

mcg./ml.), a deviation from linearity between response and concentration is observed at this concentration. All published iodimetric methods for penicillin require a greater-than-stoichiometric iodine-to-penicillin ratio; the reason has not been reported in the literature.

For the 4 penicillins studied, best linearity is obtained with 0.016 *N* iodate for penicillin G and oxacillin, and 0.024 *N* iodate for phenethicillin and ampicillin. At much higher iodate concentrations, deviations from linearity become apparent, possibly due to the increased influence of substitution reactions.

Iodine absorption on the tubing walls is minimized by using an all-glass-Teflon system beyond the point of acidification of iodate. Nevertheless, without air-scrubbing, visible deposits of iodine accumulate on the glass. Deposits also build up in the porous glass wall isolating the calomel electrode, but these can be washed out at the end of each working day. When more extensive washing

appears desirable, 3 *N* HNO₃ is pumped through the entire system for 3 hr.

The influence of iodide ion on the penicillin method is minimized by holding a high concentration of excess iodide in all streams. In view of the current belief that the platinum electrode has an adsorbed I⁻ layer (6), the iodide is considered important to avoid electrical drift.

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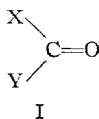
Notes

Molecular Orbital Localization Energies and Carbonyl Nucleophilic Reactivity

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Molecular orbital anion localization energies have been calculated for a number of carbonyl group-containing compounds using the LCAO-MO Hückel procedure and the ω -technique. These energies have been found to reflect very adequately the summation of electronic effects from neighboring atoms to the carbonyl group as evidenced by the excellent correlation of the energies calculated with the rate constants of base catalyzed hydrolysis.

THE RELATIVE rate of nucleophilic reactivity of a carbonyl group-containing system such as I can be of great importance from the standpoint of



drug activity and drug stability, as well as contributing to structural and mechanistic theory. Classical resonance theory has dictated that a balance of mesomeric and inductive effects derived from atoms X and Y in I should facilitate or retard the ease of hydroxyl ion attack on the carbonyl carbon, this becoming the rate-determining step in the reaction sequences. The contributions of X and Y

manifest themselves in the form of an energy barrier referred to as the free energy of activation, ΔF^\ddagger . It has been assumed that, as a good approximation, ΔF^\ddagger is composed chiefly of ΔE^\ddagger_π , the change in π electronic energy between the unreacted molecule and the transition state (1). In comparing the relative rates of reaction in a closely related set then the relationship holds

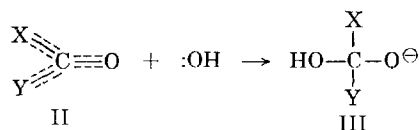
$$-RT \log \frac{k_2}{k_1} = [(\Delta E^\ddagger_\pi)_1 - (\Delta E^\ddagger_\pi)_2] \quad (\text{Eq. 1})$$

The evaluation of ΔE^\ddagger_π demands a consideration of the nature of the transition state, or a reasonable model of it, in order to base the calculations on physical reality. Among several models proposed for the transition state, the σ complex or the Wheland intermediate has appeared to be the most satisfactory simple approach in the quantum mechanical study of chemical reactivity (2). In the case of the carbonyl carbon subjected to nucleophilic attack, the Wheland intermediate is a carbon surrounded by 4 bonds, each containing 2 electrons, III.

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Justification for this model is found in the tests of Hammond's postulate; if the σ complex is an unstable intermediate in the reaction, the transition state should closely resemble it in energy (3).

A means of estimating the energy difference between II and III, known as the localization procedure (2), has been proposed by Wheland. It is based on the concept that the essential difference in π electronic energy between the 2 states is the energy required to perturb the delocalized π electrons to permit the nucleophile to attack the carbon atom. The electron contributed by the carbon atom in the ground state must now be delocalized over the remaining π system or specifically in the case of the carbonyl group system II, it must be localized on the oxygen atom, with the accompanying disruption of the π system due to loss of participation of the central carbon atom. The problem then reduces to one of calculating the energies of the ground state, E_{π} , and the transition state E_{π}^{\ominus} , and calculating the anion localization energy

$$L_c^{\ominus} = E_{\pi} - E_{\pi}^{\ominus} \quad (\text{Eq. 2})$$

The means of calculating these energies is available through the method of molecular orbitals.

The simple LCAO-MO procedures are well suited for calculations involving heteroatoms because of the relative simplicity of these calculations, and because the present crude nature of heteroatom treatments emphasizes only compatibility with as many observed properties as possible, rather than correct numerical values. In the course of quantum mechanical studies on drug molecules, the author and co-workers have arrived at a set of parameters for heteroatoms which give calculated quantities mirroring physical experience (4). These values, listed in Table I, have been derived from ionization

TABLE I.—VALUES OF h_x AND k_{cx} FOR HETEROATOMS FOR $\alpha_x = \alpha_c + h_x\beta_{cc}$

Atom X ^a	h_x	k_{cx}
$\ddot{\text{O}}$	1.3	0.8
$\ddot{\text{O}}$	2.7	0.6
$\ddot{\text{N}}$	1.7	0.7
$\ddot{\text{Cl}}$	2.8	0.5
CH_3	3.0	0.7

^aThe designation $\ddot{\text{O}}$ refers to oxygen with a core charge of 1, i.e., an oxygen donating 1 electron to the π system. In this study this would be used for the carbonyl oxygen. Similarly, $\ddot{\text{O}}$ and $\ddot{\text{N}}$ refer to heteroatoms donating 2 electrons to the π system, hence, having core charges of 2. This is used for ester- and amide type atoms in the C—X—C linkage. The values for Cl and CH₃ reflect the concept of 2 electron donation to the π system as discussed and used by Streitwieser (7).

potentials, hence, they bear a consistent relationship to each other as well as the ionization phenomena (5). In other studies in this laboratory these values have been used to calculate successfully π dipole moments and carbonyl oxygen charge densities (4).

The values listed in Table I are modifying parameters used in the expressions for the Coulomb and resonance integrals, α and β , for the heteroatom, X. The methyl group is treated as a heteroatom.

$$\alpha_x = \alpha_c + h_x\beta \quad (\text{Eq. 3})$$

$$\beta_{cx} = k_{cx}\beta_c \quad (\text{Eq. 4})$$

The integrals for the heteroatoms are commonly expressed in terms of a standard aromatic carbon atom.

There has been a further attempt to treat the failure of the simple Hückel method to account for electron correlation by using the ω technique, first suggested by Wheland and Mann (6) and later studied by Streitwieser (7). The technique employs a disposable parameter, ω , to modify the Coulomb integral based on the calculated charge density, q_i , so that

$$\alpha_i = \alpha_0 + q_i\omega\beta_0$$

The process is reiterated to a self-consistent value of the Coulomb integral. The use of this parameter effectively increases the Coulomb attraction between a π electron and a donating atom. The example of Streitwieser (7) and others (8) has been followed in using a value of 1.4 for ω .

The carbonyl-containing compounds calculated in this study (Table II) were selected to represent a

TABLE II.—SECOND-ORDER BASE HYDROLYSIS RATE CONSTANTS AND ANION LOCALIZATION ENERGIES FOR SEVERAL CARBONYL COMPOUNDS

Compd.	$\log k + 5$ (moles ⁻¹ , min. ⁻¹) ^a	L_c^{\ominus} (in β)
Urea	0.250	1.144
Acetamide	1.352	1.002
Urethan	2.079	0.966
Methyl acetate	3.945	0.804
Ethyl carbonate	5.447	0.766
Ethyl chloroformate	6.380	0.643

^a See References 9–14 for the respective kinetic data.

wide diversity of heteroatoms for X and Y in I. They were also selected so as to minimize as far as possible any steric interaction with the carbonyl group. Finally, the set selected is known or thought to undergo base-catalyzed hydrolysis by a second-order nucleophilic attack of hydroxyl ion on the carbon atom (9–14). It was further thought that success in this correlation would constitute further proof of the value of the parameters in Table I and justify their use in other studies.

Calculation of Ground State π Energies.—The value of the π energy of the ground state of each compound is obtained by the solution of a secular determinant of the Coulomb and resonance integrals of participants in the π network. The eigenvalues so derived are expressed in terms of the Coulomb and resonance integrals and each represents an energy level. Filling each level according to aufbau principles, and summing the occupied levels, the total energy of the ground state in terms of α and β is obtained.

Calculation of L_c^{\ominus} and Correlation with Base Hydrolysis Rate Constants.—From Eq. 2 the value of L_c^{\ominus} is computed in terms of β (Table II). As a test of the relative value of these energies, the

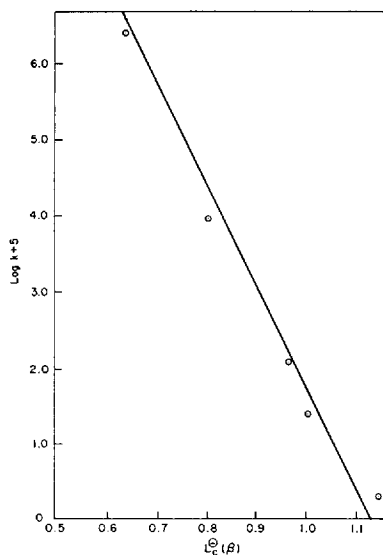


Fig. 1.—Correlation line for $\log k + 5$ vs. L_c^{\ominus} . Correlation coefficient = 0.986. Equation for line: $\log k + 5 = 15.25 - 13.57 L_c^{\ominus}$.

values calculated have been plotted in Fig. 1 along with the least squares equation. The correlation is excellent (correlation coefficient of 0.986) fully justifying the use of parameters to reflect the participation of the atoms X and Y, adequately, in the reaction studied. Also corroborated by the correlation is the use of the transition state model and accompanying mechanism for each compound studied. The parameters used and the techniques employed may further permit a prediction of relative base hydrolysis rates within the framework of the approximations made and limitations imposed.

Numerical Computations.—The numerical computations were performed on an IBM computer. The program used for the ω -Hückel calculations was translated from Fortran to Scatran.¹ The program determines the eigenvalues and eigenvectors of a real symmetric matrix, using an HDIAG subroutine, according to the method of Jacobi. The program has been further modified with the

¹ The Ohio State Computer Center language, by Evan L. Brill of the Numerical Computation Laboratory staff. The program was originally written by G. Pettit, the University of Minnesota, and modified for use with the ω technique by D. Lazdins, the University of Minnesota.

help of Douglas Fleckner of this computation laboratory, to accept core charges other than 1, for use with some heteroatoms. This is necessary in the use of the ω technique. For example, the oxygen of a carbonyl group would have a core charge of 1 while the oxygen of an ester C—O—C would have a core charge of 2.

The calculation of correlation coefficients, least squares regression line, and other statistical data were computed using standard subroutines from this numerical computation laboratory.

Summary.—The anion localization energies have been calculated for a number of simple substituted carbonyl systems undergoing hydroxyl ion-catalyzed hydrolysis. The localization energies calculated have been assumed to be, as a first approximation, a relative measure of the free energy of activation of the reactions, using the Wheland intermediate as a model for the transition state. An excellent correlation is exhibited between these calculated values and the log of the rate constants for the compounds studied.

It has thus been shown that the LCAO-MO Coulomb and resonance integral modifying parameters for the heteroatoms were well chosen and truly mirror their relative electronic interaction within the delocalized electron framework. It is also apparent that the model for transition state and the proposed mechanism of action were correctly reflected by the reaction model chosen. The correlation of the calculated localization energies with the rate constants attests to the utility of quantum chemical methods in studying and predicting drug molecule reactions, stability, and possibly even pharmacological activity.

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