Acidity in Nonaqueous Solvents. III. Bicyclo[2.2.2]octane-1-carboxylic Acids in Methanol Solution[1,2]

C. D. Ritchie and G. H. Megerle

Contribution from the Department of Chemistry, State University of New York at Buffalo, Buffalo, New York 14214. *Received October 27, 1966*

Abstract: Free energies, enthalpies, and entropies of ionization for a series of 4-substituted bicyclo[2.2.2]octane-1-carboxylic acids in anhydrous methanol have been determined. The entropies of ionization are constant within experimental error for this series in contrast to the previously reported data for a series of 4-picolinium ions in the same solvent. The entropies of ionization in methanol are about 10 eu more negative than values commonly found for carboxylic acids in aqueous solution. The source of variable entropies of ionization within reaction series is discussed.

A number of workers in the past have noted that acids show considerable variations in entropies of ionizations within similar series.[3] The entire question of enthalpy–entropy effects in reaction series adhering to linear free energy relationships has been examined in detail recently by one of us.[4] From this examination, it appears that relatively weak solvent–solute, or solvent–solvent interactions which are influenced by substitution in the solute molecule are responsible for the observed variations in entropy.

The effect of one group in the molecule on the interaction of another group with the solvent might be expected to decrease as shielding between the groups increases. This shielding is apparently not great enough in the picolinium ion series previously studied.[1a] The very useful 4-substituted bicyclo[2.2.2]octane-1-carboxylic acids[5] may, however, be more efficient in this respect.

In order to examine this question, and at the same time provide more data on which an interpretation of solvent effects on reactivity can eventually be based, we have measured the free energies, enthalpies, and entropies of ionization for a series of 4-substituted bicyclo[2.2.2]octane-1-carboxylic acids in anhydrous methanol solution.

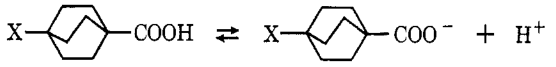
Results

The measurement of ionization constants was accomplished by the use of the electrode system previously described.[1a] The differential potentiometric method, however, was not applicable to the carboxylic acids since the slopes of the titration curves at the end points are too great. Partial neutralization techniques were, therefore, employed using the electrode system calibrated with buffer solutions of 4-hydroxymethylpyridine whose pH values are accurately known from the previous study.

Duplicate determinations on independently prepared solutions at both 0 and 25° showed a precision of 0.01 pK unit. We believe that the accuracy of the data is comparable to the precision. The accuracy of the reported values for $\Delta H°$ is *ca.* ±1.0 kcal/mole and for $\Delta S°$ is *ca.* ±3 eu.

The data obtained in this study are summarized in Table I. The pK values reported are corrected for ionic strength by the Debye–Hückel relationship and are therefore referred to a standard state of infinite dilution in methanol. The values reported for the carboxy- and carboxylate-substituted acids are corrected by the statistical factor of 2.

Table I. Thermodynamic Data for the Reaction[a]



X	pK 0.0°	pK 25.0°	$\Delta G°$ kcal/mole, 25°	$\Delta H°$ kcal/mole, 25°	$-\Delta S°$, eu, 25°
H	10.392	10.226	13.95	2.47	38.5
COO^-	10.401[b]	10.268[b]	14.01[b]	1.98	40.4[b]
COOH	10.089[c]	9.870[c]	13.46[c]	3.26	33.6[c]
OH	10.115	9.985	13.62	1.94	39.2
$COOC_2H_5$	10.077	9.933	13.55	2.15	38.2
Br	9.946	9.750	13.30	2.92	34.8
CN	9.752	9.617	13.12	2.01	37.3
$N(CH_3)_3{}^+$	9.436	9.375	12.79	0.91	39.9

[a] In methanol solution. [b] A statistical correction of −log 2 has been applied. [c] A statistical correction of +log 2 has been applied.

The present values are in reasonable agreement with the differences in pK for these compounds previously reported,[6] with the exception of the charged substituents. From the present data and the previously reported values of the equilibrium constants for the reactions of the acids with *p*-nitrophenoxide, we can evaluate the pK of *p*-nitrophenol as 11.15 ± 0.03 at 25.0°. This value is in excellent agreement with the value of 11.2 reported by Parker.[7]

Discussion

In contrast to the variable entropies of ionization for the picolinium ions in methanol previously reported,[1a]

---

[1] (a) For earlier papers in this series, see: C. D. Ritchie and P. D. Heffley, *J. Am. Chem. Soc.*, **87**, 5402 (1965); C. D. Ritchie and G. H. Megerle, *ibid.*, **89**, 1447 (1967). (b) Taken in part from a thesis submitted to the Graduate School, State University of New York at Buffalo, by G. H. Megerle in partial fulfillment of the requirements for the Ph.D. degree, Feb 1967.

[2] This work was supported by Grant No. GP-2635 from the National Science Foundation.

[3] See, for example: L. G. Hepler, *J. Am. Chem. Soc.*, **85**, 3089 (1963).

[4] C. D. Ritchie and W. F. Sager, *Progr. Phys. Org. Chem.*, **2**, 323 (1964).

[5] J. D. Roberts, W. T. Moreland, Jr., and W. Frazer, *J. Am. Chem. Soc.*, **75**, 637 (1953); H. D. Holtz and L. M. Stock, *ibid.*, **86**, 5183 (1964); C. F. Wilcox, Jr., and J. S. McIntyre, *J. Org. Chem.*, **30**, 777 (1965).

[6] C. D. Ritchie and E. S. Lewis, *J. Am. Chem. Soc.*, **84**, 591 (1962).

[7] B. W. Clare, D. Cook, E. C. F. Ko, Y. C. Mac, and A. J. Parker, *ibid.*, **88**, 1911 (1966).

the entropies of ionization for the present carboxylic acids are constant within experimental error throughout the series. This observation is particularly notable for the charged substituents. Quite generally in the past, charged groups have shown abnormal behavior in this respect.[8]

We suggest on the basis of these results that the variable entropies often noted for acids with charged substituents are due to direct interactions of solvent molecules associated with one group in the molecule with other solvent molecules associated with another group. As a specific example, we would interpret the positive entropy of ionization observed for the 4-ammoniomethylpyridinium ion in methanol and in dimethylformamide[1b] as caused by a very restrictive interaction of the solvation of the ammonio substituent with that of the pyridinium group. The relief of this interaction on ionization causes an entropy increase of *ca.* 14 eu. The same type of interaction, although less severe, is possibly the cause of the less negative entropy of ionization of the 4-hydroxymethylpyridinium ion. In the present bicyclo[2.2.2]octane-1-carboxylic acid series, we believe that this interaction of solvating molecules is prohibited by the geometry of the molecule.

The small enthalpies and large negative entropies of ionization for the carboxylic acids in methanol are similar to values commonly found for carboxylic acids in aqueous solution.[8] The fact that the entropies of ionization are about 10 eu more negative in methanol than comparable values in water can be primarily attributed to an electrostatic effect. Because of the low dielectric constant of methanol, the charged conjugate base and proton are more effective in ordering solvent molecules than they are in water.[8]

The p*K* values shown in Table I are a little higher than might have been predicted. Grunwald[9] has reported a p*K* of 9.72 for acetic acid in methanol. Trimethylacetic acid has a p*K* 0.28 unit higher than that of acetic acid in aqueous solution.[8] One might then guess a p*K* of 10.0 for bicyclo[2.2.2]octane-1-carboxylic acid in methanol. We should not, however, be surprised that this "educated guess" turns out wrong by 0.2 unit.

Experimental Section

Materials. The substituted bicyclo[2.2.2]octane-1-carboxylic acids were available from a previous study.[6] The acids were recrystallized from appropriate solvents, and their melting points then checked closely with literature values.[6] The sodium salts of the acids were prepared *in situ* in methanol solution by addition of the calculated amount of standard sodium methoxide in methanol.

Baker Analyzed reagent methanol was purified as described in the first paper of this series.[1a]

Sodium perchlorate monohydrate, obtained from Fisher Scientific Co., was dried at 200° for 48 hr. The salt was twice recrystallized from anhydrous methanol and then redried at 200°. Analysis of the salt showed less than 0.01% water, and less than 0.1% chloride.

Anhydrous perchloric acid in methanol solution was prepared from purified sodium perchlorate using the ion-exchange technique developed in the previous work.[1a] The acid solutions were stored up to 3 months at −20° without any detectable deterioration of the acid.

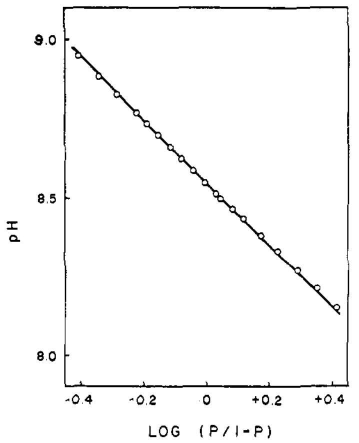


Figure 1. Plot illustrating the theoretical response of the glass electrode in the titration of bicyclo[2.2.2]octane-1-carboxylate with perchloric acid in anhydrous methanol. Data from Table II.

Determination of p*K* Values. A sample of the acid to be titrated was weighed on a Cahn Electrobalance in an argon-filled glove bag. The material was then placed directly into the titration vessel containing 20.0 ml of purified solvent. The vessel was tightly stoppered, removed from the glove bag, and positioned on a magnetic stirrer. After starting temperature equilibration of the system, the electrodes were placed in the vessel using an external argon blanket to avoid atmospheric contamination of the system. A slight positive pressure of argon was maintained on the system throughout the titration.

The sodium salt of the acid was prepared *in situ* by the addition of a calculated amount of methanolic sodium methoxide. Back titration of the salt was accomplished with perchloric acid using 0.05–0.005-ml increments of *ca.* 10^{-2} *M* acid. The electrodes reached a stable potential at 0.0° within 5 min following each incremental addition. The potential readings could be maintained for up to 30 min without any detectable drift.

After completion of the titration, the electrodes were calibrated with a buffer solution consisting of half-neutralized 4-pyridylcarbinol in purified methanol. The pH value of this buffer is known from the previous study.[1a]

Data for the titration of bicyclo[2.2.2]octane-1-carboxylic acid and the treatment of the data are presented in Table II, and shown graphically in Figure 1.

Table II. Data for the Titration of 1.020×10^{-3} *M* Sodium Bicyclo[2.2.2]octane-1-carboxylate in Methanol Solution with 0.0212 *N* Perchloric Acid at 25.0°[a]

ml	"pH"[c]	P[b]	Log $(P/(1-P))$	pK_a
0.270	8.941	0.2788	−0.413	10.162
0.300	8.883	0.3097	−0.348	10.169
0.330	8.828	0.3406	−0.287	10.173
0.360	8.766	0.3715	−0.228	10.172
0.380	8.732	0.3921	−0.190	10.176
0.400	8.696	0.4127	−0.153	10.177
0.420	8.656	0.4333	−0.117	10.173
0.440	8.620	0.4540	−0.080	10.174
0.460	8.584	0.4797	−0.044	10.174
0.480	8.547	0.4952	−0.008	10.172
0.500	8.512	0.5158	0.027	10.173
0.510	8.492	0.5261	0.045	10.173
0.530	8.462	0.5467	0.081	10.177
0.550	8.432	0.5673	0.118	10.182
0.580	8.378	0.5982	0.173	10.184
0.610	8.328	0.6291	0.229	10.181
0.640	8.272	0.6600	0.288	10.180
0.670	8.212	0.6909	0.349	10.185

[a] A plot of pH *vs.* log $(P/(1-P))$ is given in Figure 1. [b] Fraction of base titrated. [c] Meter reading on pH scale, not standardized.

---

(8) For an excellent tabulation, see R. P. Bell, "The Proton in Chemistry," Cornell University Press, Ithaca, N. Y., 1959, p 64.

(9) E. Grunwald and E. Price, *J. Am. Chem. Soc.*, **86**, 4517 (1964).