A MOLECULAR ORBITAL STUDY OF THE REACTIONS OF SYDNONES

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Abstract—MO calculations using the ω Hückel LCAO technique have been performed on several 3-alkylsydnones. Energy calculations permit predictions for protonation of the number 2 N-atom, nucleophilic attack at the number 5 C-atom, electrophilic attack at the number 4 C-atom, and free-radical attack at the number 4 C-atom. Supporting evidence for these predictions is discussed, and mechanisms of base- and acid-catalyzed hydrolysis are proposed.

In a previous report, we have described the calculation of the electronic structures of several mesoionic sydnones,[2] I. The method employed was the LCAO Hückel approximation with the added feature of treating electron correlation by the iterative "ω technique".[3] The calculated charge densities were found to yield dipole moments in close agreement with experimental data. Eigenvalue calculations were found to produce transition energies which correlated well with observed electronic spectra. These encouraging results with the sydnones enabled a considerable degree of confidence in the heteroatom parameters employed in such a complex system.

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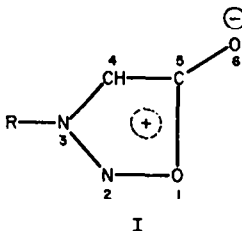
These same parameters had been previously derived, independent of the sydnone ring.[4, 5] A logical extension of the work on sydnones is a MO study of the chemical reactivity of these molecules.

MOLECULAR ORBITAL CALCULATIONS

Parameters. Within the framework of the Hückel MO theory, the variation in the Coulomb integral, α, and the resonance integral, β, for atoms and bonds involving heteroatoms is accounted for by the use of the respective parameters h_x and k_{xy} in 1 and 2.

$$\alpha_x = \alpha_c + h_x \beta_{cc} \tag{1}$$

$$\beta_{xy} = k_{xy} \beta_{cc} \tag{2}$$

To study the reactivities of the 3-alkylsydnones, it was necessary to derive parameters which would reflect the differences in mesomeric contributions of electrons to the sydnone ring made by Me, Et, i-Pr, and t-Bu groups. The model employed in calculations of Me-substituted aromatic systems, including methylsydnone, was the conjugative model proposed.[6] This model proposes that the Me group participates mesomerically with a π-electron system through a quasi p-orbital on the Me carbon atom and a quasi-π group orbital composed of a combination of the three hydrogen atomic orbitals.[6-8] The result is an extension of conjugation over two more orbitals containing one electron each. This model may be represented as in II. The values of h_x (Eq. 1) for the atoms and quasi-π orbitals and k_{xy} (Eq. 2) for the bonds between atoms are listed in Table 1. The values used for these parameters were those suggested by Coulson and Crawford.[9] This model was successfully employed in the calculation of dipole moments of toluene, 1-methylpyrrole, 1-methylpyrazole, and 3-methylsydnone from HMO-ω charge densities.[2,4]

II
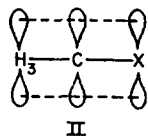
In considering the alkyl groups Et, i-Pr, and t-Bu, the mesomeric contribution would be expected to decrease as the number of H-atoms bonded to the C-atom and to the π-system decreased.[10] In this respect, the electropositivity of the quasi-π group orbitals tends to diminish and the respective Coulomb integrals decrease in the order $\alpha_{Me} > \alpha_{Et} > \alpha_{i\text{-}Pr} > \alpha_{t\text{-}Bu}$.[8]

If free rotation is allowed in the alkyl substituents, a smooth transition in the Coulomb integrals of the quasi-π group orbitals would be expected from Me to t-Bu.[8] Ehrenson found that the mesomeric effect of a C—H bond is greater than that of a C—C bond and that the relative resonance energy contribution of the C—H to the C—C bond is in the ratio 1·3 to 1·0.[8] From this relationship, the h_x parameter for the quasi-group orbital of the t-Bu group was derived (Table 1), and the same parameters for Et and i-Pr were then calculated to be proportional to the values used by Ehrenson. The Coulomb integral parameters for all of the alkyl groups are listed in Table 1.

The entire mesomeric effects of alkyl groups were assumed to be dependent upon the relative electropositivities of their quasi-π group orbitals. Thus, to a first approximation, the resonance integral parameter (Eq. 2) for the interaction between the quasi-π group orbital and the quasi-2p orbital on the alkyl carbon remains unchanged. Further, the Coulomb integral parameter (Eq. 1) for the alkyl carbon atom should not require alteration from that derived for the Me group.

The next set of parameters to be determined was concerned with the protonation of heteroatoms in heteroaromatic systems. Since the protonation of these atoms involves bond formation between the proton and the non-bonded electrons on N or O, the process results in little change in the π-system. The major change in the conjugate acid is essentially due to the increased electronegativity of the heteroatom,

caused by bonding with the positively charged proton.[11,*] This increased electro-negativity is reflected in a larger negative value for the Coulomb integral. This may be accomplished within the framework of the Hückel LCAO method by assigning a larger positive value to the Coulomb integral parameter h_x (Eq. 1).

For MO calculations employing the ω-technique, the relationship for the difference in h_x between a neutral C-atom and a carbonium ion discussed by Streitwieser[3] seemed appropriate for arriving at a value of h for a protonated heteroatom. This relationship is shown in Eq. 3. The value of $\omega = 1.4$ has been used successfully throughout this work[2] and leads to the values of the Coulomb integral parameters for protonated heteroatoms shown in Table 1. The values of h_x for the neutral heteroatoms are the same as those described previously:

$$h_x^{\oplus} - h_x = \omega \tag{3}$$

Protonation. The protonation of a heteroatom is not analogous to electrophilic substitution at an aromatic C-atom. The electrons used in bonding to the proton arise from the nonbonded orbital on the heteroatom, and are not of the proper geometry to participate in delocalization with the π-system (Fig. 1). The net result is that π-delocalization is not interrupted, but only perturbed, resulting in a different total π-energy for the conjugate acid than in the free base. The perturbation of the π-electron system due to protonation is reflected in the increased electronegativity of the protonated atom.
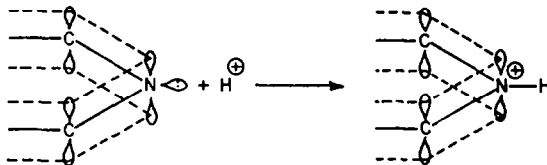

Fig. 1. Orbital representation of protonation of a heteroatom contained in a π-electron system.

Employing the appropriate parameters for the protonated heteroatoms (Table 1), the total π-energy, E_π^p, of a protonated heteroaromatic system may be calculated from the resulting eigenvalues. From Eq. 4, the difference between E_π^p of the conjugate acid and the total π-energy of the free base, E_π, provides a measure of the protonation energy, $\Delta E_{r\pi}^p$, or the π-energy required to protonate the position r on the molecule.* Application of Eq. 4 for each heteroatom should provide an indication as to which heteroatom in a system containing two or more is the most basic:

$$\Delta E_{r\pi}^p = E_\pi - E_{r\pi}^p = (n\alpha + M\beta) - (n_r\alpha + M_r^p\beta) = (M - M_r^p)\beta \tag{4}$$

These calculations were performed on 3-methylsydnone (I, R — Me). The values of $\Delta E_{r\pi}^p$ for the appropriate positions on the sydnone ring (I) are listed in Table 2. These calculations reveal that the number 2 N is the most energetically susceptible to attack by a proton. This result may have been initially unexpected from considerations of the reactant due to the fact that the exocyclic oxygen carries the highest

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* It has been brought to the author's attention that one might well bear in mind that protonation of a molecule depends upon the differences between the standard partial molal free energies of the free base and the conjugate acid. The MO calculations discussed herein approximate only the change in π-electronic energy between these two species.

negative charge.[2] However, the results of these energy calculations indicate that reaction between a positive species and one of these two positions energetically favors the number 2 N position on the sydnone ring.

Spectral data. The model employed for the calculation of protonation energies assumes a slight perturbation of the π-electrons from the increased electronegativity of the core of the protonated atom. The total π-energy of the conjugate acid may be different from the free base, but the relative spacing of the energy levels may not exhibit major displacements, to a first approximation. Thus, the major low-energy electronic transitions should not exhibit large shifts in acidic media.

The UV spectra of 3-methylsydnone in neutral and acidic media show no shift in the wavelength of maximum absorption in acid concentrations ranging from 0 to 2 times the concentration of the sydnone, on a molar basis. This tends to favor the relatively simple model of an altered Coulomb integral for the protonated atom for comparing MO quantities between the free base and the conjugate acid of a molecule.[11, *]

An attempt was made to locate the point of protonation of the sydnone ring by means of IR spectroscopy. A small N—H absorption band appears in the spectrum of 3-methylsydnone in acidic media. This band occurs in or near the region in which the C—H stretching frequency of 3-substituted sydnones also appears.[12] Although it is difficult in some instances to observe this N—H band, the lack of any bands in the O—H stretching region, and the fact that the sydnone CO peak was left unaltered by the presence of acid, further attest to the validity of the results of the protonation energy calculations (Table 2). That is to say, the ring N is protonated in preference to the exocyclic oxygen.

Nucleophilic reactivity. Nucleophilic reactivity in π-electron-containing systems has been treated by numerous MO techniques.[13] The method which has proved to be the most successful is based on the Wheland model for the transition state,[14] and has been termed localization energy.[15] In theory, this approach involves the calculation of the π-electronic energy required to traverse from the ground state of a molecule to that Wheland intermediate which approximates the transition state.[14] In the reaction energy profile, the transition state resembles the Wheland intermediate more than the reactant or the product.[16]

The free energy of activation, $\Delta F^{\ddagger}$, is defined as the free energy required to achieve the transition state from the normal ground state of the reactant molecules. To a first approximation, this energy barrier may be considered to be composed of the change in π-electronic energy, $\Delta E_{\pi}^{\ddagger}$ between the molecule in the ground state, E_{π}, and the model representing the transition state, E_{π}^{*}.[17] The relative rates of reaction within a series of related molecules may then be expressed in terms of $\Delta F^{\ddagger}$ and $\Delta E_{\pi}^{\ddagger}$ by Eq. 5. In this equation, k_1 and k_2 are the rate constants for two related reactants going to respective products.[17]

$$\Delta F^{\ddagger} = -RT \ln \frac{k_2}{k_1} = [(\Delta E_{\pi}^{\ddagger})_1 - (\Delta E_{\pi}^{\ddagger})_2] \tag{5}$$

The transition-state model for reaction of an aromatic system with a nucleophile may be represented by isolating the atom under attack from the total π-electron system. The net result is a new unsaturated fragment with the number of π-electrons
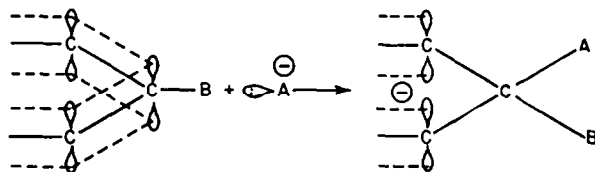
* See footnote on p. 1675.

FIG. 2. Orbital representation of σ-complex formation during reaction of a π-electron system with a nucleophile.

equal to the number in the original molecule, but distributed over a skeleton diminished by one atom (Fig. 2). This model amounts to the isolation of one atom from the π-electron system without its allotment of π-electron density. The π-energy required to attain this state may be calculated by the HMO-ω method, and is termed anion localization energy, $L_\omega^{\ominus}$[14] (Eq. 6).

$$L_\omega^{\ominus} = E_\pi - E_{r\pi}^* = (n\alpha + M\beta) - (n_r\alpha + M_r^*\beta) = (M - M_r^*)\beta \qquad (6)$$

Application of the relationship in Eq. 6 to several positions on 3-methylsydnone (I, R = Me) permitted the comparison of the relative susceptibilities of various ring positions to nucleophilic attack. The values of $L_\omega^{\ominus}$ for each of the positions examined and the various electronic configurations are recorded in Table 3.

It is apparent that this calculation predicts the *pseudo*-lactonic carbonyl C, position
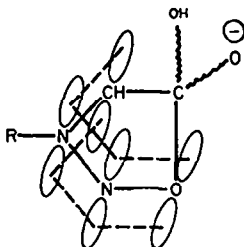

FIG. 3. Wheland intermediate for the reaction of hydroxide ion with position 5 of 3-methylsydnone.

5, to be the most energetically susceptible to attack by a nucleophile. Further, reaction at this position is greatly facilitated through the localization of a pair of electrons on the exocyclic O-atom. The Wheland intermediate that corresponds to this model of the transition state for the reaction of sydnone with hydroxide is illustrated in Fig. 3.

Intuitively, one might expect nucleophilic attack to occur at the *pseudo*-lactonic carbonyl C. Recent evidence in support of this MO prediction may be found in the work of Bellas and Suschitzky.[18] The authors isolated (N-phenyl-N-nitrosoglycyl) piperidine from the reaction of 3-phenylsydnone (I, R — Ph) with piperidine. This is the expected product from nucleophilic attack by the nonbonded electrons on the piperidine N at the *pseudo*-lactonic carbonyl C.

Electrophilic reactivity. The theoretical basis of localization energy described in the previous section may be extended to the general problem of the reaction of an aromatic system with an electrophilic reagent.[13] The model generally accepted for the transition state[13,14] is one in which two π-electrons have been localized at the

position where reaction is occurring. The remaining delocalized electron system is therefore two electrons and one atomic core less than the original system. The π-electronic energy required to localize two electrons at an atom has been termed cation localization energy, $L_\omega^\oplus$, and may be calculated by the HMO-ω method by taking the difference between the ground-state energy, E_π, and the model transition-state energy, E_π^*. The resulting equation is represented in Eq. 7.

$$L_\omega^\oplus = (M - M_r^*)\beta \tag{7}$$

The heteroatoms contained in the sydnone nucleus have nonbonded electrons which can react with an electrophile without actually involving the π-electrons. Thus, there are only two positions that could be directly susceptible to electrophilic substitution. Calculation of $L_\omega^\oplus$ for positions 4 and 5 of 3-methylsydnone (I, R = Me) was accomplished by use of Eq. 7. The results are shown in Table 4. The apparent preferred position for electrophilic attack on the sydnone ring is the carbon atom at position 4 (I). The corresponding Wheland model is illustrated in Fig. 4.
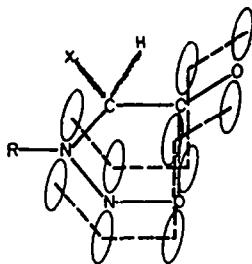

FIG. 4. Wheland intermediate for the reaction of an electrophile, $X^\oplus$, with position 4 of 3-methylsydnone.

Free-radical reactivity. The free-valence index is a comparative quantity describing the so-called "left over" π-electron density about a particular atom, r. The definition of this reactivity index appears in Eq. 8, where N_r is the sum of π-bond orders to atom r and N_{max} is the largest possible value of this sum.[19] The value of N_{max} commonly used is $\sqrt{3}$, which is the sum of the π-bond orders to the central atom of the diradical trimethylenemethane.[20]

$$F_r = N_{max} - N_r \tag{8}$$

The free-valence index has been given the physical significance of measurement of the tendency for a certain atom in a molecule to react with a free radical.[13] This index is concerned only with the reactant molecule, and completely ignores any contribution to reactivity from the energy or structure of the transition state.

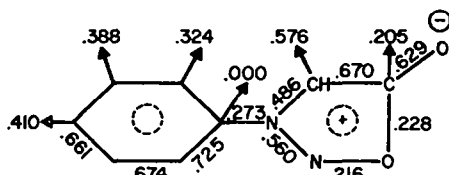The free valence of each of the appropriate carbon atoms in 3-phenylsydnone and

FIG. 5. π-Bond orders and free-valence indices for 3-phenylsydnone.

3-methylsydnone was calculated from Eq. 8. These values are shown in the usual fashion, at the points of the arrows, in Figs 5 and 6, respectively. The higher the value, the greater the expected reactivity. The numbers shown between atoms are the π-bond orders which were discussed in an earlier publication, and are used at this time to calculate the free valences.[2]
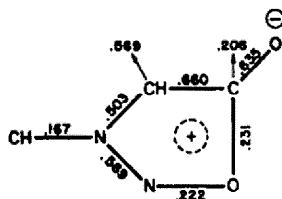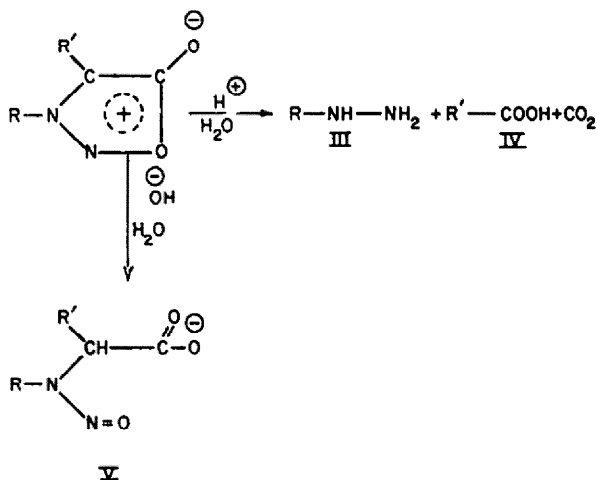

Fig. 6. π-Bond orders and free-valence indices for 3-methylsydnone.

DISCUSSION

Acid hydrolysis. One of the first reactions studied involving the sydnone ring was its hydrolysis in an aqueous acidic medium.[21,22] The products of this hydrolysis are a substituted hydrazine (III) and a carboxylic acid (IV) accompanied by the evolution of CO_2.

The kinetics of this hydrolysis reaction have been studied by Garrett with a series of 3-alkylsydnones.[23] The rates of hydrolysis were found to follow the order of alkyl substituents: t-Bu $\gg$ i-Pr $\geqslant$ Pr $\geqslant$ Me. From the experimental kinetic data, a mechanism of acid-catalyzed hydrolysis was proposed involving initial protonation of the number 2 N-atom.[23] The calculated protonation energies of methylsydnone (Table 2) are in agreement with this site of the initial protonation.

In an attempt to study the possible effect of protonation on the relative rates of acid-catalyzed hydrolysis of the alkylsydnones, protonation energies at the number 2 N-atom were calculated for 3-ethyl-, 3-isopropyl-, and 3-t-butylsydnone. The results of these calculations and the experimental hydrolysis rate constants are recorded in Table 5.[23] From the standpoint of inductive and mesomeric effects, the Et group was assumed to be eqivalent to a Pr group. The same combination of quasi-π group orbitals can be formulated on either substituent. The accompanying rate constants

indicate that little difference should be found in the energetics of the acid-catalyzed hydrolysis of 3-methyl, 3-propyl, and 3-isopropylsydnone. In fact, the enthalpies and entropies of activation for these three derivatives have been reported to be equivalent within experimental error.[23] The MO calculated protonation energies for these derivatives are also quite close (Table 5). To the extent that protonation becomes rate determining in this hydrolysis, the protonation energies (Table 5) would qualitatively predict that the rates of hydrolysis for these three derivatives should be indistinguishable. A further point may be invisioned from these calculations. The protonation energies (Table 5) indicate that the conjugate acids of the three sydnone derivatives should be present in practically the same equilibrium concentrations. Assuming that the alkyl substituents would have the same influence on the conjugate acid of the sydnone ring as on the transition state of the next step in the reaction sequence, a rate determining step involving further reaction of the conjugate acid could proceed to yield the same kinetic results.[23] Thus, a rate determining protonation is not a necessary criterion.

The case represented by 3-t-butylsydnone requires special scrutiny. The rate of hydrolysis for this derivative is considerably greater than the other derivatives (Table 5). Although the enthalpy of activation apparently does not significantly increase, the entropy of activation has been repoi'xd to increase by about 2·5 log P units from that reported for the other three derivatives. This increase has been attributed to electrical effects from the alkyl substituents.[23] However, upon comparing the calculated protonation energies in Table 5, one would not expect electronic aspects to account for the much greater rate of decomposition of the t-Bu derivative.

If electronic effects cannot explain the increase in the entropy of activation and the accompanying large increase in the rate of hydrolysis, an explanation may be found in an aggregative phenomenon deduced from a study of the NMR spectra of 3-alkylsydnones.[24] This study indicated that the ease of disruption of aggregates of sydnone molecules in solution increased with increasing size of the alkyl substituent.[24] The effect of protonation of the sydnone ring under the conditions of the reaction could lead to an even lower extent of aggregation for the bulky 3-t-butylsydnone, compared with the other three derivatives. Thus, solvolysis could proceed more readily in the former compound. In light of these findings, a mechanism for the acid-catalyzed hydrolysis of sydnones is proposed in Fig. 7.

Base-hydrolysis. At the same time that Earl *et al.* reported the products from acid hydrolysis of the sydnone ring, they also studied the products from reaction of this system with aqueous base.[21,22] This type of hydrolysis results in the regeneration of the starting N-substituted-N-nitroso-amino acid (V).

The kinetics of the base-catalyzed hydrolysis of a series of 3-alkylsydnones has also been studied by Garrett.[23] The reactivity sequence was found to be in order of the 3-alkyl-substituents Me > Pr > i-Pr > t-Bu. The kinetic data, particularly the calculated entropy of activation, led Garrett to propose a hydrolysis mechanism involving initial attack by hydroxyl ion on the number 2 N. However, this proposal is neither in agreement with the theoretical MO calculations reported here (Table 3), nor with the types of products isolated from the reaction of sydnones with amines.[18]

In an effort to assess the predictive value of the MO localization energy results (Table 3), calculations employing Eq. 6 were performed on models of ethyl-, iso-propyl-, and t-butylsydnone. The results of these calculations and the rate constants
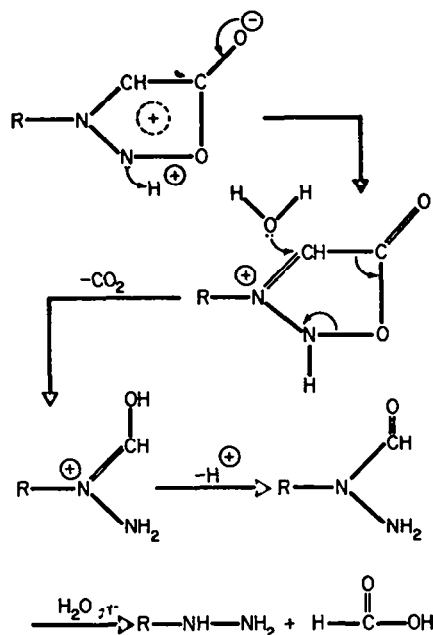
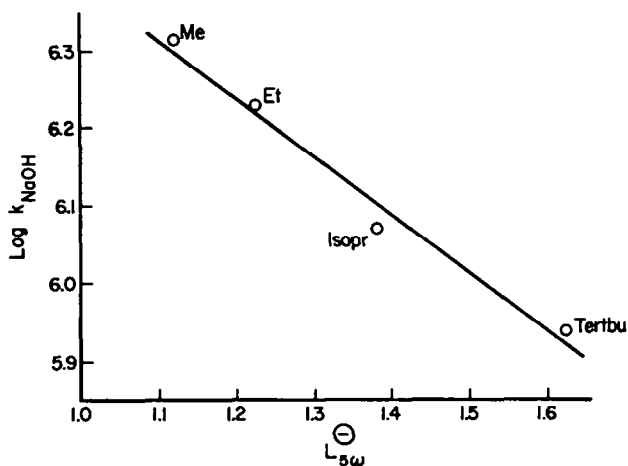FIG. 7. A possible mechanism for acid hydrolysis of 3-alkylsydnones.

FIG. 8. Relationship between anion localization energy at position 5 ($L_{5\omega}^{\ominus}$) of the sydnone ring and log $K_{[NaOH]}$ in liters/mole-sec.[23]

for base-catalyzed hydrolysis are shown in Table 6.[23] As in the case of acid hydrolysis, the Et group was assumed to be equivalent to the Pr group by virtue of their respective abilities to contribute inductively and mesomerically to π-electron delocalization.

If, indeed, attack by OH ion is a rate-determining feature of the hydrolysis of sydnones in alkaline solution, the energy of this nucleophilic reaction should be linearly related to the log of the rate constant.[5] This relationship is illustrated in

Fig. 8. The success of this correlation supports the initial prediction of a nucleophile-favoring attack at the *pseudo*-lactonic carbonyl carbon (Position 5) of the sydone ring (Table 3).

The results of these calculations may also serve to shed light on mechanistic approaches to base-catalyzed hydrolysis of sydnones. The calculated preferred point of nucleophilic attack leads to the possible reaction sequence depicted in Fig. 9, which is further supported by the previously mentioned results of the reaction of sydnone with amines.[18]
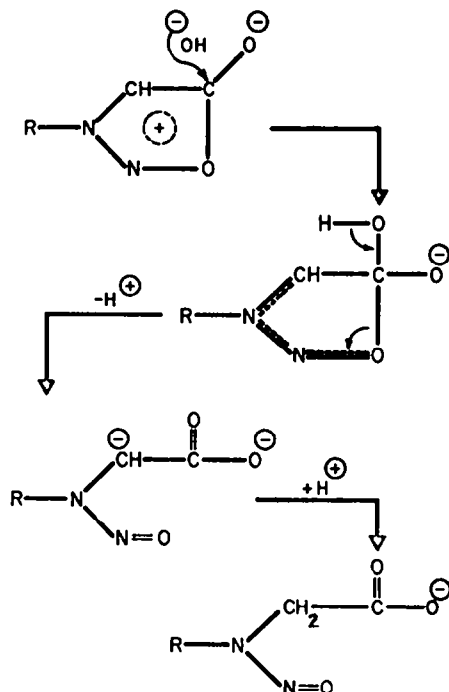

Fig. 9. Proposed stepwise mechanism of the hydrolysis of 3-alkylsydnones in basic media.

Electrophilic reactivity. The reactions of sydnones with electrophilic reagents are among the most extensively studied reactions in the chemistry of mesoionic systems.[25] However, these studies have been directed primarily toward products and reaction conditions. Little effort has been directed toward a consideration of substituent effects and relative reaction rates.

3-alkyl- and 3-aryl-substituted sydnones do undergo electrophilic substitution exclusively at the 4-position.[25] The calculated cation localization energies (Table 4) indicate that, of the possible positions on the sydnone ring, the number 4 C is energetically the most favorable point for electrophilic attack.

Oxidation of sydnones. Hashimoto and Ohta reported that, when 3-phenylsydnone (I, R = Ph) is subjected to the oxidative conditions of potassium permanganate in acetone, a product isolated from the reaction is 3,4-diphenylsydnone.[26] The authors suggested that this product could be formed through the reaction of Ph radicals at the number 4 C-atom of the sydnone ring. Experimental proof of this mechanism has not been published.

The free-valence indices calculated for 3-phenylsydnone (Fig. 5) indicate that the C-atom at position 4 of the sydnone ring should be the most favorable for free-radical

TABLE 1. COULOMB AND RESONANCE INTEGRAL PARAMETERS OF ALKYL GROUPS AND HETEROATOMS

Atom		h_x	Bond	k_{xy}
$\dot{N}$		0·8	C—$\dot{N}$	1·0
$\ddot{N}$		1·5	C—$\ddot{N}$	0·8
$\dot{O}$		1·3	C—$\dot{O}$	0·8
$\ddot{O}$		2·7	C—$\ddot{O}$	0·6
$\dot{N}^\oplus$		2·2	N—$\ddot{O}$	0·5
$\dot{O}^\oplus$		2·7	$\dot{N}$—$\ddot{N}$	0·9
$\ddot{O}^\oplus$		4·1	$H_3\equiv C$—	2·8[a]
$\equiv C$—	(α-Alkyl)	−0·1	$\equiv C$—C—	1·0
$H_3\equiv$	(Me)	−0·5	$\equiv C$—$\dot{N}$—	0·8
$H_2=$	(Et)	−0·37		
H—	(i-Pr)	−0·23		
$(CH_3)_3\equiv$	(t-Bu)	−0·08		

[a] This value is used for the resonance integral between quasi-π group orbitals and quasi 2p-orbitals of Et, i-Pr and t-Bu, as well as Me.

TABLE 2. PROTONATION ENERGIES, $\Delta E_{r\pi}^p$, FOR 3-METHYLSYDNONE (I, R = Me)

Position, r	$\Delta E_{r\pi}^p$ (in β units)[a]
1	−2·690
2	−1·754
6	−2·162

[a] The π-energy of the protonated system is greater than that of the free base, resulting in the negative energy values.

TABLE 3. ANION LOCALIZATION ENERGIES, $L_\omega^\ominus$, FOR 3-METHYLSYDNONE (I, R = Me)

Position, r	$L_\omega^\ominus$ (in β units)
2	3·876
4	4·026
5 (1 e⁻ on atom 6)	5·633
5 (2 e⁻ on atom 6)	1·120

attack. Since no further studies have been made on this reaction, the only observation that may be concluded from this calculation is its correct prediction of the product obtained experimentally.

TABLE 4. CATION LOCALIZATION ENERGIES, $L_\omega^\oplus$, FOR 3-METHYLSYDNONE (I, R = Me)

Position, r	$L_\omega^\oplus$ (in β units)
4	0·560
5	1·725

TABLE 5. PROTONATION ENERGIES, ΔE_π^ζ, FOR 3-ALKYLSYDNONES (I) AND CATALYTIC RATE CONSTANTS FOR ACID-CATALYZED HYDROLYSIS

Compound	ΔE_π^ζ (in β units)	log $k_{[HCl]}$[a]
3-Methylsydnone	−1·754	5·830
3-Ethylsydnone	−1·750	5·881[b]
3-Isopropylsydnone	−1·752	5·903
3-t-Butylsydnone	−1·746	7·279

[a] $k_{[HCl]}$ in liters/mole-sec.
[b] This is the rate constant for 3-propylsydnone.

TABLE 6. ANION LOCALIZATION ENERGIES, $L_{5\omega}^\ominus$ FOR 3-ALKYLSYDNONES (I) AND CATALYTIC RATE CONSTANTS FOR BASE-CATALYZED HYDROLYSIS[23]

Compound	$L_{5\omega}^\ominus$ (in β units)	log $K_{[N\,OH]}$[a]
3-Methylsydnone	1·120	6·318
3-Ethylsydnone	1·224	6·230[b]
3-Isopropylsydnone	1·380	6·072
3-t-Butylsydnone	1·624	5·940

[a] $K_{[Na OH]}$ in liters/mole-sec.
[b] This is the rate constant for 3-propylsydnone.

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