Journal of Medicinal Chemistry

Volume 16, Number 11 November 1973

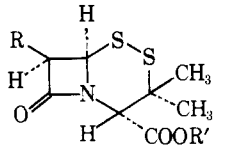
Electronic Structures of Cephalosporins and Penicillins. 2. Disulfide and β-Lactam Chromophores. Structure–Activity Relationships†

Donald B. Boyd

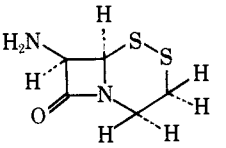
The Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana 46206. *Received March 5, 1973*

Molecular orbital calculations on a model cephalosporin molecular nucleus with a disulfide group in the six-membered ring are used to interpret the uv and DC spectra of 2-carboxy-3,3-dimethyl-8-oxo-7-phthalimido-4,5-dithia-1-azabicyclo[4.2.0]octanes. Besides the 292-nm disulfide n → σ* peak, two transitions at *ca.* 240 nm are identified as excitations between the disulfide and β-lactam chromophores. Similarly, the interaction of the β-lactam and sulfide chromophores is seen in penicillins, where hydrolytic opening of the β-lactam ring results in the disappearance of a strong, positive Cotton effect at *ca.* 233 nm. Structure-activity relationships among penicillin and cephalosporin analogs are examined. The calculated strength of the β-lactam C–N bond and the charge at the carbonyl carbon are among the factors influencing biological activity.

Biomolecules with interacting disulfide and amide chromophores pose the interesting possibility of conformational and configurational identification through a proper understanding of the chiroptical and other spectral properties of these functionalities. Studies in pursuit of this understanding have, for example, involved the antiviral acetylaranotin,[2,3] the antibiotic gliotoxin,[4] and the amino acid cystine in numerous molecular environments.[5-8] Recently, several disulfide-containing cephalosporin analogs have been synthesized,[9] and the structure of one of these, **1**, having the stereochemistry of the cephalosporin antibiotics was ascertained by circular dichroism (CD), X-ray diffraction, and nmr techniques.[10] A model structure, **2**, can be derived conceptually from **1** which has the disulfide and amide chromophores in the unique situation where the dihedral angle[10] at the S–S bond is *ca.* 60° and the amide group is distorted to the four-membered β-lactam ring. By way of contrast, the diketopiperazine disulfides[2-4] have smaller CSSC dihedral angles in the range 10–20°, and the cystines[5-8] have larger dihedral angles of *ca.* 90° or more. Consequently, a theoretical investigation of the uv absorption and optical activity of the cephalosporin analog should enhance the understanding of its chromophores and facilitate structure determinations of other molecules with disulfide and amide functionalities. For this reason, molecular orbital (MO) energy levels will be computed for **2**, and calculated uv transitions will be related to experimental data. Experience in the first paper of this series[1] indicates our MO calculations to be fairly reliable in assigning the uv and CD spectra of the molecular nuclei of other β-lactam antibiotics. Also, the absorptions of dialkyl disulfides with various dihedral angles, including 60°, have been satisfactorily predicted by our calculational approach.[11]



1, R = phthalimido; R′ = CH_3



2

In the course of our MO calculations on the molecular nuclei of penicillins and cephalosporins, a correlation was discerned between known antibiotic activities and certain computed quantum mechanical quantities. This correlation ties in with previous proposals on the mechanism of action of β-lactam antibiotics. Thus, another aspect of this paper is to examine structure–activity relationships (SAR) among β-lactam antibiotics.

Experimental Section

The MO's are calculated according to the extended Hückel (EH) all-valence-electron method. Our EH method is essentially the standard version,[12] but with a few minor modifications,[13-15] such as a Wolfsberg-Helmholz constant of 2.0 instead of 1.75 in order to give smoother charge distributions. Our EH method has proven satisfactory, as well as versatile, in studies of the nature of the "energy-rich" phosphate bonds of ATP and related polyphosphates,[13,16] the mechanism of action of ribonuclease on model cyclic phosphate esters,[17] the bonding in phosphonium ylides,[14,18] the conformation of cannabinoids,[19] and the charge distribution of adenine.[20]

Hamiltonian matrix elements are constructed from previously published formulas and parameters.[1,13] Parenthetically, we note that the 3d atomic orbitals (AO) of sulfur are assigned an energy[1] and size[21] such that they contribute significantly to the low excited states of sulfides. At least five recent papers in the literature have noted the importance of the S 3d AO's in determining uv spectra of sulfides.[1,11,22-24]

Model compound **2**, 8-oxo-7-amino-4,5-dithia-1-azabicyclo[4.2.0]octane, or more simply,[1] 7-amino-2-thiacepham, is appropriate for examining those transitions which arise *within* the molecular nucleus of **1**. Contributions from the phthalimido and carboxylate groups will, therefore, have to be reconciled with the

†For paper 1 of this series, see ref 1.

predicted transitions of **2** before a comparison can be made with the uv and CD data of **1**. Input data for the atomic coordinates of **2** are obtained by supplementing the X-ray determined[10] geometry of **1** with hydrogen atoms at standard[1] bond lengths and angles.

Theoretical values of λ_{max} are taken as the differences in the MO energy levels involved in the single electron excitations, λ_{max} (nm) = $1239.8/\Delta E$ (eV), where $\Delta E = \epsilon_m - \epsilon_n$. Intensities of absorption are judged from the oscillator strengths, $f = 0.0245\Delta E|R^{mn}$ (au)$|^2$. The transition moment integrals are computed from the coefficients, C_{pm}, of the AO's in the MO's involved in the excitation, $\mathbf{R}^{mn} = \sqrt{2}\Sigma_p\Sigma_q C_{pm}C_{qn}\langle\chi_p|\mathbf{r}|\chi_q\rangle$, where the sums run over all the valence AO's, χ_p, in the molecule and all the dipole length integrals, $\langle\chi_p|\mathbf{r}|\chi_q\rangle$, are rigorously computed.[25] A common approximation, which we do not and need not make, is the neglect of the dipole integrals between AO's on two different atoms. By including all the integrals we avoid the possibility of making allowed transitions appear to be forbidden.[26] All calculations were performed on an IBM 370/155 computer using our FORTRAN IV programs. A program for rotatory strength calculations is not at our disposal. The rotatory strength is, of course, proportional to the dot product of the electric transition moment, R^{mn}, which we do compute, and the magnetic moment.[27-31] A vanishing small value of R^{mn} would tend to negate the possibility of much optical activity arising from a transition between MO's m and n, but no quantitative assessment will be made of the extent to which a transition is magnetically allowed.

It should be recognized that we are using relatively crude wave functions, especially for the excited states. The wave functions are obtained from a one-electron Hamiltonian, without any configuration interaction (CI). A prevalent opinion is that the virtual orbital approximation and EH MO's are completely invalid for representing excited states of molecules. However, actual experience demonstrates that the *qualitative* nature of the high-lying filled and low-lying empty MO's of at least the β-lactams[2] and disulfides[11] are probably adequately described for the desired purposes. For the β-lactams, predicted λ_{max} and f values were found to be qualitatively consistent with available experimental data. Likewise, for the disulfides, the conformational dependence of the MO's, their shape, and extent of 3d orbital involvement were all consistent with experimental and earlier theoretical studies. Predicted λ_{max} values were within *ca.* 20 nm of experimental values for disulfides with a 60° dihedral angle between the two C-S bonds measured around the S-S axis. Since the current study is an extension of our previous approach to a molecule with geometrical properties not unlike those of molecules treated before, it should be possible to arrive at a reasonable qualitative comprehension of the 2-thiacepham chromophores. Moreover, EH MO's have been demonstrated to be particularly useful in other studies of the interaction of orbital energy levels and the observable consequences of these interactions.[32,33]

Inherent to our calculational approach are also the limitations due to the virtual orbital approximation and the lack of explicit treatment of interelectron repulsion integrals. The former approximation means that the excited state is described by promotion of an electron from one of the doubly occupied MO's, ψ_n, to one of the virtual MO's, ψ_m, which comes from the solution of the ground-state wave function. Changes in molecular geometry due to excitation are neglected. The fact that two-electron Coulomb and exchange integrals are not included in the calculations means, of course, that the wave functions may be obtained easily, but also it means that singlet and triplet excited states are not distinguished from each other.

To put our calculational approach in further perspective, we refer the reader to other recent calculations of electronic spectra of other molecules.[26,28,31,34-39] These treatments have employed complete and intermediate neglect of differential overlap (CNDO and INDO) wave functions. Explicit account of interelectron repulsion and CI is possible in these calculations. Although the theoretical foundation of these treatments is more apparent, they still involve a certain amount of empirical selection of energy parameters in order to achieve reasonable agreement with whatever experimental properties are under investigation. Also, being valence-electron methods, they involve some of the same approximations as does EH theory.

A further point worth discussing is the fact that our calculations of oscillator strength are done in the dipole length formalism as described above. Because magnetic moments are more easily evaluated in the dipole velocity formalism and because of other advantages,[28,40] many of the calculational studies of rotatory strength have also used the dipole velocity integrals to compute oscillator strengths. It has been our observation that whereas the two formalisms give different quantitative results (especially in the case where very approximate wave functions are used), the qualitative results of each are similar. A comparison to be published elsewhere of the oscillator strengths of the transitions in H_2S_2 demonstrates that the two formalisms can give f values of the same magnitude.

In view of the approximations and limitations discussed above, the reader is urged to keep in mind that the present study must be regarded as exploratory, and that definitive, quantitative predictions will require more sophisticated calculations.

The CD spectrum[10] of **1** consists of a negative Cotton effect at 292 nm ($\Delta\epsilon = -5.5$), two or more positive inflections in the 230-250-nm region, and a positive peak of large ellipticity ($\Delta\epsilon = +61.9$) at 220 nm. The 292-nm Cotton effect and two of the inflections change sign in the trans isomer[10] of **1**, where the disulfide linkage is in the other helical arrangement. The uv spectrum of **1** in neutral or acidified ethanol solvent displays a broad low absorption band at 294 nm (ϵ 3800 l. mol^{-1} cm^{-1}) capable of accommodating two transitions, a minimum at 263 nm (ϵ 2800), an inconspicuous shoulder at *ca.* 240 nm (ϵ 10,000), and a strong peak at 218 nm (ϵ 34,800).‡ The uv spectrum is thus dominated by the phthalimido chromophore,[41] which typically absorbs at 290 (ϵ 1770), 237 (ϵ 10,540), 229 (ϵ 16,250), and 216 nm (ϵ 39,900) as in phthalimide. In the CD, a long wavelength phthalimido transition is reported[42] at 320 nm, which presumably is electrically forbidden, and hence is not detected in the absorption spectra. However, no Cotton effects at these long wavelengths were noticed for **1**.

Results of the Spectral Calculations

The longest wavelength transition predicted for **2** is at 281 nm ($f = 0.08$). Such a transition is typical[11,43] of disulfides with a CSSC dihedral angle of 60°. The calculated λ_{max} is within about 10 nm of the observed λ_{max} 292 nm, which is reasonably close considering the limitations of the theory. Comparing the theoretical results on **2** with the theoretical results on dimethyl disulfide with an assigned 60° CSSC dihedral angle,[11] one finds that the longest wavelength transition undergoes bathochromic (from 268 to 281 nm) and hypochromic (f = 0.11–0.08) shifts due to the presence of the β-lactam ring. Whereas the shift to longer wavelength is as expected, the weakening of the intensity is not. The negative sign of the 292-nm Cotton effect indicates that the CSSC atoms are arranged in a left-handed (M) helix.[43]

Going to shorter wavelengths, the calculations predict three transitions: 250 ($f = 0.04$), 244 ($f = 0.09$), and 241 nm ($f = 0.07$). These would contribute to the uv shoulder and the CD inflections observed in the 230–250-nm region. The 241-nm wavelength is typical of the second transition ($n_b \rightarrow \sigma^*$) of disulfides with a 60° CSSC dihedral angle.[43] As discussed below, the other two transitions involve excitations between MO's localized on the disulfide moiety and MO's localized on the β-lactam moiety. Thus, the chromophores are coupled in the charge-transfer sense. Similarly, the presence of characteristic bands in the CD spectra of 1,2-dithiolane-3-carboxylates may be traced to the interaction of disulfide and carboxyl groups.[44,§] The uv spectra of some of these compounds with the disulfide and carboxyl groups separated by one carbon atom also show the effects of the coupling and mutual perturbation of these chromophores.[45]

At still shorter wavelengths the calculations predict strong transitions at 220 ($f = 0.13$) and 214 nm ($f = 0.12$), which arise from excitations into the amide π^* MO. These transitions (and other shorter wavelength ones) would be buried under the intense phthalimido absorption at *ca.* 220 nm. Previously, β-lactam $n \rightarrow \pi^*$ transitions have been

‡The uv data of **1** were kindly supplied by Dr. S. Kukolja and that of phthalimide by Mr. R. D. Miller.

§L. A. Neubert, Ph.D. Thesis, Indiana University, Bloomington, Ind., 1969.

predicted[1] in the 195–216-nm range (f = 0.17–0.48).

Having ascertained that the calculated transitions are consistent with the experimental spectra, let us ask about the forms of the MO's involved in the excitations. The character and energies of the MO's of **2** are shown in Figure 1. For comparison, the MO's of 7-aminocepham[1] and dimethyl disulfide[11] with a 60° CSSC dihedral angle are also plotted. The highest occupied (HO) and lowest empty (LE) MO's of **2** are easily identified with their counterparts in H_3CSSCH_3 (the disulfide lone pair and σ^* orbitals, respectively). The next lowest empty (NLE) MO and the NHOMO of **2** correlate with the amide π^* and n MO's of 7-aminocepham. Note that the excited state LEMO and NLEMO levels are split, so that the gap between these levels is greater than in the "parent" molecules. The lowest energy excitation (281 nm) is from the HOMO to the LEMO, or, in other words, it is a disulfide $n_a \rightarrow \sigma^*$ transition. The three predicted transitions in the 240–250-nm region are amide, NH_2 n $\rightarrow$ S–S σ^* (250 nm), S–S n $\rightarrow$ amide π^* (244 nm), and S, NH_2 n $\rightarrow$ S–S σ^* (241 nm). These absorptions are not very strong, which indicates that no great amount of charge transfer occurs between the disulfide and amide functionalities. The 220-nm transition is from the MO with lone-pair character on both the amide and amino groups to the amide π^* MO. Two strong transitions at 200 (f = 0.11) and 199 nm (f = 0.12) into the 3d MO's are predicted to occur from the S–S n and S, NH_2 n MO's, but they are not as strong as the corresponding transitions in H_3CSSCH_3 (f = 0.2–0.3).

As mentioned above, the β-lactam n $\rightarrow \pi^*$ transition is predicted by our calculations in the 195–220-nm range for model antibiotic structures. The CD spectra of penicillins and cephalosporins are rather difficult to unravel, although some experimentalists identify the β-lactam n $\rightarrow \pi^*$ transition at about this same wavelength (204–211 nm).[46-50] For instance, 6-aminopenicillanic acid (6-APA) exhibits[49] a negative Cotton effect at 208 nm at pH 3.0 and a positive inflection at 211 nm at pH 6.3. However, the conspicuous disappearance of a strong, positive Cotton effect at 233 nm in 6-APA upon hydrolytic rupture of the β-lactam ring makes this band appear to arise from the β-lactam n $\rightarrow \pi^*$ transition.[48,50] Analysis by Siemion, *et al.*, concluded that this is not the case.[49] In an attempt to assign the 233-nm band, the three chromophores of 6-APA (the β-lactam n $\rightarrow \pi^*$, the carboxyl n $\rightarrow \pi^*$, and the sulfide n $\rightarrow \sigma^*$) were considered independently, and the latter was chosen in their assignment.[49] This assignment has recently been criticized and the β-lactam n $\rightarrow \pi^*$ transition was advanced as the more likely alternative.[50] An involvement of the β-lactam π^* orbital is in better accord with our earlier investigation,[1] although the ground-state orbital is, indeed, implicated to have some sulfur character, as well as amide nitrogen character. The calculations[1] on demethyl-6-APA predicted three long wavelength transitions with relatively large oscillator strengths: 245 (f = 0.07), 209 (f = 0.06), and 199 nm (f = 0.17). These are associated, respectively, with the following MO's: S–N $\pi \rightarrow$ amide π^*, amide n $\rightarrow$ carboxyl π^*, and amide n $\rightarrow$ amide π^*. Thus, the shortest wavelength one (199 nm) is the β-lactam n $\rightarrow \pi^*$ transition, whereas the other two involve charge transfer between different chromophoric groups. Notice that the MO calculations allow for the coupling and interactions of the chromophoric groups in the molecule according to their energy and overlap. Despite the proximity of the β-lactam and carboxyl chromophores, the extent of their coupling is not large.[50] The observed 233-nm band could be associated with our computed 245-nm transition. This transition is from an occupied MO with transannular S–N π-bond character[1] to the empty amide π^* MO. Since both of these MO's involve the β-lactam nitrogen, they would change drastically upon hydrolysis of the β-lactam ring. Thus, even though the quantitative aspects of the predicted λ_{max} and f values are not as good as one would like, the qualitative character of the MO's involved offers a plausible explanation of the spectroscopic properties of penicillins. Definitive affirmation of the assignment would require more accurate wave functions, especially for the excited states, and rotatory strength calculations.

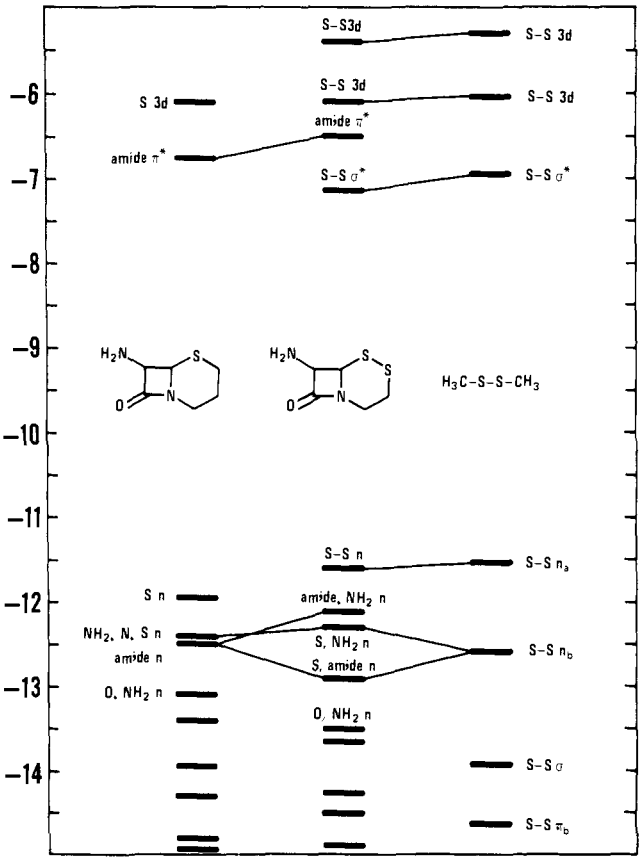


Figure 1. Energies (eV) of the MO's, ϵ_m, of 7-aminocepham (left), **2** (center), and dimethyl disulfide (right) with a CSSC dihedral angle of 60°. Those MO's below −11 eV are doubly occupied in the ground states, and the MO's above −8 eV become singly occupied in the excited states. The main character of the MO's is judged on the basis of the large coefficients, C_{pm}, in each MO. 3d designates linear combinations of the 3d AO's on the sulfur(s) and *n* designates nonbonding or lone-pair character on the specified atom(s) or group(s). The n_b level of H_3CSSCH_3 splits into two MO's in **2**, each with lone-pair character in one of the sulfurs mixed with the orbitals of another functionality. The more stable occupied MO's are not conveniently labeled because they are delocalized over several atoms. A more complete description of the MO's of the molecules on the left and right is given elsewhere.[1,11]

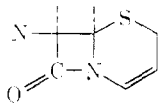
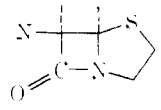
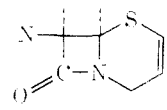
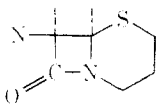
In summary, then, we have seen that in both the disulfide-containing cephalosporin analog and in the penicillins, a proper understanding of the chiroptical properties cannot be achieved by considering the chromophoric groups individually, but rather the coupling of the chromophores must be taken into consideration.

We will now turn our attention from the electronic spectra of one cephalosporin analog to the relationship of charge distribution and biological activity of β-lactam antibiotics in general.

Discussion of Structure–Activity Relationships

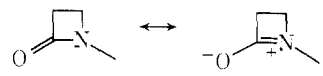
Among the better understood mechanisms of drug action is the inhibitory action of penicillin and cephalospor-

Table I. Representative EH Charge Distributions in the β-Lactam Rings of Model Nuclei of Cephalosporins and Penicillins

	 3-Cephems	 Penams	 2-Cephems	 Cephams
Q(O)	−0.95	−0.91	−1.00	−1.00
n(C=O)	0.99	1.03	0.94	0.94
Q(C)	+0.82	+0.80	+0.76	+0.75
n(C−N)	0.92	0.97	1.03	1.03
Q(N)	−0.16	−0.28	−0.15	−0.15

in antibiotics on bacterial growth. The β-lactam antibiotics bind selectively to certain enzymes involved in the biosynthesis of bacterial cell walls.[51-53] At least one transpeptidase is irreversibly inactivated in accord with the idea that acylation of the enzyme occurs following rupture of the highly reactive β-lactam bond. Therefore, it can be expected that if other criteria[54,55] for drug efficacy, such as absorption, transport, metabolism, toxicity, etc., are met, then two crucial factors remain. One is that the molecule meets the structural requirements for binding to the active site of the enzyme(s). The second is that the reactivity and strength of the β-lactam C–N bond must be optimal. In regard to the former factor, molecular model building shows that the penam and 3-cephem molecular nuclei possess shapes similar to the D-alanyl-D-alanine fragment of the normal substrate.[56-58]

In regard to the lability of the β-lactam C–N bond, there are now several pieces of evidence that this property does correlate with activity. (1) The active β-lactam antibiotics generally have a higher C=O stretching frequency in the ir than do the inactive compounds.[59-61] This suggests that in the active compounds there is a lesser degree of amide resonance



3a 3b

which concomitantly weakens the C=O bond and strengthens the C–N bond. (2) The active antibiotics have a pyramidal hybridization at the β-lactam nitrogen, which is indicative of the dominance of resonance structure **3a**.[58,62] (3) X-Ray studies show the C–N bond tends to be slightly longer in the penam and 3-cephem nuclei than in cephams and 2-cephems.[10,58,62,63] (4) Using EH and CNDO/2 MO calculations, Hermann found C–N bond strengths (as measured by Mulliken overlap populations[64] or bond energies) and carbonyl carbon charge densities of model β-lactam structures to correlate with the biological activity of some corresponding 3-substituted cephalosporin analogs.[60,65,66] CNDO/2 theory was found to do better than EH theory at representing long-range inductive effects. (5) After making allowance for steric factors, β-lactam C–N bonds are usually found to hydrolyze more readily in the biologically active penicillins and cephalosporins.[58,=]

The correlation of calculated overlap populations and net atomic charges with biological activity in Hermann's series[65] can be extended to antibiotics with different molecular nuclei as seen in Table I. It is generally recognized[66] that penicillins and Δ^3-cephalosporins have much greater antibiotic activity than Δ^2-cephalosporins or the corresponding cephams (saturated six-membered ring). Extensive tabulations of representative biological data appear elsewhere[66] and need not be repeated here. Several of the calculated quantities in Table I may be used to distinguish between nuclei known to form biologically active or inactive compounds. These include the overlap populations, n, of the C–N and C=O bonds (which are roughly inversely proportional to each other), and the positive net atomic charge, Q, on the carbonyl carbon. The overlap population is indicative of the strength of a bond.[13,64] Although other steric and electronic factors can come into play, frequently the greater the positive charge on an atom the more susceptible it is to nucleophilic attack.[17] Thus, the quantum mechanical indices of Table I appear to corroborate previous evidence that the acylating ability of the β-lactam antibiotics is related to their biological activity.

It should be emphasized, however, that the charge distributions in Table I are approximate because of the semiempirical theory used to compute them. Charge separations may be exaggerated in EH theory, although relative charges are usually correct.[20] Large geometrical differences between the models may render some comparisons unreliable. For instance, the penam nucleus is generally regarded as having greater intrinsic activity than the 3-cephem nucleus,[66] whereas the data in Table I fail to make this distinction. A further complicating factor, in addition to those mentioned above (such as availability of the drug at the site of action), is the effect of the side chains on the nuclei. It is known from empirical SAR[66] and from MO calculations[65] that the nature of the side chain can have a profound effect on the electronic structure of the β-lactam moiety and consequently on the biological activity of a compound.

Acknowledgments. Helpful discussions with M. O. Chaney, M. Gorman, R. B. Hermann, R. Hoffmann, J. M. Indelicato, N. D. Jones, S. Kukolja, M. M. Marsh, and R. D. Miller are gratefully acknowledged.

References

(1) D. B. Boyd, *J. Amer. Chem. Soc.*, **94**, 6513 (1972).
(2) R. Nagarajan, L. L. Huckstep, D. H. Lively, D. C. DeLong, M. M. Marsh, and N. Neuss, *ibid.*, **90**, 2980 (1968).
(3) R. Nagarajan, N. Neuss, and M. M. Marsh, *ibid.*, **90**, 6518 (1968).
(4) A. F. Beecham and A. McL. Mathieson, *Tetrahedron Lett.*, 3139 (1966).
(5) D. L. Coleman and E. R. Blout, *J. Amer. Chem. Soc.*, **90**, 2405 (1968).
(6) J. P. Casey and R. B. Martin, *ibid.*, **94**, 6141 (1972).
(7) U. Ludescher and R. Schwyzer, *Helv. Chim. Acta*, **54**, 1637 (1971).
(8) B. Donzel, B. Kamber, K. Wuthrich, and R. Schwyzer, *ibid.*, **55**, 947 (1972).
(9) S. Kukolja, *J. Amer. Chem. Soc.*, **94**, 7590 (1972).
(10) S. Kukolja, P. V. Demarco, N. D. Jones, M. O. Chaney, and J. W. Paschal, *ibid.*, **94**, 7592 (1972).
(11) D. B. Boyd, *ibid.*, **94**, 8799 (1972).

=J. M. Indelicato, T. T. Norvilas, R. R. Pfeiffer, W. J. Wheeler, and W. L. Wilham, unpublished results.

(12) R. Hoffmann, *J. Chem. Phys.*, **39,** 1397 (1963).
(13) D. B. Boyd and W. N. Lipscomb, *J. Theor. Biol.*, **25,** 403 (1969).
(14) R. Hoffmann, D. B. Boyd, and S. Z. Goldberg, *J. Amer. Chem. Soc.*, **92,** 3929 (1970).
(15) D. B. Boyd, *Theor. Chim. Acta*, **20,** 273 (1971).
(16) D. B. Boyd, *ibid.*, **18,** 184 (1970).
(17) D. B. Boyd, *J. Amer. Chem. Soc.*, **91,** 1200 (1969).
(18) D. B. Boyd and R. Hoffmann, *ibid.*, **93,** 1064 (1971).
(19) R. A. Archer, D. B. Boyd, P. V. Demarco, I. J. Tyminski, and N. L. Allinger, *ibid.*, **92,** 5200 (1970).
(20) D. B. Boyd, *ibid.*, **94,** 64 (1972).
(21) D. B. Boyd, *J. Chem. Phys.*, **52,** 4846 (1970).
(22) D. R. Williams and L. T. Kontnik, *J. Chem. Soc. B*, 312 (1971).
(23) D. L. Coffen, J. Q. Chambers, D. R. Williams, P. E. Garrett, and N. D. Canfield, *J. Amer. Chem. Soc.*, **93,** 2258 (1971).
(24) J. S. Rosenfeld and A. Moscowitz, *ibid.*, **94,** 4797 (1972).
(25) D. B. Boyd in "Purines: Theory and Experiment," E. D. Bergmann and B. Pullman, Ed., The Israel Academy of Sciences and Humanities, Jerusalem, 1972, p 48.
(26) R. L. Ellis, G. Kuehnlenz, and H. H. Jaffé, *Theor. Chim. Acta*, **26,** 131 (1972).
(27) R. R. Gould and R. Hoffmann, *J. Amer. Chem. Soc.*, **92,** 1813 (1970).
(28) F. S. Richardson, D. D. Shillady, and J. E. Bloor, *J. Phys. Chem.*, **75,** 2466 (1971).
(29) A. Imamura, T. Hirano, C. Nagata, and T. Tsuruta, *Bull. Chem. Soc. Jap.*, **45,** 396 (1972).
(30) C. C. Levin and R. Hoffmann, *J. Amer. Chem. Soc.*, **94,** 3446 (1972).
(31) F. S. Richardson, R. Strickland, and D. D. Shillady, *J. Phys. Chem.*, **77,** 248 (1973).
(32) R. B. Woodward and R. Hoffmann, "The Conservation of grbital Symmetry," Academic Press, New York, N. Y., 1970.
(33) R. Hoffmann, *Accounts Chem. Res.*, **4,** 1 (1971).
(34) H. W. Kroto and D. P. Santry, *J. Chem. Phys.*, **47,** 792, 2736 (1967).
(35) J. Del Bene and H. H. Jaffé, *ibid.*, **48,** 1807, 4050 (1968); **49,** 1221 (1968); **50,** 563, 1126 (1969).
(36) H. H. Jaffé, *Accounts Chem. Res.*, **2,** 136 (1969), and references cited therein.
(37) H. H. Jaffé in "Quantum Aspects of Heterocyclic Compounds in Chemistry and Biochemistry," E. D. Bergmann and B. Pullman, Ed., The Israel Academy of Sciences and Humanities, Jerusalem, 1970, p 34.
(38) G. A. Segal, *J. Chem. Phys.*, **53,** 360 (1970).
(39) P. E. Stevenson, *J. Phys. Chem.*, **76,** 2424 (1972).
(40) A. J. McHugh and M. Gouterman, *Theor. Chim. Acta*, **13,** 249 (1969).
(41) W. R. Roderick and W. G. Brown, *J. Amer. Chem. Soc.*, **79,** 5196 (1957).
(42) K. Hirayama, "Handbook of Ultraviolet and Visible Absorption Spectra of Organic Compounds," Plenum Press, New York, N. Y., 1967.
(43) M. Carmack and L. A. Neubert, *J. Amer. Chem. Soc.*, **89,** 7134 (1967).
(44) A. F. Beecham, J. W. Loder, and G. B. Russell, *Tetrahedron Lett.*, 1785 (1968); M.-O. Hedblom, *ibid.*, 5159 (1970).
(45) G. Bergson, G. Claeson, and L. Schotte, *Acta Chem. Scand.*, 16, 1159 (1962), and references cited therein.
(46) 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.
(47) R. Nagarajan and D. O. Spry, *J. Amer. Chem. Soc.*, **93,** 2310 (1971).
(48) C. E. Rasmussen and T. Higuchi, *J. Pharm. Sci.*, **60,** 1608 (1971).
(49) I. Z. Siemion, J. Lisowski, B. Tyran, and J. Morawiec, *Bull. Acad. Pol. Sci., Ser. Sci. Chim.*, **20,** 549 (1972).
(50) F. Snatzke, *ibid.*, **21,** 167 (1973).
(51) J. L. Strominger, P. M. Blumberg, H. Suginaki, J. Umbreit, and G. G. Wickus, *Proc. Roy. Soc., Ser. B*, **179,** 369 (1971).
(52) P. M. Blumberg and J. L. Strominger, *Proc. Nat. Acad. Sci. U. S.*, **68,** 2814 (1971).
(53) R. Hartmann, J.-V. Höltje, and U. Schwarz, *Nature (London)*, **235,** 426 (1972).
(54) R. G. Jones, *Amer. Sci.*, **58,** 404 (1970).
(55) A. E. Bird and J. H. C. Nayler, *Med. Chem., Ser. Monogr.*, 11, 277 (1971).
(56) D. J. Tipper and J. L. Strominger, *Proc. Nat. Acad. Sci. U. S.*, **54,** 1133 (1965).
(57) B. Lee, *J. Mol. Biol.*, **61,** 463 (1971).
(58) R. M. Sweet and L. F. Dahl, *J. Amer. Chem. Soc.*, **92,** 5489 (1970).
(59) R. B. Morin, Abstracts of the 148th National Meeting of the American Chemical Society, Chicago, Ill., Sept 1964, p 14.
(60) R. B. Morin, B. G. Jackson, R. A. Mueller, E. R. Lavagnino, W. B. Scanlon, and S. L. Andrews, *J. Amer. Chem. Soc.*, **91,** 1401 (1969).
(61) E. Van Heyningen and L. K. Ahern, *J. Med. Chem.*, 11, 933 (1968).
(62) R. M. Sweet in "Cephalosporins and Penicillins: Chemistry and Biology," E. H. Flynn, Ed., Academic Press, New York, N. Y., 1972, p 280.
(63) G. L. Simon, R. B. Morin, and L. F. Dahl, *J. Amer. Chem. Soc.*, **94,** 8557 (1972).
(64) R. S. Mulliken, *J. Chem. Phys.*, **23,** 1833 (1955).
(65) R. B. Hermann, *J. Antibiot.*, **26,** 223 (1973).
(66) M. Gorman and C. W. Ryan, ref 62, p 532.