

The relationship between calculated charge densities and chemical shifts for the α , β , and carbonyl carbons is of some interest. Horsley and Sternlicht² noted that the ^{13}C nmr titration shifts of C_α and C_β for several amino acids were in the direction of decreased shielding on deprotonation, while the ^1H nmr titration shifts of their directly bonded protons were in the direction of increased shielding. Other authors³⁻⁶ have tended to follow them in interpreting these results as evidence that the carbon atoms become slightly more positive in each deprotonation step, due to an electric field induced polarization of the C-H bonds. Our CNDO/2 carbon charge densities (Table III) indicate that although C_β does become more positive in both the amino and carboxyl titrations, C_0 becomes more negative, and C_α becomes more negative overall. The same CNDO/2 calculations indicate that the α and β hydrogens become more negative in each deprotonation step,¹⁹ in agreement with proton nmr results (2). Thus our results suggest that although some bond polarization occurs, the observed deshielding on deprotonation is often the result of a decrease in excitation energy that more than compensates for an increase in electron density. Most of our calculated chemical shifts agree in sign with the observed shifts, lending some support to this model.

It would appear that some caution is needed in using either ^{13}C chemical shifts or the ^1H chemical shifts of directly bonded hydrogens as an indication of changes in carbon charge density close to a site of ionization.

Conclusions

This study has shown clearly the usefulness of computer fitting of individual ^{13}C nmr titration curves in order to obtain accurate ionization constants (pK values) and chemical shift changes from the data. The technique should have great potential in peptide and protein systems, particularly when a carbon atom is influenced by more than one ionization.

The amino acids provide a challenging test for theoretical investigations of the electronic features important in determining ^{13}C chemical shifts. On the basis of CNDO/2 calculations we have rationalized the overall trends in the amino acid titration shifts. For carbons near the titration sites the overall deshielding results from competition between the deshielding effect

(19) Typical changes are -0.10 charge unit for α and -0.07 charge unit for β hydrogens on going from cation to anion.

of a decrease in excitation energy and the shielding effect of an increase in electron density on deprotonation. For more remote carbons the titration shifts follow electron density. The extension of this qualitative model to provide a detailed explanation of all of the observed titration shifts requires an improved molecular orbital method, possibly based on finite perturbation techniques.

Experimental Section and Details of Calculation

Materials. The amino acids and histidine derivatives (Schwarz/Mann and Sigma) were dissolved in H_2O at concentrations near 0.1 g/ml; at pH values where solubility was limited saturated solutions were used. Titrations with HCl and NaOH were performed directly in the nmr sample tubes using a micro combination electrode and digital pH meter.

Nmr. ^{13}C spectra at 25.16 MHz and $31 \pm 2^\circ$ were recorded on a Varian XL-100-15 spectrometer in pulsed Fourier transform/proton noise decoupled mode. Peak positions were measured relative to 5% dioxane dissolved in the external D_2O used for locking;⁶ bulk susceptibility corrections and the effect of changes in salt and solute concentrations during the titrations were determined to be less than the experimental error of ± 0.1 ppm. Chemical shifts in the figures are reported relative to TMS using the relation $\delta_{\text{TMS}} = \delta_{\text{dioxane}} - 67.3$ ppm.

pK Calculations. The amino acid titration curves were computer fitted as a sum of simple proton association equilibria using a model equation of the form

$$\delta_{\text{obsd}} = \delta_{\text{min}} + \sum_{i=1,n} [\Delta_i 10^{(pK_i - \text{pH})}] / [1 + 10^{(pK_i - \text{pH})}]$$

where δ_{obsd} is the observed ^{13}C chemical shift, δ_{min} is the minimum chemical shift in the protonated form of the amino acid, and Δ_i and pK_i are the chemical shift and ionization constants, respectively, for the i th protonation transition. Details of the least-squares program used are given in ref 6.

Molecular Orbital Calculations. A modified version¹² of the standard CNDO/2 computer program¹¹ was used to calculate ^{13}C chemical shifts. The diamagnetic contribution (σ_d) was evaluated from local charge densities.²⁰ The paramagnetic contribution (σ_p) was calculated by the average energy approximation of Pugmire and Grant¹⁴ and by the sum-over-states method¹⁶ as described above. All C, N, and O atoms were included in the σ_p calculation. Bond angles, bond distances, and conformation averaging for alanine, phenylalanine, and histidine were as previously described.¹² For glutamic acid a single conformation was used in which all backbone carbons were trans and all other groups were staggered.

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Communications to the Editor

An Anomalous Brønsted Relationship for β -Diketones

Sir:

Considerable interest has recently been expressed in the various interpretations¹⁻³ given, to what after all

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has been known for some time, namely that the acidities of the nitroalkanes, CH_3NO_2 , $\text{CH}_3\text{CH}_2\text{NO}_2$, and $(\text{CH}_3)_2\text{CHNO}_2$, increase in this order whereas the rates of hydroxide-catalyzed deprotonation decrease in the same sequence. Subsequent studies⁴ illustrate the greater sensitivity of substituent effects on rates than on

(4) F. G. Bordwell, W. J. Boyle, Jr., and K. C. Yee, *J. Amer. Chem. Soc.*, **92**, 5926 (1970).

equilibria in the systems $\text{ArCHCH}_3\text{NO}_2$ and $\text{ArCH}_2\text{-CHCH}_3\text{NO}_2$. Although the existence of an inverse relationship, with the necessary corollary that the Brønsted exponent cannot be taken as a guide to the position of the transition state along the reaction coordinate, has been predicted¹ for other carbon acids, none, prior to the present work, has been observed.

Potentiometric measurements of the acidities of various β -diketones and detritiation studies of the solvent (water) catalyzed rates of ionization (Table I)

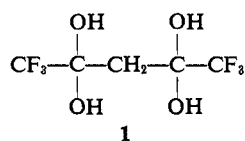
Table I. Acidities and Water-Catalyzed Rates of Detritiation of Various β -Diketones at 25°

β -Diketone	$\text{p}K_a^a$	Lit. value	$10^5 k_1^T$, sec^{-1}
Acetylacetone	8.99	8.93 ^b	66.5
Trifluoroacetylacetone	6.79	6.3 ^b	33.3
Hexafluoroacetylacetone	5.3	4.35 ^b	15.1
Benzoyltrifluoroacetone	6.54	6.3 ^b	38.3
<i>p</i> -Nitrobenzoyltrifluoroacetone	5.38		72.8
<i>p</i> -Methoxybenzoyltrifluoroacetone	6.94		21.6

^a Uncorrected for either enol or hydrate content. The values refer to C-H ionization, those for the hydrates being considerably higher.⁷ ^b J. C. Reid and M. Calvin, *J. Amer. Chem. Soc.*, **72**, 2948 (1950).

show that fluorine substitution increases the acidities of the first three compounds much as expected whereas the rates decrease by a factor close to 2 for each trifluoro group substituted. In contrast to these findings substituent effects on both rates and acidities in the benzoyltrifluoroacetones are entirely normal.

This anomalous behavior, resulting as it does from increasing fluorine substitution, can best be seen by comparing the benzoylacetones and benzoyltrifluoroacetones. In the first series the enol content is usually high (~30%)⁵ and the extent of hydration small whereas the opposite is true for the fluorine-containing β -diketones. It has previously been observed,⁶ for example, that hexafluoroacetylacetone exists in aqueous solution mainly as the dihydrate (1) and ionizes at a very



slow rate even in the presence of such a strong base as sodium hydroxide. This is no doubt due to the very small amount of unhydrated ketone present⁷ and lends support to the belief that, contrary to some recent work,⁸ enolization is still the mechanism for base catalyzed halogenation of aliphatic ketones in aqueous solution.⁹

The successful operation of the Brønsted equation depends on the fact that as the base or acid is varied the potential energy curves should still have the same shape and same position along the reaction coordinate axis. However in going from benzoylacetone to benzoyltrifluoroacetone the activation energy for the ionization reaction increases by nearly 6 kcal, while the entropy of activation becomes considerably less negative. These

differences reflect the importance of hydrogen bonding and hydration in the fluorinated compounds and clearly the necessary conditions for the operation of the relationship no longer prevail.

The effects of fluorine substitution may also lead to an anomalous Brønsted relationship in another series of carbon acids as a number of workers¹⁰ have concluded from deuterium exchange studies that an α -fluorine substituent increases the kinetic acidities of polyhaloaliphatic hydrocarbons whereas for a series of substituted fluoronitromethanes the equilibrium acidities decrease.¹¹

Factors other than hydration must be important for these compounds.

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Application of Kinetics in Highly Basic Media to the Determination of Carbon (and Other) Acidities

Sir:

Although the acidities of carbon acids cover a wide range,¹ ($-3 < \text{p}K_a < 30$) two methods, the competitive² and acidity function approach,³ are more widely used than any of the other methods in determining the $\text{p}K_a$'s. However, both have serious limitations, and in this communication a new and versatile method, that incorporates several advantages, is introduced.

The method has its origin in the ability of dipolar aprotic solvents such as dimethyl sulfoxide to not only dramatically increase the basicity of aqueous hydroxide solutions but also the rates of many chemical reactions.⁴ The procedure entails measuring the rates of detritiation of a "standard" carbon acid in a series of dimethyl sulfoxide-water solutions containing a fixed concentration of base (0.010 M in the present work), *i.e.*, over an H- range. The procedure is then repeated in the presence of a second acid that is appreciably ionized under these conditions. The resulting decrease in hydroxide ion concentration (and hence H-) is reflected in a decrease in the rate of detritiation of the "standard" carbon acid. Provided that the second-order rate constant for detritiation in a particular solvent system is indeed constant and that no catalysis of the detritiation by the anion formed from the more acidic acid (A_2H) occurs, the new hydroxide ion concentration is given by

$$[\text{OH}^-]_2 = [\text{OH}^-]_1 \frac{k_2^T}{k_1^T}$$

k_1^T and k_2^T are the pseudo-first-order rate constants for detritiation in the absence and in the presence of the second acid, respectively. Then

$$[\text{A}_2^-] = [\text{OH}^-]_1 - [\text{OH}^-]_2$$

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