

Table I. Solvolysis Rates of Cyclic Secondary Tosylates at 25°

R-OTs R =	σ_{τ}^*	$-\log k_{\text{obsd}}^a$ (AcOH) [80E]	$-\log k_{\text{calcd}}^a$ (AcOH) [80E]	$\log k_{\text{obsd}} - \log k_{\text{calcd}}$
Cyclopentyl (1)	-0.48 ^{b-d}	(5.78) ^e [3.37] ^f	(5.87) [4.61]	0.09 1.24
Cyclohexyl (2)	0.10 ^{b-d}	(7.32) ^e [6.12] ^g	(7.37) [5.72]	0.05 -0.40
Cycloheptyl (3)	-0.47 ^{c,h}	(5.54) ^e	(5.89)	0.35
Cyclotridecyl (4)	0.00 ^{c,h}	(6.65) ⁱ	(7.11)	0.45
Cyclopentadecyl (5)	0.06 ^{c,h}	(6.90) ⁱ	(7.26)	0.36
Cycloheptadecyl (6)	0.06 ^{c,h}	(6.89) ⁱ	(7.26)	0.37
7-Norbornyl (7)	1.31 ^{b,j}	(13.68) ^j [12.45] ^k	(10.52) [8.04]	-3.16 -4.40
2-Adamantyl (8)	-0.21 ^{b,i,l}	(8.23) ^m [7.62] ^m	(6.56) [5.13]	-1.67 -2.49
7,7-Dimethyl-endo-2-norbornyl (9)	-0.62 ^{b,q}	(7.20) ^o	(5.50)	-1.70
anti-7-Norbornenyl (10)	-0.45 ^{b,i}	(3.43) ^p	(5.94)	2.51
7-Norbornadienyl (11)	-0.12 ^{i,q}	(0.79) ⁱ	(3.99)	3.81
exo-2-Benzonorbornenyl (12)	0.14 ^{i,q}	(5.60) ^r	(7.47)	1.87
exo-2-Norbornyl (13)	-0.74 ^{b,s,t}	(4.62) ^u [3.64] ^v	(5.19) [4.11]	0.57 0.47
endo-2-Norbornyl (14)	0.20 ^{q,t}	(7.14) ^u [6.40] ^v	(7.63) [5.91]	0.49 -0.49
7,7-Dimethyl-exo-2-norbornyl (15)	-0.90 ^{q,q}	(3.59) ^o	(4.77)	1.18
1-Methyl-exo-2-norbornyl (16)	-0.86 ^{q,v}	(2.91) ^{p,m}	(4.87)	1.96
6,6-Dimethyl-endo-2-norbornyl (17)	0.60 ^{q,w}	(8.35) ^u	(8.67)	0.32
1-Methyl-endo-2-norbornyl (18)	0.00 ^{q,v}	(7.03) ^{q,m}	(7.11)	0.08
Cyclobutyl (19)	0.35 ^{c,h}	(5.72) ⁱ	(8.02)	2.30

^a AcOH = acetic acid; 80E = 80% (v/v) aqueous ethanol; conversion factors for solvent and leaving group change are those commonly used, references 11 and 19a. ^b Average value from tertiary chloride and *p*-nitrobenzoate. ^c H. C. Brown and M. Borkowski *J. Amer. Chem. Soc.*, **74**, 1894 (1952). ^d H. C. Brown and W. J. Hammar, *ibid.*, **89**, 6378 (1967). ^e S. Winstein, *et al.*, *ibid.*, **74**, 1127 (1952). ^f J. M. Harris, unpublished results. ^g P. v. R. Schleyer, *et al.*, unpublished results. ^h σ_{τ}^* from tertiary chloride. ⁱ H. C. Brown and G. Ham, *J. Amer. Chem. Soc.*, **78**, 2735 (1956). ^j Reference 22a. ^k P. v. R. Schleyer, *et al.*, *J. Amer. Chem. Soc.*, **91**, 5386 (1969). ^l Reference 14. ^m Reference 2. ⁿ H. C. Brown and S. Ikegami, *J. Amer. Chem. Soc.*, **90**, 7122 (1968). ^o S. Winstein, *et al.*, *ibid.*, **87**, 378 (1965). ^p Reference 11. ^q σ_{τ}^* from tertiary *p*-nitrobenzoate. ^r H. C. Brown and G. L. Tritel, *J. Amer. Chem. Soc.*, **88**, 1320 (1966). ^s K. L. Servis, *et al.*, *Tetrahedron*, **24**, 1247 (1968). ^t H. C. Brown, *et al.*, *J. Amer. Chem. Soc.*, **86**, 1248 (1964). ^u P. v. R. Schleyer, *et al.*, *ibid.*, **87**, 375 (1965). ^v H. C. Brown and M. H. Rei, *ibid.*, **86**, 5004 (1964). ^w H. C. Brown, *et al.*, *ibid.*, **90**, 7122 (1968).

excellent agreement (Table I). Compounds 7-9 are indicated^{1,18,22} to react without nucleophilic or neighboring group assistance (a k_c process),¹⁸ and, as expected, the predicted rates containing 10²-10⁴ assistance are too large by this amount. The validity of the σ_{τ}^* derivation is also corroborated by examination of known^{22,23} anchimerically assisted (k_A)¹⁸ substrates 10-12; observed rates are equal to or greater than the predicted assisted rates.

The following generality results: those compounds with rates equal to or greater than predicted are assisted (k_s or k_A) and those reacting slower than predicted are unassisted. *exo*-2-Norbornyl (13) provides an important¹⁻⁶ illustration. Olah, *et al.*,⁵ have convincingly shown that the norbornyl cation is non-classical. The question arises as to the extent to which the transition state for the solvolysis of 13 resembles the cation intermediate;⁵ can participation lag behind ionization?^{1,4} Our results dispel this possibility; the agreement of observed and predicted rates shows that solvolysis of this compound is assisted and that σ participation must be concerted with ionization. Interestingly, the solvolysis of *endo*-2-norbornyl (14) is also indicated to be normal; that is, its rate is consistent with a k_c process.^{2,3} Similar predictions obtain for the other norbornyl derivatives 15-18. Finally, the

acetolysis rate for cyclobutyl (19) tosylate (100 times faster than predicted) is only consistent with the strong σ participation others have proposed for this reaction.²⁴

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(24) K. B. Wiberg, B. A. Hess, Jr., and A. J. Ashe, III, ref 2, Chapter 26.

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¹³C-¹³C Coupling Constants in a Series of ¹³C-Enriched Amino Acids

Sir:

While ¹³C nmr has become an increasingly popular tool in the study of peptides, none of the studies published to date has concerned ¹³C coupling constants. This is predominantly because of the poor sensitivity and low natural abundance of the ¹³C nucleus. Use of ¹³C-enriched materials reduces these problems very greatly, opening new opportunities for ¹³C nmr studies of peptide structure and conformation. A number of studies in systems other than peptides have appeared,¹

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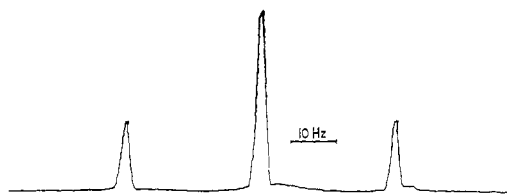


Figure 1. The ^{13}C spectrum of the carbonyl carbon of alanine at 250 Hz sweep width. Fourier transform of 1000 scans.

making general characteristics of these couplings reasonably well understood.

For this study amino acids were separated from a uniformly labeled 45% ^{13}C protein hydrolysate obtained from Merck of Canada, Ltd. The observable ^{13}C - ^{13}C coupling constants are shown in Table I.

Table I. ^{13}C - ^{13}C

Amino acid	Carbons	J (Hz) ^a	Amino acid	Carbons	J (Hz)
Gly	C_0 - α	59.6	Ile	C_0 - α	59.2
Gly ^b	C_0 - α	53.6		α - β	32.5
Ala	C_0 - α	59.6		β - γ_1	33.9
	α - β	34.3		β - γ_2	33.0 ± 0.8
Asp	C_0 - α	59.8		γ_2 - δ	34.9
	α - β	37.6	Leu	C_0 - α	59.6
	β - γ	55.7		α - β	32.8
Phe	C_0 - α	59.9		β - γ	32.4 ± 0.4
	α - β	32.3 ± 0.6		α - γ - δ_1	34.3 ± 0.6
	β - γ	43.7 ± 0.6		γ - δ_2	34.3 ± 0.6
Ser	C_0 - α	59.2	Val	C_0 - α	59.1
	α - β	36.4		α - β	32.2
Glu	C_0 - α	59.6		β - γ_1	34.4
	α - β	33.7		β - γ_2	33.7
	β - γ	36.3			
	γ - δ	54.7			

^a Estimated error ± 0.25 Hz except as noted. ^b In water, pH 7. All other values measured in 6 N HCl solution.

All spectra were run on a Bruker HX-90 spectrometer operated in the Fourier transform mode, and all coupling constants reported are the mean of at least three separate measurements. The output contained 2048 points per spectrum, and most spectra were taken at a sweep width of 250 Hz, giving an intrinsic resolution of 0.12 Hz/point. A few spectra could only be obtained at a sweep width of 500 Hz for instrumental reasons. All protons were noise decoupled, and temperature control was not used, so the sample temperature was approximately 50°. All amino acids were studied in 6 N HCl, but glycine was examined in water at pH 7 as well. No couplings beyond one bond were seen.² Spectra of terminal carbons consisted of the uncoupled singlet and a doublet due to coupling to the adjacent carbon. Non-terminal carbons gave spectra consisting generally of a singlet, two doublets, and a doublet of doublets resulting from molecules with both adjacent carbons being ^{13}C . Because this doublet of doublets contained the same information as the two doublets resulting from molecules with only one nearest neighbor ^{13}C , coupling

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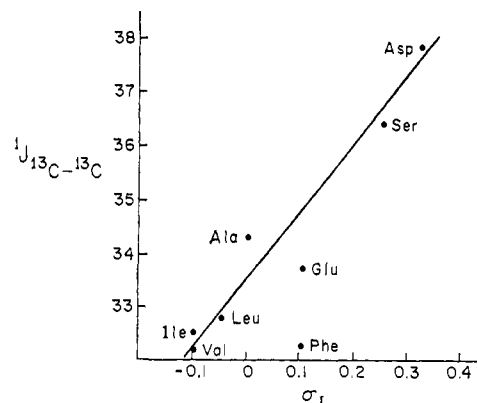


Figure 2. Correlation of C_α - C_β coupling constants with the Hammett inductive parameter σ_I . Because there is no σ_I parameter for $-\text{COOH}$, the value for $-\text{COOCH}_3$ is used for Asp.

constants obtained from nonterminal carbon spectra could be checked for internal consistency to increase the accuracy of the measurement. The spectra uniformly showed peak widths at half height of 2 Hz. Peak widths were not smaller for glycine (with only two carbons and therefore no coupling beyond one bond) which indicates that the peak widths were limited not by unresolved ^{13}C - ^{13}C couplings beyond one bond but by instrumental homogeneity or perhaps residual ^{13}C - ^1H coupling due to incomplete PND. A typical spectrum is shown in Figure 1.

With regard to the data in Table I, two points should be noted. First, the C_0 - C_α coupling constants are very nearly the same throughout the series, exhibiting a range of 0.8 Hz, from 59.1 to 59.9 Hz, a range only slightly greater than the experimental error. These values are slightly higher than the coupling constant of 56.7 Hz reported for acetic acid,^{1b} while the one-bond coupling constants to the side-chain carboxyl carbons of aspartic and glutamic acids are somewhat below the acetic acid value. The C_0 - C_α coupling constant for glycine decreases 6.0 Hz going from the protonated to the unprotonated form. This is the same difference reported for the ionization of benzoic acid.³ Second, in a series of C_α - C_β coupling constants observed, a rough correlation exists between the coupling constant and the Hammett σ_I parameter⁴ for the β substituent (Figure 2). Only in the case of phenylalanine, where a noninductive effect must be postulated, is a very large deviation observed. This is in agreement with similar empirical observations in other systems, in which it has been noted that electron-withdrawing substituents or substituents of high electronegativity lead to higher coupling constants.^{1b,d,5} It is clear both that none of these correlations is rigorously grounded in theory^{1b} and that different factors become significant for different series of compounds. For example, the apparent substituent effects in the amino acids of this study are significantly at variance with those in the corresponding ethyl compounds.^{1d} Whether these differences can be related in a useful way to electronic structure or conformation is a problem for the future. For example, some of the

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differences might be due to specific conformational preferences with respect to rotation about the $C_\alpha-C_\beta$ bond, a consideration which does not enter for the ethyl compounds. When factors like this are evaluated with confidence then studies of $^{13}\text{C}-^{13}\text{C}$ coupling constants such as this will become a useful addition to other nmr studies of peptide conformation and function.

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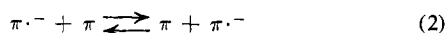
Equilibrium Studies by Electron Spin Resonance. VII. The Use of Time-Averaged Electron Transfer Kinetics to Determine Free Ion-Ion Pair Equilibrium Constants

Sir:

Although esr spectroscopy has proven itself to be the most promising tool for the investigation of the nature of ion pairing in solution, there still exists only one esr technique for the determination of the thermodynamic equilibrium constant for the dissociation of ion pair into free ion (eq 1).¹ To utilize this technique



one must be able to observe the esr spectra of the ion pair and free ion simultaneously.² However, it has been previously pointed out that the conditions for simultaneous observation of the free ion and ion pair are met only rarely.³ This means that for the vast majority of free ion-ion pair equilibria there is no experimental method for the determination of the equilibrium constant. Here we wish to report a time averaging technique based upon the electron transfer rates from anion radical to neutral molecule (eq 2).



Since these rates are readily obtainable,⁴ the technique described here should be applicable for the determination of ion pair dissociation equilibrium constants for a variety of anion radical ion pairs.

It has been previously observed that anion radicals in hexamethylphosphoramide (HMPA) are virtually fully dissociated,⁵ but the addition of alkali metal salts to these anion radical solutions in HMPA results in the formation of the ion pair,⁶ which in some cases can be observed simultaneously with the free ion.⁷ Chang

and Johnson⁸ have demonstrated that the rate of electron exchange (eq 2) for naphthalene systems is slower for the ion pair than it is for the free ion. In agreement with these results we have found that the addition of NaClO_3 to solutions of the free anion radical of *p*-dinitrobenzene in HMPA formed by reduction with sodium⁹ resulted in a smooth decrease in the rate of electron transfer with increasing concentration of sodium cation.¹⁰

The rate constant for the electron transfer between the free *p*-dinitrobenzene anion radical and neutral molecule was determined by esr line broadening under slow exchange conditions utilizing the low field esr line (Figure 1).

Since the observed rate constant for the electron exchange reaction (k_{obsd}) decreases with addition of Na^+ , this value must be a weighted average between the rate constant for the free ion k_{ex}^0 and that for the ion pair (k_{ex}'). This relationship is given by eq 3 providing that

$$k_{\text{obsd}} = \{(\alpha)k_{\text{ex}}^0 + (\beta)k_{\text{ex}}'\} / \{(\alpha) + (\beta)\} \quad (3)$$

the two-jump model (ion pair-free ion) adequately represents the system.

The thermodynamic equilibrium constant for the ion pair dissociation is given by $K_{\text{eq}} = (\alpha)(\text{Na}^+)/(\beta)$, where (Na^+) represents the concentration of added salt since the concentration of added salt is larger by more than two orders of magnitude than the anion radical concentration. Combining this equation with eq 3, we obtain the expression

$$1/(k_{\text{obsd}} - k_{\text{ex}}^0) = K_{\text{eq}}/(\text{Na}^+)(k_{\text{ex}}' - k_{\text{ex}}^0) + 1/(k_{\text{ex}}' - k_{\text{ex}}^0) \quad (4)$$

K_{eq} was obtained from the slope of a plot of $1/(k_{\text{obsd}} - k_{\text{ex}}^0)$ vs. $1/(\text{Na}^+)$ as shown in Figure 2. k_{ex}' was obtained from the intercept, $1/(k_{\text{ex}}' - k_{\text{ex}}^0)$. Typical data for a single experiment are shown in Table I.

Table I. The Observed Rate Constant for the Electron Exchange Reaction with Added NaClO_3

$(\text{Na}^+), M$	$k_{\text{obsd}}, M^{-1} \text{sec}^{-1}$	$(\text{Na}^+), M$	$k_{\text{obsd}}, M^{-1} \text{sec}^{-1}$
0	1.90×10^8	0.309	1.631×10^8
0.164	1.75×10^8	0.321	1.615×10^8
0.184	1.732×10^8		

It should be noted here that the intercept of the plots of line width vs. the concentration of neutral molecule (Figure 1) vary with the concentration of added salt as shown in Figure 3. Further, this variation is dependent upon the concentration of the anion radical. For this reason k_{obsd} must be determined for each salt concentration using the same anion radical solution, and k_{ex}^0 and k_{ex}' will vary slightly from experiment to experiment. However, the data from all experiments using different anion radical concentrations fit on the same line in Figure 2; thus $k_{\text{ex}}' - k_{\text{ex}}^0$ is a constant for each experiment.

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