

An Attempted Application of the Extended Hückel Molecular Orbital Approach to Reactions Involving Charged Species

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The semi-empirical extended Hückel molecular orbital (EHMO) and non-empirical self consistent field molecular orbital (SCF-MO) methods have been used to study protonation reactions of acids, amides and esters. The work has been extended to the charged intermediates and subsequent products in their "hydrolysis" reactions.

Ein semiempirisches, erweitertes Hückel-Verfahren sowie *ab initio* SCF-MO-Rechnungen wurden zur Untersuchung der Protonierung von Säuren, Amiden und Estern, deren ladungstragender Abkömmlinge und ihrer Folgeprodukte herangezogen.

La méthode de Hückel étendue semi-empirique (EHMO) et la méthode du champ self-consistant non empirique (SCF MO) ont été utilisées pour l'étude des réactions de protonation des acides, des amides et des esters. Ce travail a été étendu aux intermédiaires chargés et aux produits résultants lors de leur «hydrolyse».

Introduction

Extended Hückel Molecular Orbital (EHMO) calculations on reaction intermediates have been successfully used to predict the endo-exo adduct ratios in Diels-Alder reactions [1] and also the position of both acid and base catalysed bromination of 2-butanone [2]. The latter study involved one charged intermediate, the enolate anion of 2-butanone, but apart from this work we are unaware of any other attempt to use the EHMO method in a reaction sequence involving charged intermediates. The object of the present study was to examine the positively charged intermediates in a series of acid catalysed hydrolytic reactions.

Three classes of compounds, amides, esters (both hydrolysis) and carboxylic acids (O^{18} exchange in the carbonyl group) undergo similar acid-catalysed reactions. These are depicted in Fig. 1. The familiar Ingold notation [3] is used.

Hoffmann [4] has examined a series of carbonium ions using the EHMO approach. However none of the ions used in his study contained hetero-atoms and comparison with the intermediates in Fig. 1 is difficult. Further, in his calculations on protonated unsaturated hydrocarbons the total energy of the bases or conjugate acids was not presented and hence one cannot deduce the proton affinities.

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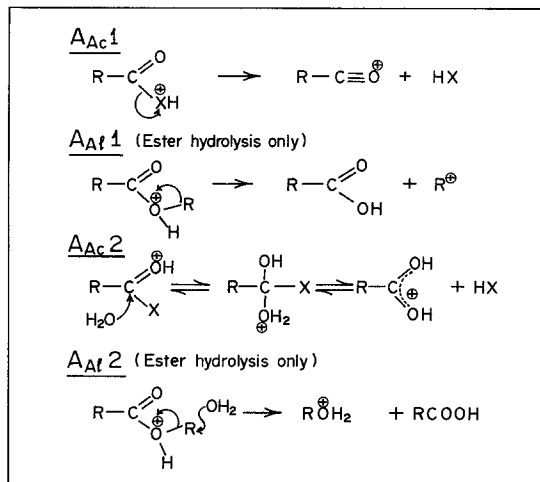


Fig. 1. Acid catalysed hydrolysis mechanisms [X = NH₂ (amide), OH (acid), OR (ester)]

Methods of Calculation

A modified version of Hoffmann's EHMO program [5] was used on an IBM 7094-II computer. Slater orbital exponents [6] (H: 1.000; C: 1.625; N: 1.950; O: 2.275) and Pritchard and Skinner's ionization potentials [7] were used as input parameters. The off-diagonal terms (H_{ij} values) were evaluated using the Wolfsberg-Helmholtz formula [5, 8], $H_{ij} = 0.5 K (H_{ii} + H_{jj}) S_{ij}$, with $K = 1.75$.

The SCF calculations were also done on the IBM 7094-II computer using, as before [9], an extensively modified version of the Polyatom system [10]. All calculations used a medium basis set with five *s* and two *p* functions on carbon and oxygen and two *s* functions on hydrogen.

Geometry

The bond lengths and angles for the neutral molecules were obtained from a standard compendium [11] and are given in Fig. 2. The data for the conjugate acids and reaction intermediates are not available in the literature and, since minimization of total energy with respect to bond length by the EHMO method has been shown to result in grossly incorrect bond lengths [5], intuitive estimates of bond lengths were made for the various reaction intermediates. However the EHMO method has been shown to be quite reliable in predicting the most stable rotamer [5] and in this work conformational studies were performed on all assumed structures to obtain the most stable form.

Results and Discussion

1. Protonation Study

The initial step in all acid catalysed hydrolysis reactions is a rapid protonation followed by one of the slower, rate determining steps shown in Fig. 1. The site of protonation is believed to be one of the hetero atoms and the bulk of chemical

evidence [12, 13, 14, 15, 16] indicates that the carbonyl oxygen is probably the preferred position for all these bases. However the $A_{Ac}1$ mechanism, which occurs frequently in concentrated aqueous mineral acids, requires protonation of the ether oxygen of esters [17] and the nitrogen of amides [18].

Table. Calculated ΔE values and experimental protonation energies in the gas phase and aqueous sulphuric acid (kcal/mole)

Molecule	Calculated energy		Proton affinity	$-\Delta G$ (solution)	
	EHMO	<i>ab initio</i> SCF			
Water	74.0	181.2 ^a	167 ^c , 151 ± 3^d	-2.46	-9.09 ^j
Ammonia	110.1	220.2 ^a	200 ^c , 206.4 ^f , 202 ^g	12.62 ^k	
Carbon monoxide	157.2	120.1 ^a	131 ^h	-	
Methanol	77.6	-	167 ^c	-3.00 ^l	
Formic acid	{carbonyl protonated	78.9	208.9 ^b	162 ± 3^i	< -10.91 ^m
	{hydroxy protonated	76.7			
Acetic acid	{carbonyl protonated	72.2	184 \pm 3 ⁱ	-8.73 ⁿ	
	{hydroxy protonated	77.4			
Formamide	{carbonyl protonated	91.4		-3.54,	-3.75 ^o
	{amino protonated	97.6			
Methyl acetate	{carbonyl protonated	71.6		-9.89 ^p	
	{methoxy protonated	81.0			

^a Ref. [19].

^b Hopkinson, A. C., K. Yates, and I. G. Csizmadia: (unpublished).

^c Munson, M. S. B., and J. L. Franklin: J. physic. Chem. **68**, 3191 (1964).

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Accurate experimental values for the enthalpy difference associated with the *gas phase* protonation (proton affinity) of many weak bases are available in the literature. Recently we have shown that *ab initio* SCF-MO calculations using Gaussian type functions as atomic orbitals give very good agreement with experimental proton affinity values for neutral and negatively charged species [19]. Both experimental and calculated values (a) by the EHMO method and (b) by the more reliable *ab initio* method, are shown in the Table.

The proton affinities calculated by the EHMO method are all too small, with the exception of that for carbon monoxide. However all have the correct sign and order of magnitude. The SCF calculations over-estimate the proton

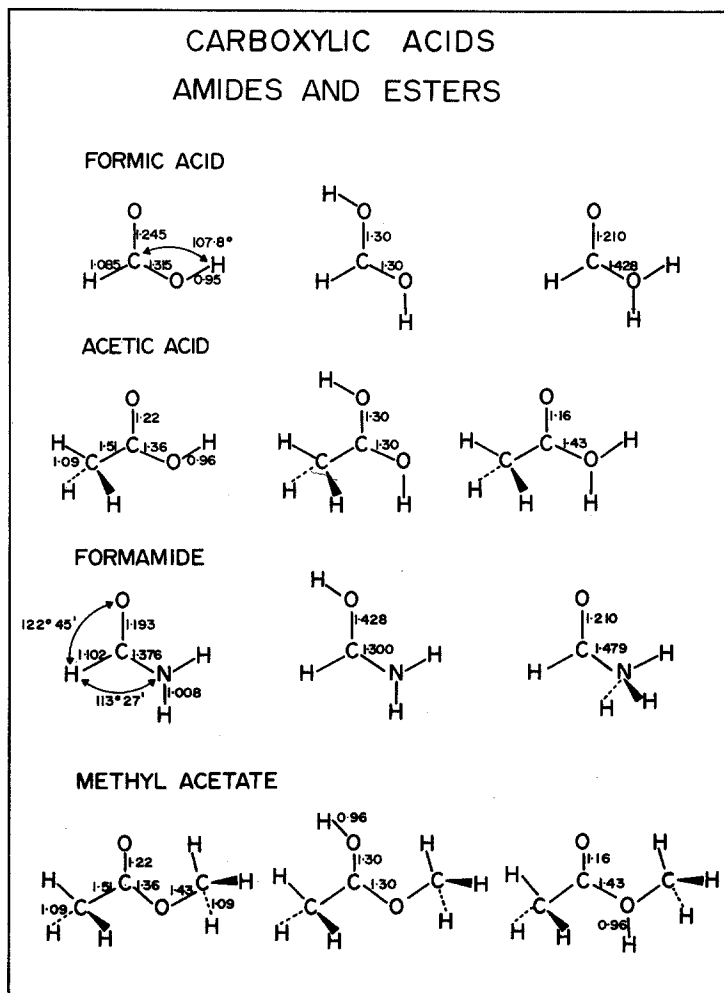
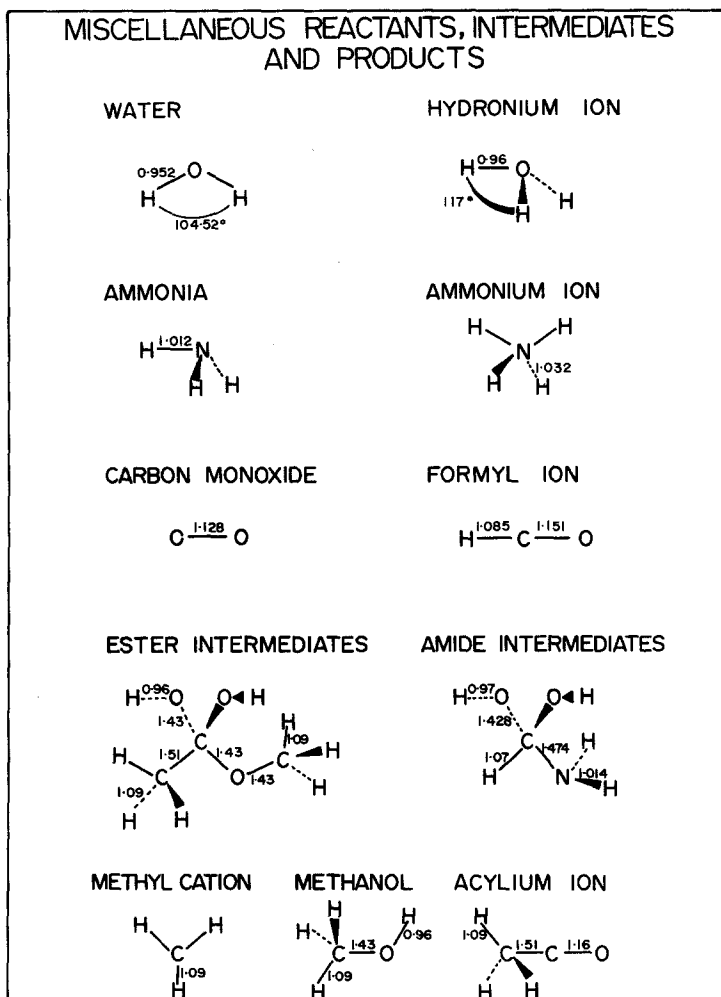


Fig. 2. Geometries used for reactants, intermediates and products.

affinity but rapidly approach the experimental value as the basis set is increased [19]. The EHMO calculations on the compounds containing two hetero-atoms predict the opposite site of protonation from that observed experimentally, except for formic acid. However, all the experimental data on protonation refers to the ions in solution where the carbonyl protonated species is probably stabilised more than the $-OX$ protonated species by hydrogen bonding with water (see Section 3). The more reliable *ab initio* SCF calculations on formic acid predict the carbonyl protonated species to be the more stable in agreement with both experiment [13, 15] and the EHMO calculations.

The protonation equilibrium of weak bases in aqueous solution is governed primarily by the free energies and entropies of solution of the base, its conjugate acid, the hydronium ion and water. Consequently, although the energy difference calculated by the EHMO method on the base and its conjugate acid gives a fair



[Bond angles not specified are either 120° or tetrahedral]

correlation with the experimental proton affinity (not 1:1), molecular orbital theory cannot be expected to predict (a) the correct order of basicities for a heterogeneous series of bases in solution, or (b) the protonation reaction of weak bases like amides, esters and carboxylic acids to be endothermic.

Extended Hückel MO calculations usually result in large charge separations in molecules (seen most easily from the very high calculated dipole moments). Hoffmann [4] observed that the charge given to hydrogen atoms depends only on the charge of the adjacent atom. The present study confirmed this observation and showed that on protonation almost all the total positive charge being introduced was located on the hetero-atom accepting the proton and on the incoming proton itself. The charge densities of formamide and its two conjugate acids are given in Fig. 3, both before and after charge iteration [20]. After iteration the charges decrease and both the protonated species acquire a positive charge on

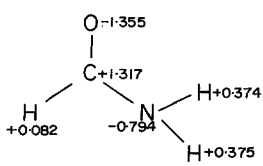
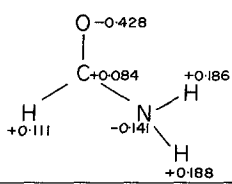
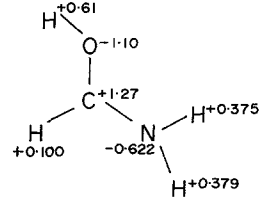
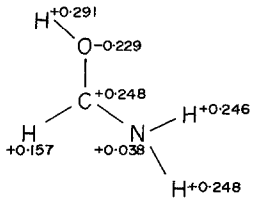
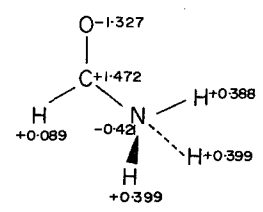
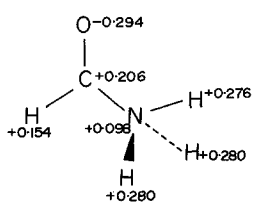
CHARGE DENSITIES FROM INITIAL CALCULATION	CHARGE DENSITIES AFTER ITERATION
	
	
	

Fig. 3. Atomic charges on formamide and its two conjugate acids before and after charge iteration

nitrogen. Also the positive charge on the carbon atom is decreased, but after iteration the conjugate acids have larger positive charges than the neutral molecule and hence would be more prone to nucleophilic attack by water, as observed experimentally (*A2* hydrolysis).

2. Hydrolytic Study

In the second step of the hydrolysis pathway the conjugate acid either decomposes spontaneously (*A1*) or is attacked by water (*A2*) (see Fig. 1). Only the $A_{A1}2$ mechanism has not yet been observed experimentally; this was not examined in the present investigation.

The $A_{Ac}1$ and $A_{A1}1$ Mechanisms

a) *Methyl Acetate*. Calculations on both the *A1* mechanisms for the hydrolysis of methyl acetate gave incorrect energy profiles (see Fig. 4). The CH_3CO^+ and CH_3^+ ions which are believed to be transient intermediates reacting rapidly with solvent, were predicted to be the most stable.

b) *Formamide*. The energy profile for formamide (Fig. 5) is similar to that for the $A_{Ac}1$ mechanism for methyl acetate, although if the products are considered to be carbon monoxide, water and ammonium ion, then the overall reaction is endothermic. Again the formyl ion intermediate is predicted to be very stable. Recent experimental work on the proton affinity of carbon monoxide has resulted

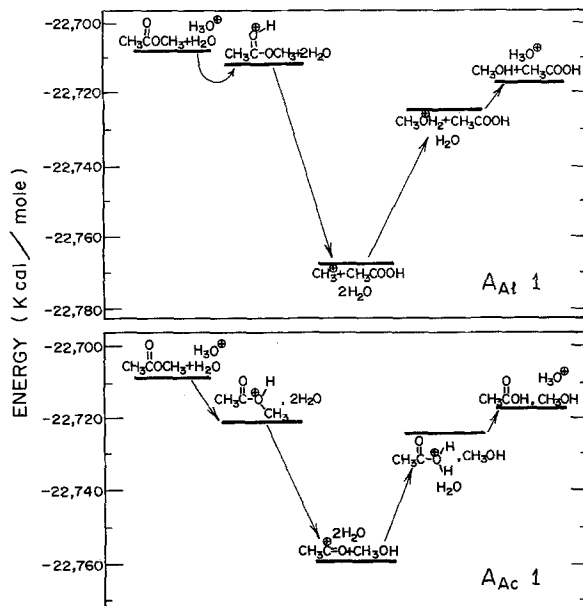


Fig. 4. The A1 hydrolysis pathways for methyl acetate

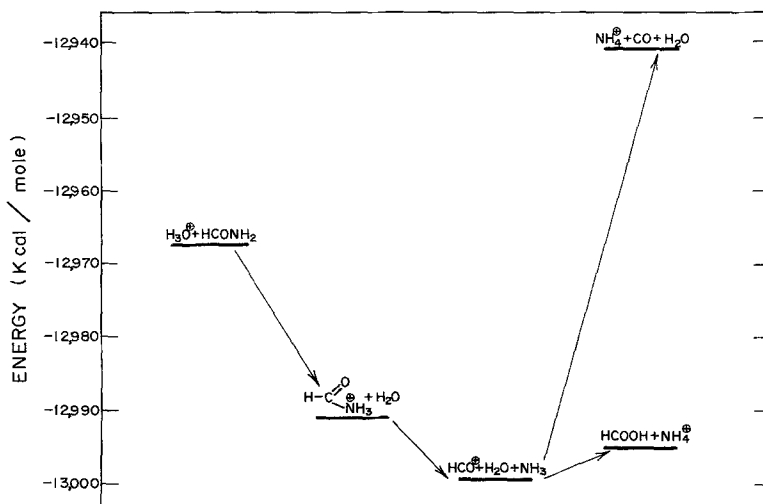
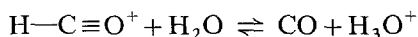


Fig. 5. The A1 hydrolysis pathway for formamide

in a value of 131 kcal/mole for this gas phase reaction [21]. In solution the proton would be transferred to a base, but even the reaction



is calculated to have $\Delta E = 110$ kcal/mole compared with an experimental value of $\Delta H = 20$ kcal/mole. In the mass spectra of amides, esters and carboxylic acids $\text{R}-\text{C}\equiv\text{O}^+$ is the principal ion. Hence the calculations, which are strictly for a gas phase reaction, may not be in error and the explanation may be that the energy profile is reversed by solvation.

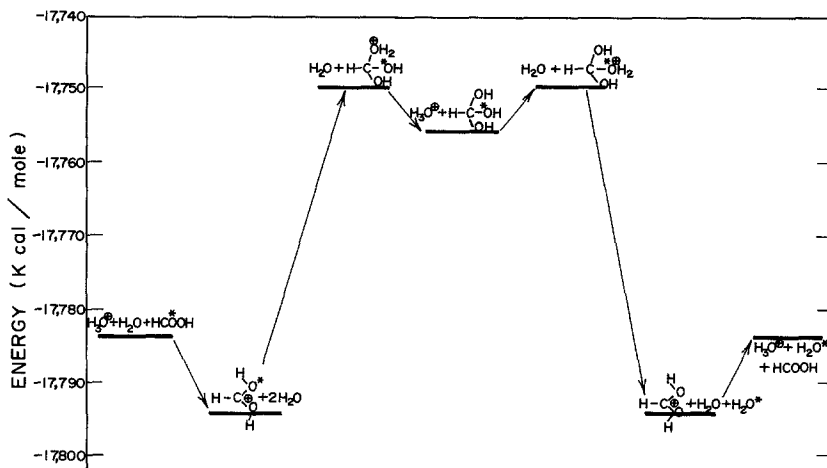
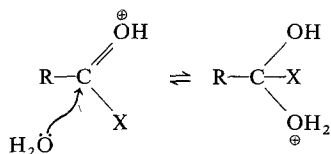


Fig. 6. The A_2 hydrolysis pathway for formic acid

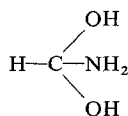
c) *Formic Acid*. The $A_{Ac}1$ "hydrolysis" of formic acid was studied extensively. The cleavage of the $C-\overset{+}{O}H_2$ bond of $-OH$ protonated formic acid was found to occur without any activation energy. The same behaviour was found with both A_1 hydrolysis mechanisms for esters and we conclude that the EHMO method does not predict the existence of a transition state. This is not necessarily an error caused by the approximations in the EHMO method since recently *ab initio* calculations have failed to predict the existence of energy barriers in the reaction of ammonia with hydrogen chloride [22] and the transfer of a proton from hydrogen fluoride to a hydride ion [23].

The $A_{Ac}2$ Mechanism

In this, the most common hydrolysis mechanism, the planar carbonyl protonated acids, amides and esters are converted to tetrahedral intermediates in the rate determining step.



The reaction profiles for formic acid, formamide and methyl acetate (Figs. 6, 7 and 8) agree with experimental observation, excepting the initial and final protonation steps. The reactants are more stable than the intermediates but less than the products. The energy decrease on protonation is observed experimentally for gas phase reactions and can be easily reversed by solvation (see Section 3). The formamide calculations give a large energy difference between the $-OH$ and $-NH_2$ protonated intermediates (43.5 kcal/mole) predicting that



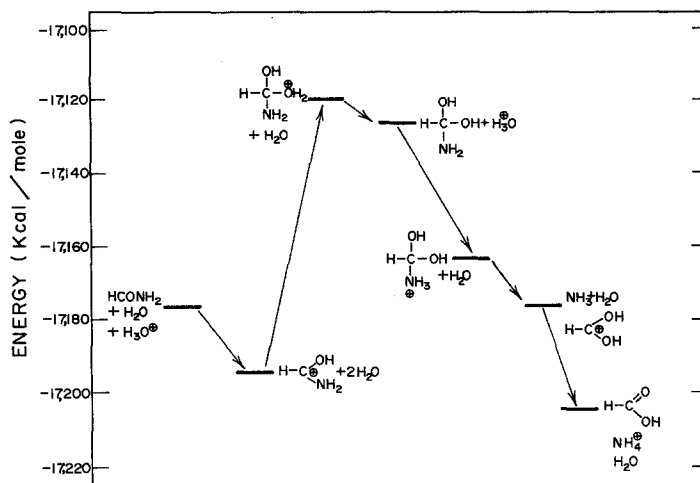


Fig. 7. The A2 hydrolysis pathway for formamide

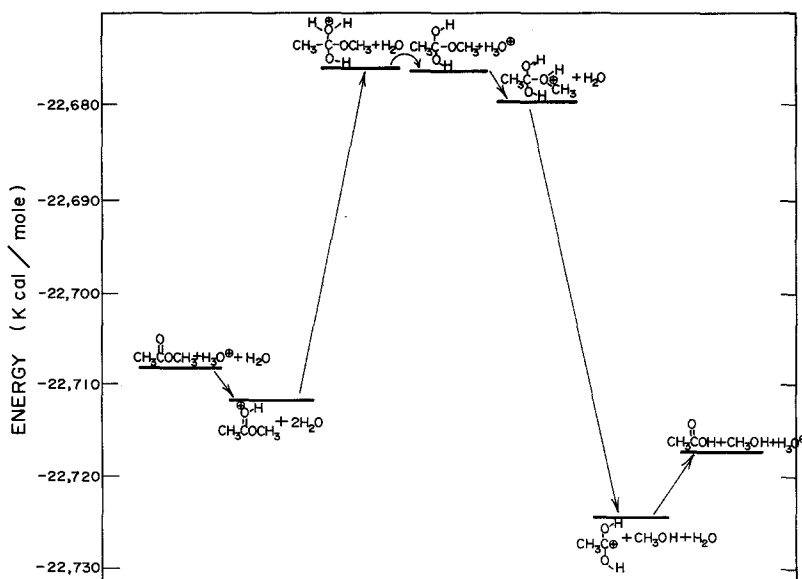
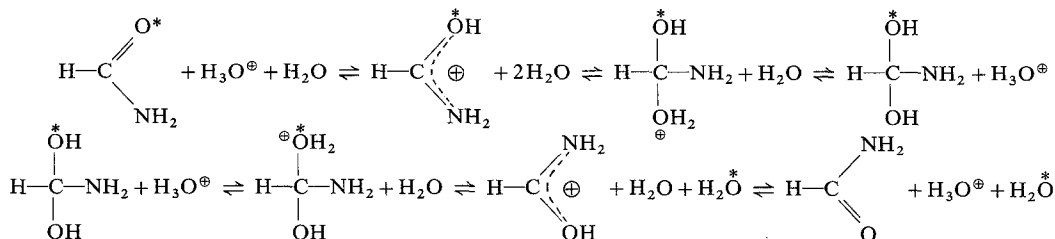


Fig. 8. The A2 hydrolysis pathway for methyl acetate

will preferentially protonate on nitrogen and hydrolyse. Protonation of OH would result in O¹⁸ exchange, which is not observed experimentally [24].



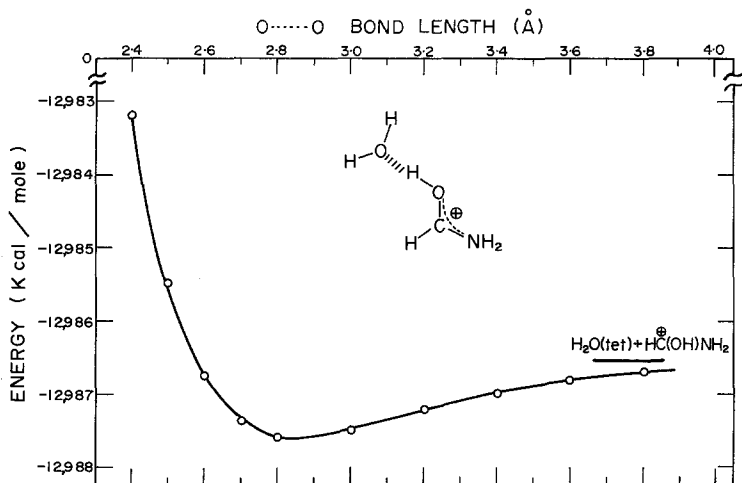
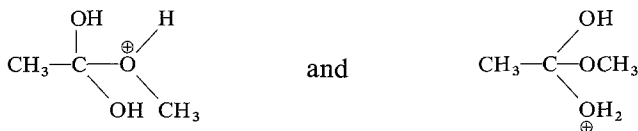


Fig. 9. Variation of energy with O ... O distance for oxygen protonated formamide

The difference between the energies of the corresponding ester intermediates



is similar (3.6 kcal/mole) explaining the experimentally observed O^{18} exchange [25].

3. Solvation Study

Throughout this work we have stressed the importance of solvation in determining the stability of all species. This is particularly important when a molecule has a positive charge and is capable of hydrogen bonding with the solvent. Attempts to calculate the heat of solvation of the O- and N-protonated forms of formamide resulted in the curves shown in Figs. 9 and 10. Initially only one water molecule was introduced, each time on a hydrogen atom at the site of protonation. The O-protonated amide gave a minimum at 2.8 Å with a stabilisation of 1.03 kcal/mole, whilst the N-protonated species showed no stabilisation by solvation. This stabilisation by solvation of the isomer calculated to be the less stable was insufficient to revert the energies of the two conjugate acids to the experimentally observed order. Also calculations on H_9O_4^+ , varying all the O...O distances simultaneously, provided further evidence that the EHMO method fails to attribute sufficient stabilisation to solvation. The experimental value [26] for the hydration of the hydronium ion (H_3O^+) is 100 kcal/mole; the EHMO calculations gave 2.64 kcal/mole.

The EHMO calculations predicted the initial and final steps i.e. the protonation reactions in the hydrolysis pathways to be exothermic in agreement with

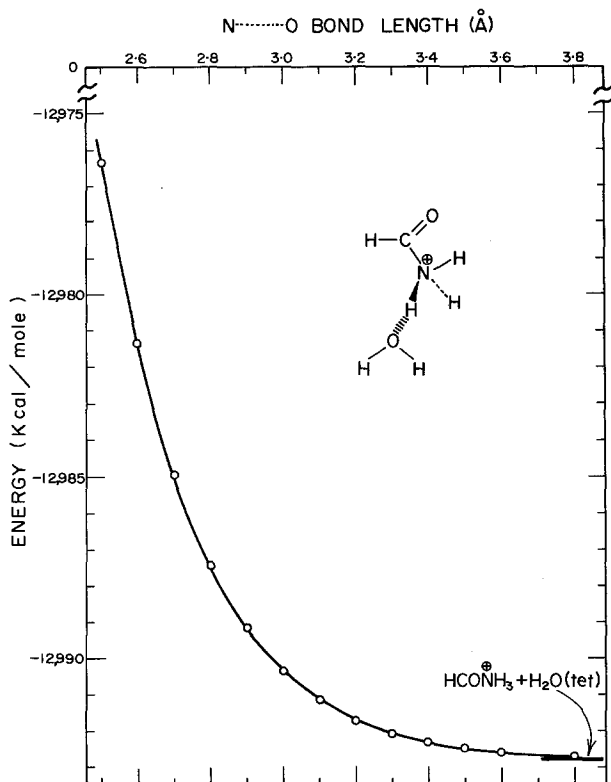


Fig. 10. Variation of energy with N ... O distance for nitrogen protonated formamide

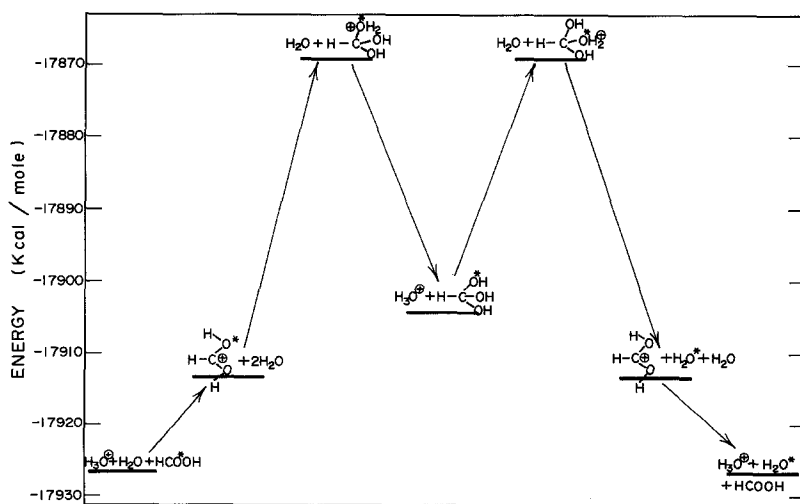


Fig. 11. The A2 "hydrolysis" profile for formic acid after addition of empirical solvation energies

experimental observation in the gas phase but contrary to observation in solution. This disagreement in experimental results is caused by the large solvation energy of the hydronium ion compared with that of other species. An empirical calculation, adding 33 kcal/mole for every hydrogen bond to the energy predicted by the EHMO method for the charged species and 5 kcal/mole per hydrogen bond for all neutral species was found to make the initial and final protonation steps *endothermic* (Fig. 11).

Conclusions

Attempts to correlate energy differences from EHMO calculations on the bases and conjugate acids (theoretical proton affinities) with experimental proton affinities gave agreement within a factor of two but the results are not as good as those provided by *ab initio* calculations. This rough agreement between experimental and theoretical proton affinities suggests that the failure to obtain a correlation between experimental pK_{BH^+} values and theoretical proton affinities is due to neglect of solvation and not the EHMO method of calculation. However attempts to calculate energies of solvation by the EHMO method failed badly.

The almost consistent prediction of the wrong site of protonation of acids, amides and esters is more difficult to rationalise. Perhaps gas phase protonations occur at a different site from in solution and the effect may again be explicable in terms of solvation. We are currently attempting to resolve this problem by doing *ab initio* calculations with large basis sets using Gaussian type functions as atomic orbitals (AO) in the LCAO-MO-SCF framework.

If one accepts that the endothermic nature of the initial and final protonation steps are due to neglect of the large solvation energy of the hydronium ion, then

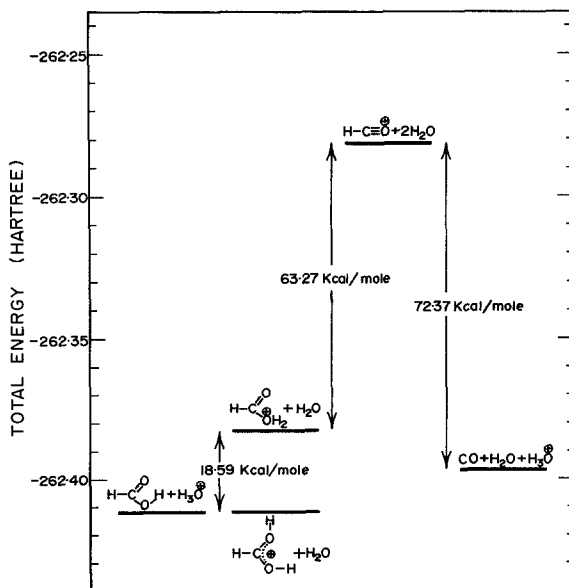


Fig. 12. SCF calculations on the *A1* "hydrolysis" pathway for formic acid

the EHMO calculations give an adequate description of the $A_{Ac}2$ reaction sequences. However on all the $A1$ profiles the transient intermediates (CH_3^+ , CH_3CO^+ , $H-C\equiv O^+$) are predicted to be the most stable. These species do not have strongly acidic protons like the other charged species on the reaction profiles and cannot be heavily solvated and hence stabilised by hydrogen bonding with the solvent. However a study of the $A_{Ac}1$ decomposition of formic acid, using *ab initio* calculations gave results which were in agreement with experiment (Fig. 12).

The complications caused by solvation make it difficult to judge the versatility of the EHMO method when applied to the mechanisms of reactions in solution. The proton affinities (gas phase protonations) are the only reactions in the present study which are not complicated by solvation energies (Table). The EHMO calculations gave energies which have the correct sign but are too small by a factor of two. This may result from using incorrect energies for the coulomb integrals. The H_{ii} values, usually taken to be the atomic ionisation potentials of the neutral atoms, should be larger for a positively charged species. This would result in a larger stabilization energy for the ion and hence a larger proton affinity. However it is difficult to decide exactly what increase in H_{ii} values is required to put neutral molecules and ions on the same energy scale and the EHMO method should therefore be used very cautiously in comparing species with different charges.

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