[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE FLORIDA STATE UNIVERSITY]

Effects of the Trifluoromethyl Group. IV.[1,2] The pK's of ω-Trifluoromethyl Amino Acids

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The pK's of seven amino acids containing a trifluoromethyl group have been determined. The effect of the trifluoromethyl group on the pK's is discussed.

That the trifluoromethyl group exerts a strong inductive and hyperconjugative effect is exemplified by its marked influence on the dissociation constants of amines,[3] carboxylic acids[4,5] and alcohols.[6-8] In the course of a study designed to elucidate the chemical[2] and biochemical[9] properties of the trifluoromethyl group, the pK's of the following amino acids have been determined: 6,6,6-trifluoronorleucine,[9] 5,5,5-trifluoroleucine,[10] 5,5,5-trifluorononorvaline,[9] 4,4,4-trifluorovaline,[10] 2-amino-4,4,4-trifluorobutyric acid,[2] 3-amino-4,4,4-trifluorobutyric acid[2] and 4,4,4-trifluorothreonine.

Experimental

Preparation of Amino Acids.—The syntheses of the fluorinated amino acids have been described elsewhere.[2,9,10]

Materials.—All water was distilled and de-ionized on strong acid and base ion-exchange resins. The hydrochloric acid solutions were made from redistilled concentrated hydrochloric acid and standardized indirectly against potassium acid phthalate. The sodium hydroxide solutions were made from 50% sodium hydroxide and standardized against Bureau of Standards potassium acid phthalate.

Apparatus.—The glass electrode was a Beckman #1190-80. The Ag–AgCl electrode was made by anodizing the looped end of a carefully cleaned silver wire in 0.1 M hydrochloric acid for 5–10 min. at 2 milliamps.

The e.m.f. measurements were made with a Beckman Model GS pH meter in conjunction with a Rubicon type B potentiometer.[11] All measurements were made at 25.00 ± 0.01°. A slow stream of nitrogen was employed to exclude carbon dioxide.

Method.—The electrodes were calibrated with 0.002 M HCl (see section on calculations).

Each amino acid (0.2–0.3 milliequiv.) was weighed directly into the cell. It was successively neutralized with appropriate volumes of dilute hydrochloric acid and sodium hydroxide. Two points were measured for each pK_1 and two points for some of the pK_2 determinations and one point for the others. All points were in the range of 30–80% neutralization of the dissociating group involved, and most were in the 40–60% range. At each point the e.m.f. readings were taken over a half-hour period. Usually the readings were constant after ten minutes. In calculating concentrations, the contribution of the amino acid to the total volume was computed using the partial specific volume of the corresponding unfluorinated amino acid.[12]

A separate determination was made of the ionization constant of the hydroxyl group of trifluorothreonine using a Beckman type E high pH glass electrode.

Calculations.—The cells used for the pK determinations are glass/HCl, amino acid/AgCl–Ag and glass/HCl, amino acid, NaCl/AgCl–Ag for which the measured e.m.f. is given by the relation

$$E = E^* - (RT/F) \ln a_{H^+}a_{Cl^-} \qquad (1)$$

where a represents activity. E^* is characteristic of the particular glass and Ag–AgCl electrodes used and is evaluated by measuring E for a hydrochloric acid solution, for which $a_{H^+}a_{Cl^-}$ is accurately known.[13]

The equations of Smith, Taylor and Smith[14] were used to evaluate the data for pK_1 and pK_2. At 25°

$$pK_1 - \log \frac{\gamma_{A^+}}{\gamma_{A^\pm}\gamma_{H^+}} = \frac{E - E^*}{0.05916} + \log M_{Cl^-} + \log \frac{M_{Cl^-} - M_{H^+}}{M_A - M_{Cl^-} + M_{H^+}} + \log \gamma^2_{HCl} \qquad (2)$$

$$pK_2 + \log \frac{\gamma_{A^-}}{\gamma_{A^\pm}\gamma_{Cl^-}} = \frac{E - E^*}{0.05916} - \log M_{Cl^-} + \log \frac{M_A - M_{Na^+} + M_{Cl^-} + M_{OH^-}}{M_{Na^+} - M_{Cl^-} - M_{OH^-}} \qquad (3)$$

A, $A^\pm$, A^+ and A^- are total amino acid, zwitterionic, cationic and anionic amino acid, respectively. Molarity and activity coefficient are signified by M and γ, respectively. The one assumption made is that $\log \gamma^2_{HCl}$, in equation 2, has the same value in the amino acid solutions as it has in pure HCl of the same ionic strength. This was shown to be a valid assumption by Nims and Smith.[15] The dissociation of the hydroxyl group of trifluorothreonine was calculated with the equation

$$pK_3 + \log \frac{\gamma_{A^{-2}}}{\gamma_{A^-}\gamma_{Cl^-}} = \frac{E - E^*}{0.05916} + \log M_{Cl^-} + \log \frac{2M_A - M_{Na^+} + M_{Cl^-} + M_{OH^-}}{M_{Na^+} - M_A - M_{Cl^-} - M_{OH^-}} \qquad (4)$$

The left hand sides of equations 2, 3 and 4 will be referred to as pK^*_1, pK^*_2 and pK^*_3, respectively.

Discussion

The pK^*'s are shown in Table I with the ionic strengths at which they were measured. Except for the case of trifluorothreonine, the two determinations of pK^*_1 were at the same ionic strength, and the average value is shown in Table I. The average difference between calculated values was 0.002 unit. In those cases where pK^*_2 was determined at two points the values are not averageable since the ionic strengths differ. In all four cases pK^*_2 was higher at the higher ionic strength.

(1) This investigation was supported by a research grant, number C-1461 from the National Cancer Institute of the National Institutes of Health, Public Health Service.

(2) Paper III of this series, H. M. Walborsky and M. E. Baum, *J. Org. Chem.*, **21**, 538 (1956).

(3) A. L. Henne and J. J. Stewart, THIS JOURNAL, **77**, 1901 (1955).

(4) H. M. Walborsky and M. Schwarz, *ibid.*, **75**, 3241 (1953).

(5) A. L. Henne and C. J. Fox, *ibid.*, **75**, 5750 (1953); **76**, 479 (1954).

(6) A. L. Henne and W. C. Francis, *ibid.*, **75**, 991 (1953); A. L. Henne and R. L. Pelley, *ibid.*, **74**, 1426 (1952).

(7) E. T. McBee, W. F. Marzluff and O. R. Pierce, *ibid.*, **74**, 444 (1952).

(8) R. N. Haszeldine, *J. Chem. Soc.*, 1757 (1953).

(9) H. M. Walborsky, M. Baum and D. F. Loncrini, THIS JOURNAL, **77**, 3637 (1955).

(10) D. F. Loncrini, "Synthesis of Omega Trifluoromethyl Amino Acids," Doctoral Dissertation, Florida State University, 1956.

(11) A. L. Barcarella, E. Grunwald, H. P. Marshall and E. L. Purlee, *J. Org. Chem.*, **20**, 747 (1955).

(12) E. J. Cohn and J. T. Edsall, "Proteins, Amino Acids and Peptides," Reinhold Publishing Corp., New York, N. Y., 1943, p. 159.

(13) H. S. Harned and B. B. Owen, "The Physical Chemistry of Electrolyte Solutions," Reinhold Publishing Corp., New York, N. Y., 1943, p. 547.

(14) P. K. Smith, A. C. Taylor and E. R. B. Smith, *J. Biol. Chem.*, **122**, 109 (1937).

(15) L. F. Nims and P. K. Smith, *ibid.*, **101**, 401 (1933).

TABLE I

Compound	Ionic strength	pK_1*[a]	Ionic strength	pK_2*[b]
6,6,6-Trifluoronorleucine	0.0238	2.164	0.0292	9.463
5,5,5-Trifluoroleucine	.0390	2.045	.0416	8.942
			.0518	8.952
5,5,5-Trifluoronorvaline	.0390	2.042	.0485	8.916
4,4,4-Trifluorovaline	.0390	1.537	.0485	8.098
			.0524	8.107
2-Amino-4,4,4-trifluoro-butyric acid	.0390	1.600	.0486	8.169
			.0525	8.173
3-Amino-4,4,4-trifluoro-butyric acid	.0391	2.756	.0486	5.822
			.0525	5.840
4,4,4-Trifluorothreonine	.0390	1.553	.0365	7.781
	.0261	1.555	.0583	12.67[c]
			.0609	12.64[c]

[a] $pK^*_1 = pK_1 - \log \gamma_{A^+}/\gamma_{H^+}\gamma_{A^\pm}$. [b] $pK^*_2 = pK_2 + \log \gamma_{A^-}/\gamma_{Cl^-}\gamma_{A^\pm}$. [c] Values for $pK^*_3 = pK_3 + \log \gamma_{A^{-2}}/\gamma_{A^-}\gamma_{Cl^-}$.

In Table II are listed dissociation constants for compounds possessing the CF_3 group and for corresponding unfluorinated compounds. The effect of the strongly electronegative CF_3 group in lowering the pK is seen to be very large at small distances from the dissociating group and still appreciable in trifluoronorleucine. It has been suggested[5] that the relatively low pK of $CF_3(CH_2)_3COOH$ compared to that of n-valeric acid may be due to intramolecular hydrogen bonding between the carbonyl oxygen and the hydrogen atoms α to the CF_3 group, forming a six-membered ring. It is found in the present work that trifluoroleucine, which has only one hydrogen atom adjacent to the CF_3 group, has essentially the same pK_1 as trifluoronorvaline, which has two. In addition, trifluoronorleucine, for which hydrogen bonding would involve an unlikely seven-membered ring, also has a relatively low pK_1.

TABLE II

COMPARISON OF FLUORINATED AND RELATED UNFLUORINATED COMPOUNDS

Compound[a]	pK_{COOH}	pK_{NH_2}	ΔpK_{COOH}[b,c]	ΔpK_{NH_2}[b,c]
6,6,6-Trifluoronorleucine	2.164	9.463		
Norleucine	2.334	9.833	0.17(4)	0.37(4)
2,5-Diamino-n-valeric acid	1.94	8.65	.39(4)	1.2(4)
5,5,5-Trifluoroleucine	2.045	8.942		
Leucine	2.329	9.747	.28(3)	0.81(3)
5,5,5-Trifluoronorvaline	2.042	8.916		
Norvaline	2.318	9.806	.26(3)	0.89(3)
4,4,4-Trifluorovaline	1.537	8.098		
Valine	2.286	9.718	.75(2)	1.62(2)
2-Amino-4,4,4-trifluorobutyric acid	1.600	8.169		
2-Aminobutyric acid	2.284	9.831	.68(2)	1.76(2)
2,3-Diaminopropionic acid	1.33	6.80	.95(2)	3.0(2)
4,4,4-Trifluorothreonine	1.554	7.781		
Threonine	2.088	9.100	.54(2)	1.32(2)
3-Amino-4,4,4-trifluorobutyric acid	2.756	5.822		
3-Aminobutyric acid	3.60[d]	10.19[d]	.84(2)	4.37(1)
5,5,5-Trifluoro-n-valeric acid	4.50[e]			
n-Valeric acid	4.86[f]		.36(3)	
4,4,4-Trifluorobutyric acid	4.15[g]			
n-Butyric acid	4.82[f]		.69(2)	
3,3,3-Trifluoro-n-propylamine		8.7[h]		
n-Propylamine		10.7		2.0(2)
2,2,2-Trifluoroethylamine		5.7[h]		
Ethylamine		10.82[f]		5.1(1)

[a] pK values for the amino acids were taken from ref. 13, chapt. 4 and ref. 17. [b] $\Delta pK = pK$ of reference compound minus pK of compound with polar substituent. [c] The number in parentheses is the number of carbon atoms separating the dissociating group from the polar group. [d] Value for β-alanine. [e] Ref. 5. [f] N. A. Lange "Handbook of Chemistry," Handbook Publishers, Inc., Sandusky, Ohio, 1946. [g] A. L. Henne and C. J. Fox, THIS JOURNAL, **73**, 2323 (1951). [h] Ref. 3.

Since for eleven aliphatic amino acids studied by Smith and co-workers[15,16] $-\log \gamma_{A^+}/\gamma_{H^+}\gamma_{A^\pm}$ was zero or very small and positive at low ionic strength, it is likely that the values of pK^*_1 reported here are very close to the thermodynamic equilibrium constant pK_1 (equation 2). However, Smith, *et al.*, found that the quantity $\log \gamma_{A^-}/\gamma_{A^\pm}\gamma_{Cl^-}$ was more variable in magnitude and direction, therefore pK^*_2 probably differs from the thermodynamic equilibrium constant pK_2 (equation 3).

(16) P. K. Smith, A. T. Gorham and E. R. B. Smith, *J. Biol. Chem.*, **144**, 737 (1942).

A more consistent explanation of the long range influence of the CF_3 group is available in the "direct effect,"[17] in which account is taken of the electrostatic influence of a polar group on the work required to remove a proton from the dissociating group. This theory as developed by Kirkwood and Westheimer,[18] has been applied with success to acids having charged or dipolar substituents.

(17) An excellent discussion of this topic is given in C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, pp. 728–733.

(18) J. G. Kirkwood and F. H. Westheimer, *J. Chem. Phys.*, **6**, 506 (1938).

Table II shows that the influence of the CF_3 group on the dissociating groups of the amino acids is in each case, where data are available, of about the same magnitude as in monofunctional compounds of equal distance between groups. The pK for the hydroxyl group of 4,4,4-trifluorothreonine, 12.7, may be compared with $pK = 12.3$ for 2,2,2-trifluoroethanol.[7]

Comparison of 6,6,6-trifluoronorleucine(pK_1 2.16, pK_2 9.46) with ornithine (2,5-diaminopentanoic acid, pK_1 1.84, pK_2 8.65), and 2-amino-4,4,4-trifluorobutyric (pK_1 1.60, pK_2 8.17) with 2,3-diaminopropionic acid (pK_1 1.33, pK_2 6.80) gives some measure of the relative effect of the strong dipole[19] CF_3 and the charged group, $^+NH_3$. A similar comparison is available in ω-CF_3 and ω-$^+NH_3$ aliphatic carboxylic acids. As would be expected, the effect of the charged group is considerably the greater, especially when close to the dissociating group.

(19) J. D. Roberts, R. L. Webb and E. A. McElhill, THIS JOURNAL, **72**, 408 (1950); J. J. Conradi and N. C. Li, *ibid.*, **75**, 1785 (1953).

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Carbanions Additions in the Reaction of Aromatic Hydrocarbons with Monoölefins[1a,b,c]

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Alkylaromatic hydrocarbons which contain a benzylic hydrogen atom react with monosubstituted ethylenes, such as propylene, 1-butene and 1-octene in the presence of alkali, and an organoalkali compound prepared *in situ* at about 250–320° to form 1:1 adducts. Propylene reacts with toluene, ethylbenzene, isopropylbenzene and diphenylmethane yielding isobutylbenzene, 2-phenyl-3-methylbutane, 2-phenyl-2,3-dimethylbutane and 1,1-diphenyl-2-methylpropane, respectively. 1-Butene and 1-octene with toluene give 2-benzylbutane and 2-benzyloctane. Under similar conditions toluene and isobutylene react to give neopentylbenzene. Benzene reacts with ethylene to form small amounts of ethylbenzene, *sec*-butylbenzene and biphenyl. *t*-Butylbenzene on reaction with ethylene under similar conditions forms *o*-, *m*- and *p*-*t*-butylethylbenzene. The reaction of benzene with isobutylene yields *t*-butylbenzene, isobutylbenzene and biphenyl. The experimental results, which are interpreted by a carbanion chain mechanism, indicate that the mode of addition of carbanions to unsymmetrical olefins is determined entirely by polar rather than by steric factors. The mode of addition reveals that the primary alkylcarbanions are more stable and more easily formed than the secondary and tertiary ones. Several aspects of the carbanions and of their reaction mechanism are discussed.

There are only a few reports in the literature in which organoalkali compounds were added to monoölefins. Ziegler and Gellert[3] described the reaction of primary alkyllithium compounds with ethylene under pressure to yield a series of adducts. The reaction failed, however, with other olefins. Bartlett and co-workers[4] reported the addition of isopropyllithium and *t*-butyllithium to ethylene at atmospheric pressure and low temperature. When propylene was substituted for ethylene only a small amount of an unidentified polymeric material was obtained. The reaction of several alkylaromatic hydrocarbons, which have at least one benzylic hydrogen, with ethylene in the presence of sodium and a "promoter" recently has been described.[5] There are also a few patents in which similar reactions are claimed to take place in the presence of sodium[6] or organosodium compounds.[7]

The purpose of the present study was to investigate the reaction of alkylaromatic hydrocarbons containing a benzylic hydrogen with simple monoolefins other than ethylene, in the presence of sodium and a substance capable of forming an organosodium compound. Another objective of the present experiments was to determine whether benzene and *t*-butylbenzene under similar conditions would react with olefins.

Results

Propylene and Aromatic Hydrocarbons.—The experimental condition used and the results obtained are summarized in Tables I and II. The "promoters" employed were anthracene, *o*-chlorotoluene and dimethylmercury. The yield of isobutylbenzene produced from the reaction of toluene with propylene, amounting to about 10 to 23 mole per cent., was based on the propylene charge and not on the propylene reacted.[8]

Ethylbenzene, isopropylbenzene and diphenylmethane yielded on reaction with propylene, respectively, 2-phenyl-3-methylbutane (3-methyl-2-butyl)-benzene, 2-phenyl-2,3-dimethylbutane (2,3-dimethyl-2-butyl)-benzene and 1,1-diphenyl-2-methylpropane. The yield of the latter amounted to 51%. The adducts obtained from the interaction of one mole of aromatic hydrocarbons with one mole of propylene were comparable in purity, according to infrared spectra, with the respective

(1) (a) Paper V of the series of Base Catalyzed Reactions. For IV see H. Pines and H. E. Eschinazi, THIS JOURNAL, **78**, 1178 (1956). (b) Taken in part from a dissertation submitted by Victor Mark to the graduate school in partial fulfillment of the requirements for the Ph.D. degree, October, 1955. (c) Presented in part before the Division of Organic Chemistry, American Chemical Society Meeting, March 29-April 7, 1955.

(2) Predoctoral Fellow, Universal Oil Products Co. 1953-54; E. I. du Pont de Nemours and Co., 1954-1955.

(3) K. Ziegler and H. G. Gellert, *Ann.*, **567**, 195 (1950).

(4) P. D. Bartlett, S. Friedman and M. Stiles, THIS JOURNAL, **75**, 1771 (1953).

(5) H. Pines, J. A. Vesely and V. N. Ipatieff, *ibid.*, **77**, 554 (1955).

(6) G. M. Whitman, U. S. Patent, 2,448,641 (1948); *C.A.*, **43**, 1057 (1949).

(7) E. L. Little, Jr., U. S. Patent, 2,548,803 (1951); *C.A.*, **45**, 8554 (1951).

(8) A 4% yield of isobutylbenzene based on propylene charged, was previously found by treating 1 mole of toluene with 0.8 mole of propylene in the presence of 0.27 g. atom of sodium and 0.014 mole of di-*t*-butyl peroxide at 200°. Unpublished work by H. Pines and J. A. Vesely from the Universal Oil Products Co., Riverside, Ill.