

The Addition of Carbanions to the Carbonyl Group in the Gas Phase

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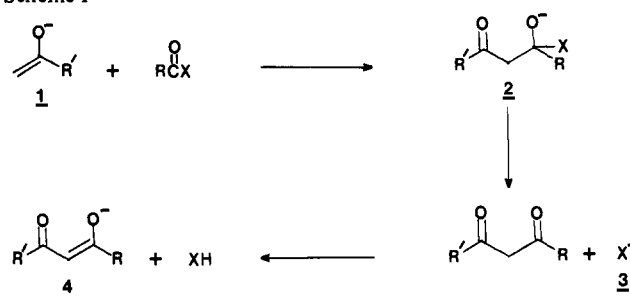
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Abstract: The reaction of a variety of carbanions with esters in the gas phase proceeds by an addition-elimination-deprotonation mechanism, similar to that for the Claisen condensation in solution. The observed ion-molecule reactivities are analyzed in terms of a triple-minimum reaction coordinate. The thermochemistry of the various barriers along this coordinate explains the occurrence or absence of the condensation product. The effect of solvation on the reaction coordinate and the nature of the reactants is discussed.

The formation of a carbon-carbon bond by the attachment of a carbanion to a carbonyl group is of considerable importance as a synthetic method.¹ The mechanisms of such reactions—the Claisen, aldol, Dieckmann condensations, etc.—have been extensively investigated,² though there are still points of dispute regarding them. Since most carbon acids such as ketones and esters are less acidic than protic solvents, it has often been the practice to run these reactions under conditions of reversible, partial formation of the enolate. Under such conditions in protic solvents, the nature of the counterion should not be critical. If the enolate is formed irreversibly in dipolar aprotic solvents,³ however, the counterion and the nature of the solvation should be of considerable importance.⁴ It has been claimed⁵ and disputed⁶ that such factors are important in determining yield and stereochemistry in these reactions. In order to determine what part solvation and metal chelation play in the outcome of carbanion reactions, we have examined these ionic processes in the gas phase by using ion cyclotron resonance spectrometry.

Previous studies of reactions of anions with a carbonyl group in the gas phase have mostly dealt with noncarbon nucleophiles such as alkoxides or halides.^{7,8} In contrast to solution-phase results, addition-elimination mechanisms are not usually seen in the gas phase if some other reaction can occur such as β -elimination,⁹ displacement on the alcoholic α -carbon of esters,¹⁰ or removal of a formyl proton with decarbonylation.⁹ For those instances where none of the above reactions are feasible such as

Scheme I



with acyl halides, then an exchange of halide with the anionic nucleophile is seen, with a tetrahedral oxyanion structure suggested as a local *maximum* along the potential surface.⁷ Carbanions have been observed to react with nitrous esters¹¹ in a mechanism similar to that proposed here for carboxylic esters: addition, elimination, and then proton transfer. No regular study of substituent effects on the mechanism and thermochemistry of carbanion attack on a carbonyl group has been done for any of these systems, however.

Experimental Section

Instrumentation. A home-built trapped-mode ion cyclotron resonance (ICR) spectrometer was used for all the work reported here. It is similar to that reported in the literature,¹² save that it is equipped with a capacitance bridge detector¹³ currently utilizing field sweep mode for mass scans. An MKS Baratron Type 146 capacitance manometer was used in the 10^{-6} – 10^{-3} torr range to calibrate the Granville-Phillips Type 270 ionization gauge controller with a Huntington Mechanical Labs Bayard-Alpert gauge. Mass scans were normally done at 153.56 kHz, except when masses beyond the 14-kG range of the magnet required a lower (typically 100- or 75-kHz) frequency. Rate constants were obtained at as high a magnetic field as practical to minimize collisional ion loss from the cell. We obtain a rate constant for the reaction $\text{CH}_4^+ + \text{CH}_4 \rightarrow \text{CH}_5^+ + \text{CH}_3$ of $(1.06 \pm 0.11) \times 10^{-9} \text{ cm}^3 \text{ molecule}^{-1} \text{ s}^{-1}$, in good agreement with the average literature value¹⁴ of $(1.11 \pm 0.04) \times 10^{-9} \text{ cm}^3 \text{ molecule}^{-1} \text{ s}^{-1}$.

Materials. Most of the chemicals used in this work were obtained commercially and purified by distillation or preparative GC before use. Neopentyl acetate and trifluoroethyl acetate were prepared by stirring the appropriate alcohol with 1.1 equiv of acetyl chloride for 30 min, followed by basic workup and distillation. The thioformate esters were prepared by stirring the thiol with 2 equiv of acetic formic anhydride plus 0.01 equiv of pyridine for 24 h, followed by basic workup and distilla-

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Table I. Reactivities in Claisen-Type Condensations of Esters and Carbanions

carbanion	ester	result ^a	$\Delta H^\circ(1)^b$	$\Delta H^\circ(2)^c$	$\Delta H^\circ(3)^d$
PhCH ₂ ⁻	HCO ₂ CH=CH ₂	C ^h	-15	1	-13
CH ₂ CN ⁻	HCO ₂ CH=CH ₂	C	-14	3	g
CH ₃ SOCH ₂ ⁻	HCO ₂ CH=CH ₂	C	-15	f	g
MeOCOCH ₂ ⁻	HCO ₂ CH=CH ₂	C	-9	0	-22
<i>t</i> -BuCH ₂ OCOCH ₂ ⁻	HCO ₂ CH=CH ₂	C	-9	0	-22
CF ₃ CH ₂ OCOCH ₂ ⁻	HCO ₂ CH=CH ₂	C	-9	0	-22
CH ₃ COCH ₂ ⁻	HCO ₂ CH=CH ₂	C	-6	0	-23
CH ₂ =CHO ⁻	HCO ₂ CH=CH ₂	C ⁱ	-5	2	-26
PhCOCH ₂ ⁻	HCO ₂ CH=CH ₂	tr	-1	1	-29
CH ₂ NO ₂ ⁻	HCO ₂ CH=CH ₂	tr	-1	4	g
CF ₃ COCH ₂ ⁻	HCO ₂ CH=CH ₂	N	6	7	-39
(CH ₃ CO) ₂ CH ⁻	HCO ₂ CH=CH ₂	N	15	4	g
Me ₂ C=CHO ⁻	HCO ₂ CH=CH ₂	CH ₂ =CHO ⁻	-4	2	...
MeOCOCH ₂ ⁻	CH ₃ CO ₂ CH ₂ CF ₃	C	-6	5	-18
CF ₃ CH ₂ OCOCH ₂ ⁻	CH ₃ CO ₂ CH ₂ CF ₃	C	-4	5	-20
CH ₃ COCH ₂ ⁻	CH ₃ CO ₂ CH ₂ CF ₃	C	-3	5	-18
CH ₂ =CHO ⁻	CH ₃ CO ₂ CH ₂ CF ₃	C ^j	-1	5	-20
MeCH=CHO ⁻	CH ₃ CO ₂ CH ₂ CF ₃	C ^k	-5	2	-27
MeOCOCH ₂ ⁻	HCOSMe	C	f		
CH ₂ =CHO ⁻	HCOSMe	C	f		
CH ₂ =CHO ⁻	HCOSPh	PhS ⁻	f		
MeOCOCH ₂ ⁻	CH ₃ CO ₂ Me	N	-4	22	-35
<i>t</i> -BuCH ₂ OCOCH ₂ ⁻	CH ₃ CO ₂ CH ₂ <i>t</i> -Bu	N	-4	18	-26
PhCH ₂ ⁻	HCO ₂ Me	tr	-9	21	-28
CH ₃ SOCH ₂ ⁻	HCO ₂ Me	tr	-9	f	g
CH ₂ CN ⁻	HCO ₂ Me	tr	-8	23	g
CH ₃ COCH ₂ ⁻	HCO ₂ Me	N	3	18	-39
CH ₂ =CHO ⁻	HCO ₂ Me	N	4	20	-39
CH ₂ =CFO ⁻	CH ₃ COF	C ^e	-1	15	-31

^a Abbreviations: C = Claisen product 4 observed as in Scheme I; tr = Claisen product 4 observed only under unquenched conditions; N = no 4 observed under any conditions. ^b Enthalpy for addition step of Scheme I (kcal/mol). ^c Enthalpy for elimination step of Scheme I (kcal/mol). ^d Enthalpy for proton transfer step of Scheme I (kcal/mol). ^e From ref 7b. ^f Insufficient thermochemical data exist for any estimates. ^g Insufficient thermochemical data exist but are undoubtedly more negative than -20 kcal/mol. ^h $k = (2.0 \pm 0.2) \times 10^{-10} \text{ cm}^3 \text{ molecule}^{-1} \text{ s}^{-1}$, efficiency²¹ = 0.14. ⁱ $k = (1.3 \pm 0.2) \times 10^{-10} \text{ cm}^3 \text{ molecule}^{-1} \text{ s}^{-1}$, efficiency²¹ = 0.07. ^j $k = (1.25 \pm 0.2) \times 10^{-10} \text{ cm}^3 \text{ molecule}^{-1} \text{ s}^{-1}$, efficiency²¹ = 0.07. ^k $k = (1.0 \pm 0.1) \times 10^{-10} \text{ cm}^3 \text{ molecule}^{-1} \text{ s}^{-1}$, efficiency²¹ = 0.06.

tion.¹⁵ The mixed anhydride¹⁶ was prepared by stirring equimolar amounts of acetic anhydride and 97% formic acid for 1 h at room temperature and then for 1 h at 45 °C. It was used without further purification. Dihydropyran was refluxed in 10% HCl (0.1 equiv) for 1 h, followed by neutralization and extraction to give 2-hydroxytetrahydropyran, bp 87–91 °C (21 mm). NMR and GC analyses indicate less than 2% of the open-chain isomer 5-hydroxypentanal is present.

The primary ions for all work were CH₃O⁻ or (CH₃)₃CCH₂O⁻. These were formed from methyl nitrite¹⁷ and neopentyl nitrite, respectively, at 0.0–1.0-V electron energy (filament minus trapping voltages). The neopentyl nitrite was obtained by the general method for butyl nitrite¹⁸ using neopentyl alcohol instead. The product exhibits the following: NMR (CCl₄) δ 0.97 (s, 9 H), 4.38 (s, 2 H); bp 28–32 °C (100 mm). All compounds were degassed by several freeze–pump–thaw cycles on the ICR foreline before introduction into the main vacuum system.

Results

The carbanions shown in Table I were generated by deprotonation of their conjugate acids with methoxide or neopentoxide. When in the presence of $(1\text{--}3) \times 10^{-6}$ torr of the esters shown, the production of an ion corresponding in mass to 4 in Scheme I was taken as preliminary evidence that the successive addition, elimination, and proton-transfer reactions shown had occurred. In all cases, the reaction of 1 to give 4 was confirmed by double resonance.

In none of the cases tried was an ion corresponding to the addition product 2 seen. Since such addition ions are formed with excess energy, they either revert to reactants or fragment to some different set of products and thus are not usually observed at the low pressures utilized in trapped ICR.¹⁹ Ions corresponding to

3 were likewise not seen, except in the few cases noted in Table I. Because ICR does not yield any structural information concerning the ions other than their mass/charge ratio, we cannot state that 4 has the structure shown and that a Claisen-type condensation has occurred. Nevertheless, ions of the proper mass are seen for a wide variety of neutral and ionic reactants. This combined with other gas-phase studies of nucleophilic reactions⁷ and the solution-phase analogues² lead us to believe that 4 is the structure shown, though not necessarily of that stereochemistry.

Table I shows that carbanions less basic than the enolate of acetophenone are unreactive toward the esters used. Esters with simple aliphatic alcohol groups are unreactive with the enolates, though the highly basic carbanions formed from toluene, acetonitrile, and dimethyl sulfoxide do give small amounts of Claisen product with methyl formate. These last reactions are only observed in the unquenched mode²⁰ so that the reaction efficiency is less than 0.005 of collision rate.²¹ If no α -hydrogens are present in the β -dicarbonyl compound formed in the elimination step, then 4 is not seen, as in the case of Me₂C=CHO⁻ as nucleophile. If the leaving group 3 is not basic enough to deprotonate the β -dicarbonyl compound such as with PhS⁻, then 3 and not 4 is observed. There are other possible sources of 3, however, as discussed below.

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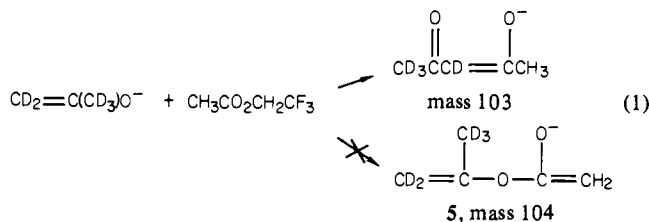
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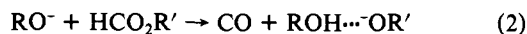
The enolates used as nucleophiles here are ambident ions and thus could also attack the carbonyl group at their oxygen terminus. If this is followed by departure of the leaving group and then proton transfer from the acetate ester to the leaving anion, then structures such as **5** could be formed, with mass the same as that for Claisen product **4**. Transesterification reactions such as this are seen in certain cases. Methoxide reacts with neopentyl acetate to give both the $M-1$ anion of that ester ($k = 2.8 \times 10^{-10} \text{ cm}^3 \text{ molecule}^{-1} \text{ s}^{-1}$ or 0.12 efficient) as well as 73^- , corresponding to the $M-1$ of the transesterification product, methyl acetate ($k = 1.6 \times 10^{-10} \text{ cm}^3 \text{ molecule}^{-1} \text{ s}^{-1}$ or 0.07 efficient). Similarly, methoxide reacting with trifluoroethyl acetate gives both 141^- and 73^- . In the neopentyl case, the leaving alkoxide is capable of deprotonating methyl acetate even at thermal energies. Trifluoroethoxide should not be basic enough to remove the α -proton of methyl acetate when thermal; the transesterification reaction that produces it, however, is 19-kcal/mol exothermic. This excess energy deposited in the products is sufficient to drive the 7-kcal/mol endothermic proton transfer and cause the proton transfer to occur before the cluster complex breaks up.

For enolate nucleophiles reacting at oxygen with formate esters, the product vinyl formate should not be acidic enough to give up a proton to the leaving group.²³ Acetate esters do have an acidic site; however, reaction 1 gives mass 103⁻ but no 104⁻, ruling out



oxygen attack. Removal of a deuteron from the propenyl site rather than the α -CH₃ site in **5** is considerably endothermic even for methoxide.²²

Formate esters were used to avoid problems with two enolates being present. It is known that formate esters can react with anions via decarbonylation to form the cluster ion **6**, as in (2).⁹



No cluster ions corresponding to **6** were seen for vinyl formate or the thioformates, though it was observed for methoxide plus methyl formate. It is possible that such reactions do occur, but the cluster ion breaks up into ROH and R'O⁻ due to excess energy.²⁴ The net reaction cannot be differentiated from simple transesterification on the basis of the ion signals alone. Reactions of this type that were observed include methoxide on vinyl formate to give CH₂=CHO⁻ and the enolate on HCOSPh to give PhS⁻. It is also possible that isobutyraldehyde enolate on vinyl formate reacts either by reaction 2 and subsequent cluster ion breakup to give CH₂=CHO⁻ or by transesterification to give HCO₂CH=CMe₂ plus enolate; however, other enolates of comparable basicity give no CH₂=CHO⁻ with vinyl formate. In this case, we suspect carbon addition has occurred as with the other enolates but no subsequent proton transfer, due to the lack of acidic protons. The cluster ion of **3** bound to the β -dicarbonyl compound simply breaks up with CH₂=CHO⁻ as the leaving group.

Discussion

The reaction pathway as envisioned in Scheme I involves nucleophilic displacement at carbonyl, followed by a proton transfer. Both of these reactions have been shown to proceed along double-minimum potential surfaces in the gas phase, with appreciable intermediate barriers that slow the reaction rates to some small fraction of the collision rate.^{7,25} We thus envision the Claisen

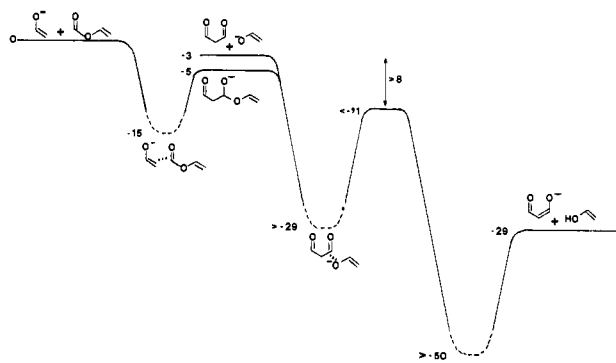


Figure 1. Reaction coordinate for vinyl formate plus acetaldehyde enolate. All energies are in kcal/mol.

condensation proceeding on the surface shown in Figure 1.

The relative energies, or more conveniently, the enthalpies, of the reactants and final products may be obtained from known heats of formation,²⁶ from estimates from group additivity,²⁷ and from negative ion thermochemistry furnished by gas-phase acidities.²² For anions whose basicity has not been experimentally determined such as **4**, we have made reasonable assumptions based on known substituent effects; e.g., since CH₃CHO is 2.4 kcal/mol more acidic in terms of ΔH_f° than (CH₃)₂CO, then malonaldehyde is probably ca. 3–4 kcal/mol more acidic than acetylacetone.²⁸ The enthalpy of tetrahedral structure **2** can be obtained in a similar manner. The ΔH_f° for the corresponding alcohol is estimated from group additivity and then its acidity estimated from the ρ_1 of 17.0 for the alcohols in the gas phase.²² With this estimate of acidity, we can calculate ΔH_f° for the tetrahedral structures **2** from eq 3, and from this, the enthalpies of reaction for the three steps in

$$\Delta H_f^\circ(\text{RO}^-) = \Delta H_{\text{acid}}^\circ(\text{ROH}) - \Delta H_f^\circ(\text{H}^+) + \Delta H_f^\circ(\text{ROH}) \quad (3)$$

Scheme I. These are presented in Table I. Considering the method of estimation of acidity for both the tetrahedral structure and the β -carbonyl compounds, the estimates for each reaction as written probably have uncertainties of up to ± 4 kcal/mol.

This method of determining the relative enthalpy of the addition step is different from that of Asubiojo and Brauman,^{7b} who found the difference in energy between the tetrahedral ion and the reactants for halide exchange in acyl halides by varying that energy in RRKM calculations until the experimental reaction efficiency was reproduced. That approach puts the tetrahedral structure 6–8 kcal/mol below the reactants, comparable to the addition step here. The lack of acidity data for the relatively unstable²⁹ α -haloalcohols mandated their calculational approach. The large polarizability contribution by the α -chlorines to stabilization of the anion obviates the $\sigma_{1\rho_1}$ approach to the acidity and may explain the large apparent electron affinity of the α -chloroalkoxy radical.^{7b}

The depths of the three wells on the reaction coordinate are not directly known. An exact knowledge of the well depths is not critical, however, since we only wish to calculate the reaction efficiency, which is the ratio of the rate for the excited cluster ion's decomposition toward products compared to the total flux out of the well. Thus it is the ratio of the number of states over each maximum flanking the well up to the energy level of interest that determine the efficiency;⁷ the density of states for the reactant cluster ion cancels out of the normal RRKM expression, and knowledge of the exact well depth is not necessary. It would be of interest to know approximate well depths, however, to better visualize the reaction coordinate. Binding energies for proton-

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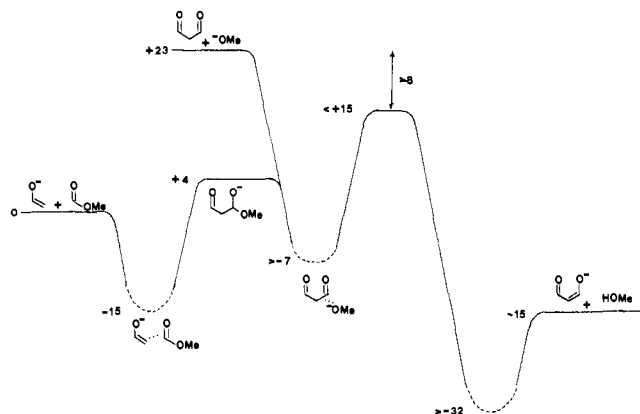
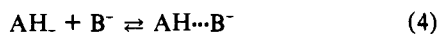


Figure 2. Reaction coordinate for methyl formate plus acetaldehyde enolate. All energies are in kcal/mol.

bound cluster ions are known and have been quantitated with eq 5.³⁰ This equation with a few exceptions holds to ± 2 kcal/mol



$$\Delta H^\circ(4) = 0.2 \Delta H^\circ_{\text{acid}(\text{acceptor})} - 0.134 \Delta H^\circ_{\text{acid}(\text{donor})} \quad (5)$$

for a variety of structures, not all of which involve heteroatom donors or acceptors such as HCCl_3 , CH_3CN , etc. It is a reasonably good method of estimating the depth of wells for the second and third cluster ions which formally involve hydrogen bonding; though due to the delocalized anions here and the uncertainty of eq 5, we take $\Delta H^\circ(4)$ as only an upper limit to the well depth. The first cluster ion does not formally involve hydrogen bonding due to the low acidity of the formate ester.²² On the basis of the data by Brauman and co-workers^{7b,31} concerning the binding strength of Cl^- to CH_3COCl and on the higher nucleophilicity (see Methyl Cation Affinities section) of the enolates used here, a well depth of 15–20 kcal/mol is not unreasonable. In all the above estimates, the enolates were assumed to be oxygen bases in terms of acidity,^{22c} since hydrogen bonding is more likely to occur at that site and not carbon.

The top of the barrier for the final proton transfer is probably at least 7–8 kcal/mol below the level of the β -dicarbonyl compound and ion 3, since that is the difference in barrier heights needed to reproduce by RRK calculations the experimental rate of $2 \times 10^{-12} \text{ cm}^3 \text{ molecule}^{-1} \text{ s}^{-1}$ for thermoneutral proton transfer between a ketone and its enolate.²⁵ The exothermicity of the proton transfer will make the difference between these levels even larger, so that the barrier to proton transfer will usually lie below that for the tetrahedral ion, except as noted below. The difference is thus taken as greater than 8 kcal/mol.

With these data, we may now construct reaction coordinate diagrams for specific cases as given in Figures 1–3. Figure 1 is for a typical successful reaction, that of acetaldehyde enolate on vinyl formate. The enthalpy difference between the tetrahedral addition product and starting materials favors the reaction toward products, tempered by the fact that three degrees of rotational freedom are lost on going to the addition ion. With similar enthalpy, the reaction efficiency through this well should be somewhat slower than that seen for the halide exchange at carbonyl.^{7b} The reduced rate is attributable to the polyatomic nature of the nucleophile here and resulting change in degrees of freedom.^{7b} The second well, involving breaking of the leaving group bond and proton transfer, is also highly favored by exothermicity. Since there is no loss of external rotation on going from the first to second maxima and since the proton-transfer maximum is considerably looser than the tetrahedral intermediate, the reaction

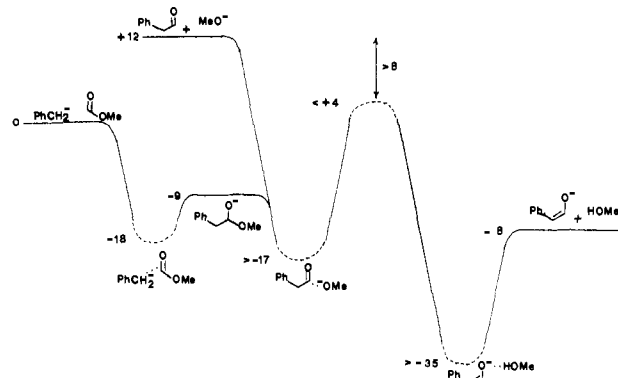


Figure 3. Reaction coordinate for methyl formate plus benzyl anion. All energies are in kcal/mol.

efficiency through the second well should be even higher than that for the first. In addition, it should be larger than that for the directly measured proton-transfer rate, since in the present case, two reactants are not being combined with resulting loss of degrees of freedom. Finally, both exothermicity and separation of products with resulting gain of rotational degrees of freedom will give the final well a very high efficiency. The separation of products can overcome a considerable enthalpy barrier: for isotope exchange in Cl^- plus CH_3COCl , due to the symmetry of the reaction coordinate,⁷ the observed efficiency must equal the product of the efficiencies for crossing each well. If the efficiency for producing the tetrahedral ion in the symmetric isotope exchange reaction $\text{Cl}^- + \text{CH}_3\text{COCl}$ is x , then the efficiency for the ion's separation to products is $1 - x$. For the observed^{7b} efficiency of 0.05, the efficiency across the second well must be 0.947, in spite of a 7-kcal/mol energy difference disfavoring products. In the present case where the energy difference is favorable for the final well, the efficiency must be virtually unity. With these aspects in mind, Figure 1 indicates that the first well is the main determinant of the overall rate.

The reactions of the more nucleophilic carbanions with trifluoroethyl acetate follow a very similar surface, save for the fact the excited tetrahedral ion enters the proton-transfer part of the coordinate *below* the energy of the free leaving group anion plus the β -dicarbonyl compound rather than above it as for vinyl formate in Figure 1. This should favor products even more than in the vinyl formate case, due to the relative number of states involved. Let us postulate a cluster ion with two possible decomposition reactions over barriers of unequal energy and also assume that the density of states above each barrier is similar. Then at energies for the cluster ion just above the higher barrier, there is a considerable difference in the number of states above each barrier up to the ion's energy, and the reaction efficiency will greatly favor the exothermic direction. As the ion's energy increases, this difference becomes a small part of the total number of states and the reaction efficiency drops, approaching 0.5. This seemingly paradoxical situation—the higher in energy the reactant is, the slower an exothermic reaction goes—is another example of the reactivity–selectivity principle.³³

Table I indicates that when the first step becomes endothermic due to lowered nucleophilicity of the carbanion, no product is seen. This is consistent with Figure 1; if the tetrahedral ion is raised above reactants in energy, then both entropy and enthalpy will reduce the reaction efficiency across the first well to near zero, regardless of the favorability of the later steps. Figure 2 illustrates another unsuccessful case, an enolate plus methyl formate, where the ester contains a poor leaving group. The reaction is blocked both by an inefficient addition (poor leaving groups often are poor electron-withdrawing groups) as well as a high proton-transfer barrier relative to the entrance into the second well. The trace amount of product seen for the reaction of a more nucleophilic carbanion with methyl formate is explicable in terms of

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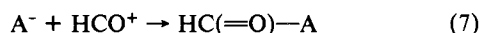
Table II. Methyl Cation Affinities, Formylium Affinities, and Proton Affinities for Selected Anions^a

anion	affinities		
	H ⁺ ^b	CH ₃ ⁺ ^{c,d}	HCO ⁺ ^{d,e}
HO ⁻	390.7	276	251
PhCH ₂ ⁻	379.4	279	232
CH ₃ O ⁻	379.2	270	244
CH ₃ CH ₂ O ⁻	376.1	266	241
CH ₃ SOCH ₂ ⁻	372.1	274	
CH ₂ CN ⁻	372.1	274	224
F ⁻	371.5	257	
MeOCOCH ₂ ⁻	371.0	270	226
MeCOCH ₂ ⁻	368.8	269	223
HCOCH ₂ ⁻	366.4	266	220
CF ₃ CH ₂ O ⁻	364.4	249	224
PhCOCH ₂ ⁻	363.2	263	218
CH ₂ CHO ^{-f}	359.8	247	217
FCOCH ₂ ⁻	359.4	267	212
CH ₃ S ⁻	359.0	257	
CH ₂ NO ₂ ⁻	358.7	260	215
HS ⁻	353.5	249	
CF ₃ COCH ₂ ⁻	350.3	247	195
CH ₃ CO ₂ ⁻	348.5	238	198
PhS ⁻	338.9	237	
Cl ⁻	333.4	226	212

^a kcal/mol. ^b $\Delta H^\circ_{\text{acid}}$.²² ^c $-\Delta H^\circ$, eq 9. ^d Data from ref 22, 26, and 27. ^e $-\Delta H^\circ$, eq 7. ^f As an oxygen base.

Figure 3. The addition process in this case is quite favorable in enthalpy. The efficiency across the second well should be low, due to a high proton transfer barrier, but within the uncertainty of the calculations, the barrier top is close to the level of the reactants. The estimate of more than 8 kcal/mol down from methoxide plus phenylacetaldehyde is a lower limit in this case, since the reaction of a localized anion with a ketone is faster than that of a delocalized anion.^{25,22a} Thus the reaction is not totally blocked, and a product could form at a relatively slow rate.

Methyl Cation Affinities. The thermochemical calculations necessary to generate reaction coordinates such as are shown in Figures 1–3 are subject to considerable uncertainty for the present cases. They can be much more difficult to generate if the neutral or ionic data needed to estimate ΔH°_f for the various maxima and minima along the coordinate are not available, due to missing groups^{26b,27} or unstable compounds.²⁹ It would be useful to have some simple relationship that would allow evaluation of the ability of anions to displace leaving groups at a carbonyl center. It has already been pointed out that the proton affinity of the anion, $-\Delta H^\circ(6)$, is only an approximate measure of the anion's reactivity



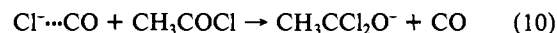
toward a carbon site. A more applicable measure of an anion's nucleophilicity in displacement at a carbonyl site would be $-\Delta H^\circ(7)$, its affinity for HCO⁺. This is in essence the half-reaction for the addition and elimination steps in Scheme I. The values for this process in Table II show that it can vary considerably from the proton affinity. For example, methoxide and benzyl anion have virtually the same proton affinity, but the HCO⁺ affinities favor methoxide attachment by 12 kcal/mol. The observation that benzyl anion displaces methoxide, in opposition to this prediction, can be explained in terms of Figure 3. Since the methoxide plus phenylacetaldehyde state is not on the reaction coordinate, the HCO⁺ affinities are only indirectly pertinent to the observed rates. They are measures of thermal equilibria, not kinetics. What is important to the kinetics is reaction 8, the affinity



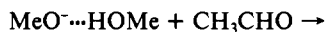
of an anion for some carbonyl group such as H₂C=O to give a tetrahedral product ion. Data for this reaction in general are not easy to obtain, since for oxyanions the product ion is the M - 1

ion of a hemiacetal. These are usually unstable with respect to RO⁻ and the aldehyde.³⁴ A structural analogue to this reaction is the methyl cation affinity, $-\Delta H^\circ(9)$. The anion in both cases reacts with an electrophilic sp² carbon, to give a product with reduced positive charge on a carbon rehybridized to sp³. Such methyl cation affinities are much more accessible, since only one anion is involved and ΔH°_f for the methylated product is readily available.^{26,27} These affinities are presented in Table II. In regards to the anion pair mentioned above, the benzyl anion has a greater affinity for CH₃⁺ than does methoxide by 9 kcal/mol in line with observed reactivities. In every successful Claisen reaction in Table I, the methyl cation affinity of the attacking carbanion is greater than that of the leaving group by at least 4 kcal/mol. There are unsuccessful reactions where this also holds, but in those cases the failure can be ascribed to problems in the proton-transfer step. With such data, plus proton affinities, all observed reactivities in the present work can be rapidly rationalized.

Addition Products. For none of the reactions tried here was any addition product corresponding in mass to **2** or **7–9** observed. In general, the products of exothermic ion-molecule addition reactions are not observed at the low pressure of ca. 10⁻⁶ torr utilized in the ICR.¹⁹ Such addition ions either revert to reactants or, as here, fall apart to some other fragments if exothermic channels are available. Only in rare cases, where no exit mode other than back to reactants is available and the molecular structure is right, are bimolecular addition products stabilized via radiative emission.^{35,38} Addition ions can be stabilized, however, by the present of a single molecule of solvent which can depart with the excess energy.^{7,19,31} This has been used to create an anion-carbonyl adduct as in reaction 10, where the carbon



monoxide can depart with the excess energy.^{7b} We have generated monosolvated enolates via reaction 12, using the Riveros reaction 11.⁹ The enolate generated in this manner is totally unreactive



toward vinyl formate or trifluoroethyl acetate. No aldol product was seen with acetaldehyde, even though this should be 14 kcal/mol exothermic from the bare enolate plus acetaldehyde. The lack of reaction can be ascribed to the type of solvation used. The hydrogen bond strength in the enolate cluster ion is calculated to be 21 kcal/mol from eq 5. This reduces ΔH° for the addition step by that amount, making it endothermic by 16–21 kcal/mol and stopping all reaction. The problem here is that not only does the solvent provide a sink for excess energy but it also reduces the reactivity of the anion. The protic methanol is too good a solvent for the anion. The carbonyl addition is successful for Cl⁻⋯CO and Cl⁻⋯BrCH₃ since here the attached molecule is a dipolar aprotic solvent, and these are known to be poorer solvents for localized anions.⁴ A method of generating more weakly solvated carbanions is needed to allow stabilization of the addition products here.

Tetrahedral Ions vs. Cluster Ions. Further information about the tetrahedral ion **2** and its relationship to the loose cluster in the first or second wells can be obtained by generating it in an alternate fashion. As mentioned above, the anion of a hemiacetal is a reasonable model for the tetrahedral ion but hemiacetals are not normally isolable.³⁴ For 5-hydroxypentanal, however, the cyclic hemiacetal is favored by ca. 1.7 kcal/mol over the open-chain form³⁶ and is readily obtainable.³⁷ The anion may be drawn in several forms as shown in Scheme II.

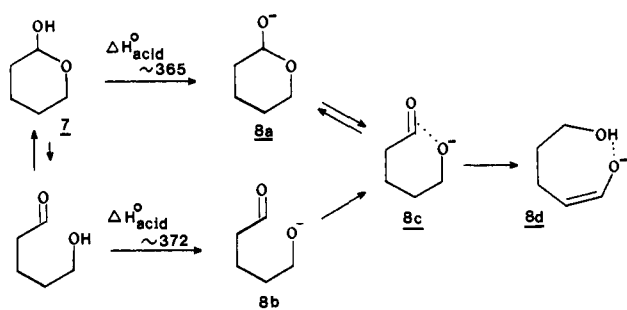
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Scheme II

Table III. Double-Resonance Results for Reaction of 2-Hydroxytetrahydropyran (THP-OH) with Various Bases A^{-a}

AH	$\Delta H^\circ_{\text{acid}}^b$	THP-O ⁻ + AH ^{-c}	A ⁻ + THP-OH ^{-c}
PhCH ₂ OH	369.6	-	+
Me ₂ C=NOH	366.7	-	+
<i>t</i> -BuCH=NOH	364.6	-	+
CF ₃ CH ₂ OH	364.4	-	+
MeSH	359.0	-	-
<i>t</i> -BuSH	354.7	-	-
CH ₃ CO ₂ H	348.5	+	-

^a PhCH₂O⁻ as primary base. ^b Reference 22. ^c Symbols: + = base line (exothermic) double resonance for the reaction as shown; - = endothermic double resonance.⁴³

Based on group additivity²⁷ estimates of ΔH_f° for 5-hydroxypentanal and its hemiacetal **7**, plus reasonable extrapolations for $\Delta H^\circ_{\text{acid}}$ from known acidities of comparable structures,²² we estimate that the open-chain alkoxide **8b** is 15 kcal/mol less stable than the cyclic alkoxide **8a** but that the cluster ion **8c** is of comparable energy to **8a** if we assume a 17-kcal/mol stabilization due to clustering, as estimated earlier from the data of Asubiojo and Brauman.⁷ For entropic reasons cluster ion **8c** should be favored over **8a**, and so the M - 1 produced by deprotonation of the hemiacetal could be **8c**.

The hydrogen bond cluster ion **8d** should be even more stable than **8c** by 16 kcal/mol, as predicted by eq 5. To arrive at the *cis*-enolate required for such a hydrogen bond to form, starting with **8b** or **8c**, however, requires considerable strain as indicated by molecular models. Similarly, to properly line up the hydrogen bond in **8d** while maintaining planarity in the enolate π system involves eclipsing interactions along the methylene chain, which are not taken into account in the ΔH_f° calculation. On this basis alone we cannot rule out **8d** as the structure of the ion. Experimental evidence for **8c** as the preferred form comes from double resonance data for proton transfer between **7** and other acids. If cluster ion **8c** forms the open-chain hydroxypentanal upon reprotonation, it should be less basic than **8b** by the amount of its clustering energy. It should therefore take a considerable stronger conjugate acid to reprotonate **8** than is needed to remove the proton of **7**. Table III shows that when **8** is produced by near-thermoneutral proton transfer to PhCH₂O⁻, formed by thermal electron impact on its nitrite ester, a difference in apparent acidity and basicity of 12 ± 3 kcal/mol is seen. This implies a clustering enthalpy of 20 ± 3 kcal/mol. Since the alkoxide is 38 kcal/mol more nucleophilic toward CH₃⁺ than Cl⁻ is, as shown in Table II, it is not unreasonable that it could be 9 ± 3 kcal/mol more tightly clustered to a carbonyl group.^{7,28} The relative electrophilicities of the carbonyl carbons of RCHO and RCOCl should not be drastically different due to offsetting polar and resonance effects in the acid chloride. If the ion is **8d**, then reprotonation to the open chain form should not occur until the acid has $\Delta H^\circ_{\text{acid}}$ of 339 kcal/mol, or 10 kcal/mol more acidic than observed. The observed onset is thermochemically consistent with reprotonation of **8d** to the cyclic hemiacetal, though this seems a rather extensive reorganization to occur.

In addition, we have observed that alkoxide ions of C₄ or greater will cluster bimolecularly in the ICR to give cluster ions RO⁻·HOR at reasonable rates ($0.7 - 2.0 \times 10^{-10}$ cm³ molecule⁻¹ s⁻¹).

The rate constant is independent of pressure over a 15-fold range; we believe radiative emission is the principal stabilizing mode, with possibly some contribution from collision with neutrals.³⁸ Delocalized oxyanions such as enolates are not observed to undergo such exothermic cluster reactions with alcohols. This argues against the exothermic intramolecular rearrangement of **8c** to **8d**. Similarly, while cyclohexanol readily clusters with its alkoxide, **8** does not react in this manner with **7**, consistent with it being **8c** rather than **8a** or **8b**.

Since 20 kcal/mol appears to be a reasonable well depth for an alkoxide clustered to a carbonyl compound, what effect does this have on the reaction coordinates in Figures 1-3? The depth of the second well, down from the carbonyl compound plus alkoxide leaving group as calculated from eq 5, is considerably deeper than 20 kcal/mol. If the shallower well is adopted, then no qualitative change should occur for the "good" condensations represented by Figure 1; the second well is still below the tetrahedral ion, and the change in depth does not affect reaction efficiency. For the cases represented by Figures 2 and 3 with poor alkoxide leaving groups but relatively stable tetrahedral ions, the cluster ion is now comparable in energy to the tetrahedral ion, as in **7**. It is likely, however, that for the more acidic intermediates PhCH₂CHO and CH₂(CHO)₂, there is an appreciable component of hydrogen bonding in the clustering interaction not present in **8c** and thus a deeper well. This should overall not affect the rationalizations of reactivity.

The Effect of Solvation. The reaction coordinates shown in Figures 1-3 are very different from that envisioned for the solution-phase reaction.² In solution, one expects the tetrahedral ion **2** to be higher in energy than the carbanion and ester reactants, with the loose cluster ions flanking it even higher, as true transition states. In contrast the proton-transfer maximum in the gas phase remains a maximum upon solvation.³⁹ These changes can be rationalized as the effects expected for solvation of the various species by protic solvents. Aqueous ion solvation energies are known to be quite large, the largest being -266 kcal/mol for H⁺; more typically Cl⁻ has ΔH_s° (g → H₂O) = -81.5 kcal/mol.⁴⁰ There is an effect of delocalization of charge on ion solvation also; localized ions are more solvated than delocalized ones, all other things equal.⁴¹ Both the reactant carbanion **1** and the tetrahedral ion **2** should be well solvated by a protic solvent, since the charges are relatively localized.⁴ In itself, this should not shift their energy levels; however, the solvation of the neutral reactant ester, though much smaller than for ions,^{40e} should nevertheless result in a larger reduction in energy due to solvation for the reactants than for the intermediate **2**. The balance should raise the intermediate ion above reactants.

The cluster ions in the first two wells should be much less solvated than **1** or **2** upon going to aqueous solution due to their delocalized nature. A highly delocalized ion such as acetylacetonate can be 30 kcal/mol less solvated than highly localized ions in H₂O.⁴⁰ Assuming a ΔH_s° (g → H₂O) for the cluster ions of -70 kcal/mol as opposed to ca. -110 kcal/mol for enolates and alkoxides would give the solution reaction an E_{act} of 15 kcal/mol

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for $\text{CH}_2=\text{CHO}^-$ plus $\text{HCO}_2\text{CH}=\text{CH}_2$. This is a reasonable size for a bimolecular exchange at a carbonyl group.⁴⁴

For the proton-transfer part of the reaction coordinate, both the maximum and minima are highly delocalized structures. Solvation should not change their relative energies greatly, resulting in the maximum remaining so. It should be noted that the difference in enthalpy between the bottom of the second well and the proton-transfer maximum is comparable in size to E_{act} for such proton transfers in solution.⁴² Such a solvation scheme could make proton transfer rate limiting as is often seen in solution.²

One of the most fundamental kinetic concepts in solution is that of the rate-limiting step. The overall rate of a reaction is controlled only by the free-energy difference between the highest energy transition state and the reactants. The nature of the reaction coordinate at all other points is irrelevant to the rate, though not to the nature of the product. In the gas phase, we have seen that this is not necessarily the case for the same reaction, however. The observed gas-phase rate is a function of the product of the

efficiencies across all the wells. This difference is ascribable to the different nature of the energetics involved. In the gas phase as in Figure 1, the reacting species are chemically activated to an energy greater than any of the "transition states" along the reaction coordinate. For this adiabatic reaction the rate is therefore not limited by any transition state but rather by the quantum properties of their excited states. Figure 2 resembles the solution-phase cases more in that a barrier above the adiabatic level exists. The rate is slowed, exactly as predicted by the usual solution-phase arguments, to less than 0.001 of collision rate, below the time window of the ICR. Thus solution-phase intuition does qualitatively work in ion-molecule reactions; it is only that there is such a narrow range between no barrier, as in Figure 1, and one sufficient to block any observable reaction, as in Figure 2, that it is rare to find cases where we know the energetics precisely enough to ascribe the observed rate to a true potential barrier and not to its manifestation in excited states. Figure 3 may represent such a case, but the estimated energetics are too uncertain to say for sure.

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Acknowledgment. We thank the donors of the Petroleum Research Fund, administered by the American Chemical Society, and the Research Corp., for support of this work.

The Relationship between Substituent-Induced Energy and Charge Effects in Proton-Transfer Equilibria

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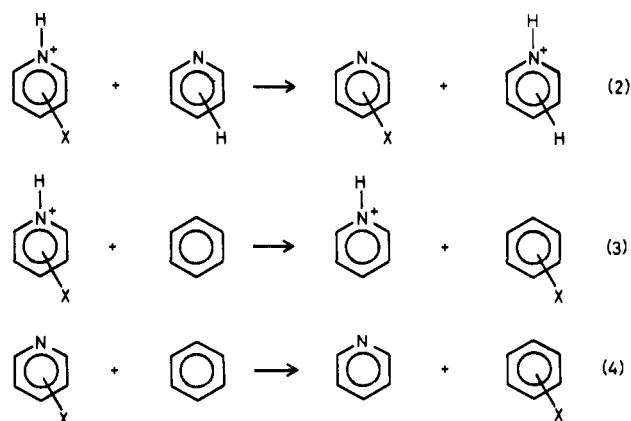
Contribution from the Department of Chemistry, University of California, Irvine, California 92717, and the Department of Organic Chemistry, La Trobe University, Bundoora, Victoria, Australia 3083. Received June 16, 1980

Abstract: The relationship between substituent-induced changes in energy and in charge is investigated for various proton-transfer equilibria by using ab initio molecular orbital theory at the minimal basis STO-3G level. Linear relationships are found between the proton affinities of a variety of nitrogen, oxygen, and carbon bases and the electron populations of hydrogen atoms attached to the acidic center. Similar relationships are usually not followed by the charge on other atoms. These findings are interpreted by reference to calculations on model compounds.

Introduction

(a) **Energy Calculations.** Ab initio molecular orbital calculations at the minimal basis set STO-3G level¹ have proven remarkably successful in the reproducing the experimental gas-phase energies for a variety of isodesmic proton-transfer reactions. For example, it has been shown² that theoretical energies for processes 1, $\text{XCH}_2\text{NH}_3^+ + \text{HCH}_2\text{NH}_2 \rightarrow \text{XCH}_2\text{NH}_2 + \text{HCH}_2\text{NH}_3^+$ (1) describing the effect of a β -substituent, X, on the proton affinity of methylamine, accurately parallel the measured reaction enthalpies for a wide range of substituents. Other examples include proton-transfer equilibria involving substituted quinuclidines,³ phenols,⁴ pyridines,⁵ and anilines.⁵

Theoretical calculations also allow for partitioning of the substituent effect into components arising from each of the protonated and unprotonated forms. Thus, for example, the total effect of a substituent X on the proton affinity of pyridine (eq 2) may be broken down into its effect on the protonated molecule (i.e., eq 3) minus the corresponding effect on neutral pyridine (i.e., eq 4). Analyses of this type,⁶ carried out on substituted pyridines,⁵ anilines,⁵ phenols,⁴ and benzoic acids,⁷ have shown that the effect of substituents on proton affinity arises primarily from interactions in the charged form.



(b) **Charge Calculations.** Ab initio calculations at the STO-3G level have also been used to obtain charge distributions according

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