric factors.

7-Amino-7-methoxy-3-cephem. Comparison of the spectra of cephalosporins with and without a 7-methoxyl group indicates that the group imparts a very slight (~4 nm) red shift of the 260-nm band and a larger (~12 nm) shift and intensification of the 230-nm band.[4,5] Calculations were done on **9** to be compared to **1** to see if the theory would qualitatively produce these same effects.

Two strong transitions were found for **9**: a HOMO → LEMO excitation at 302 nm ($f = 0.31$) and a NHOMO → LEMO excitation at 285 nm ($f = 0.17$). The LEMO of **9** is quite similar to that of **1**, *i.e.*, it has C=C π^* and C=O π^* character. But the HOMO and NHOMO of **9** have the characteristics of the HOMO and NHOMO of **1** mixed together

LEMO ($\epsilon = -7.62$ eV):

$$-0.43(C_3\ 2p_y) + 0.41(C_4\ 2p_y) + 0.48(C_8\ 2p_x) - 0.61(C_8\ 2p_y) + 0.35(O_9\ 2p_y)$$

HOMO ($\epsilon = -11.72$ eV):

$$+0.44(S_1\ 3p_z) + 0.30(S_1\ 3p_y) + 0.34(C_3\ 2p_y) + 0.27(C_4\ 2p_y) - 0.38(N_5\ 2p_y)$$

NHOMO ($\epsilon = -11.97$ eV):

$$+0.33(S_1\ 3p_z) + 0.43(S_1\ 3p_y) - 0.37(C_3\ 2p_y) + 0.35(N_5\ 2p_y)$$

The linear combinations of the HOMO and NHOMO correspond to each having some enamine π character and some sulfur lone-pair character. Significantly, the computed long-wavelength line (302 nm) is slightly (5 nm) red-shifted from the 297 nm computed for **1**. The short-wavelength line (285 nm) is also red-shifted, and by a larger amount (40 nm) from the corresponding 245-nm line in **1**. The oscillator strength of the latter line is, however, predicted to be essentially unchanged (0.17 in both **1** and **9**). Thus, the theory is successful in qualitatively matching most of the experimentally observed trends.

7-Amino-2-cephem. Although a single λ_{max} has been recorded[4] for a Δ^2-cephalosporin at 232 nm (extinction coefficient 5600), the spectrum actually can be interpreted as consisting of several overlapping bands. CD has been used to detect at least two of the absorptions, both of which have positive Cotton effects of large ellipticity. A 237-nm band has been associated[4] with the α,β-unsaturated sulfide portion of the molecule, and a 199-nm absorption presumably arises from the β-lactam ring. Earlier studies on 2-cephems also indicate multiple absorption bands in the 220–300-nm region.[34]

Calculations give four fairly intense lines: HOMO → LEMO at 258 nm ($f = 0.44$), HOMO → NLEMO at 245 nm ($f = 0.21$), NNHOMO → LEMO at 223 nm ($f = 0.18$), and NNHOMO → NLEMO at 213 nm ($f = 0.26$). The levels and forms of these MO's are as follows

NLEMO ($\epsilon = -6.67$ eV):

$$-0.32(C_2\ 2p_y) + 0.36(C_3\ 2p_y) + 0.40(N_5\ 2p_y) + 0.39(C_8\ 2p_x) - 0.64(C_8\ 2p_y) + 0.33(O_9\ 2p_y)$$

LEMO ($\epsilon = -6.94$ eV):

$$-0.33(S_1\ 3d_{xy}) - 0.27(C_2\ 2p_z) - 0.47(C_2\ 2p_y) + 0.30(C_3\ 2p_z) + 0.52(C_3\ 2p_y) + 0.38(C_8\ 2p_y)$$

HOMO ($\epsilon = -11.47$ eV):

$$+0.40(S_1\ 3p_z) + 0.27(S_1\ 3p_x) + 0.56(S_1\ 3p_y) - 0.47(C_3\ 2p_y)$$

NNHOMO ($\epsilon = -12.50$ eV):

$$-0.38(N_5\ 2p_x) + 0.44(N_5\ 2p_y) - 0.38(O_9\ 2p_y)$$

The NLEMO is a complex mixture of the C=C π^* and amide π^* orbitals. The LEMO is constituted from the π^* orbital of the SC=C moiety, whereas the HOMO is simply the π orbital of this moiety. The NNHOMO is an ordinary amide n orbital with lone-pair character on N_5 and O_9. Thus, the strongest and lowest energy excitation is described as SC=C $\pi \rightarrow \pi^*$. The second strongest transition is amide n → π^* and occurs at a wavelength typical for this chromophore (213 nm). The other two computed transitions arise from electron jumps between the α,β-unsaturated sulfide and β-lactam moieties and also appear quite strong.

Other Aspects of the Charge Distributions. It has been proposed[32,34] that the d orbitals of sulfur in 3-

(33) D. B. Boyd, *J. Amer. Chem. Soc.*, 91, 1200 (1969); *Theor. Chim. Acta*, 20, 273 (1971).

(34) J. D. Cocker, S. Eardley, G. I. Gregory, M. E. Hall, and A. G. Long, *J. Chem. Soc. C*, 1142 (1966).

cephems may be involved in excited states with transannular bonding between sulfur and N_5 and C_8. From our calculations, it is possible to conclude that this is not the case, at least for those transitions giving rise to the strong absorptions.

For all the sulfur compounds treated here, one or more of the three lowest-lying empty MO's has predominantly empty S 3d character, so that energy-wise these orbitals are accessible. However, the exact calculation of the oscillator strengths gives very low transition probabilities to these orbitals. For instance, in **1** the *f* values for excitation from the three highest filled MO's into the NLEMO, which is predominantly empty S 3d (Table I), range from 0.002 to 0.029. These are less than 10% of the *f* value for the HOMO → LEMO transition. Although not much importance can be attached to the absolute magnitudes of our *f* values, they should be significant on a relative basis for comparison among themselves. Likewise, the sulfur lone-pair orbitals give rise to weak absorption. Again using **1** as an example, the excitations from the NHOMO (Table I) into the three lowest virtual orbitals have oscillator strengths in the range 0.002–0.055. The sulfide chromophore has been found to give rise to small oscillator strengths by other calculations also.[35] From simple valence concepts,[30] it has been commonly accepted that the sulfide chromophore involves a $n \rightarrow \sigma^*$ transition, *i.e.*, an electron is excited from the sulfur lone pair to an S–C σ^* orbital. Our calculations suggest that the excited state involves considerable 3d character or, in other words, the σ^* character arises from at least partial population of the 3d AO's with their unique nodal character. Other recent MO calculations[35] also stress the importance of 3d orbitals in the low excited states of sulfides.

The Mulliken population analyses[6] of the wave functions of **1** and **5** are given in Figure 3. From the character of the MO's of these compounds (Tables I and II), it is possible to deduce what effect the various excitations will have on the atomic charges and bond strengths. Similarly, complete removal or addition of an electron may have an effect on the chemistry of these compounds which is interpretable in terms of the character of the HOMO or LEMO, respectively, of the compounds. An examination of this subject will not be attempted in the present paper, however.

The degree of success which we have obtained in spectral assignments and structural predictions is indicative of the fact that careful application of the theory can lead to useful interpretations. Refinement of our exploratory calculations is clearly desirable. Whereas the numerical results must be considered skeptically, the qualitative conclusions on the shapes of the MO's of the cephalosporins and penicillins are more likely to endure and to provide a practical basis for the further study of these compounds.

(35) D. R. Williams and L. T. Kontnik, *J. Chem. Soc. B*, 312 (1971).

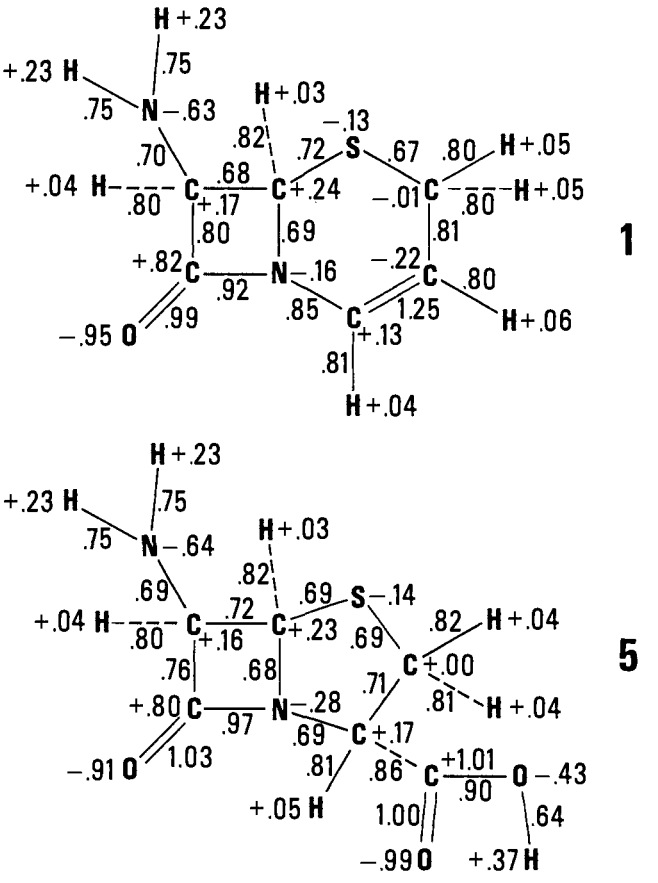


Figure 3. Net atomic charges (signed numbers) and overlap populations (unsigned numbers) for **1** and **5**. As is inherent in EH theory, the charge separations between atoms are exaggerated with respect to self-consistent field results (see, *e.g.*, W. J. Hehre and J. A. Pople, *J. Amer. Chem. Soc.*, **92**, 2191 (1970)). Large polarity in the molecules is reflected in the rigorous and point charge dipole moments of 8.5 and 7.4 D, respectively, for **1**, and 7.7 and 9.0 D for **5**. The directions of the rigorous dipole moment vectors are described by the *x*, *y*, and *z* components: −1.06, −7.54, −3.68 D in **1**, and +3.38, −3.53, −5.97 D in **5**. The coordinate system is described elsewhere in this paper, and the convention of + to − for vector direction is used (see ref 24).

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