

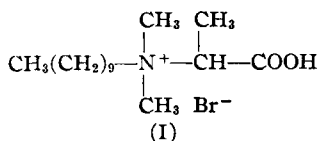
Measurement of the Apparent Dissociation Constants of Some Betaine Salts by Spectropolarimetry

By SHARON BONKOSKI and J. H. PERRIN

It is shown that spectropolarimetry can be used to measure dissociation constants in the same manner as spectrophotometry when the rotations of the species involved in the equilibrium differ sufficiently. The salts of *N*-decyl-*N*, *N*-dimethyl alanine (betaines) have a pK_a' of approximately 1.75 at 25° in an ionic strength of 0.10.

IT HAS LONG been realized that the optical rotation of acids depends upon their degree of ionization; for example, Britton and Moss (1) found *l*-malic acid to have a molecular rotation of -0.325 while its di-anion has a value of -1.60 at the NaD line. They found the rotations to be additive for various mixtures of the undissociated and dissociated acid species, but the small differences in rotation make dissociation constant estimation difficult by this method. However, rotations of optically active acids are greatly enhanced at lower wavelengths, and in the last few years commercial instrumentation has become available, permitting reproducible measurements of optical rotatory dispersion (ORD) down to 200 $m\mu$. The type of ORD curve obtained for an optically active acid depends upon the absorbing groups present and their position relative to the optically active centers, as well as the number and positions of the optically active centers; however, one expects some anomalous behavior due to the absorption of the carboxylic acid group in the region of 210–215 $m\mu$ (2).

Hydrobromide and hydrochloride salts of the ampholytic surfactant *N*-decyl-*N*, *N*-dimethyl alanine (I) behave as monobasic acids, the nitrogen



being quaternary. The salts exhibit anomalous ORD curves as expected for amino acid derivatives, and have been shown to have the first peak of a probable Cotton effect with zero rotation just below 220 $m\mu$, the region of absorption due to carboxyl groups (3). Both the acids and their anions have peaks in the region of 230 $m\mu$, and there are sufficient differences in the molecular rotations of the two species to permit pK_a determinations at wavelengths below 235 $m\mu$.

EXPERIMENTAL

Preparation of Betaines—The salts of the betaines were prepared as previously described, from optically active dimethyl alanines and decyl bromide (3, 4), and the purities checked by NMR, ORD, and melting points (3).

ORD Measurements—All measurements were made at $25 \pm 0.2^\circ$ in a Cary model 60 spectropolarimeter (Applied Physics Corp., Monrovia, Calif.). The pH measurements were made using a

Beckman research pH meter (Beckman Instruments, Fullerton, Calif.). Preliminary pH measurements of the betaine solutions suggested that the apparent dissociation constants (pK_a') were below 2.0, and so the rotation of the undissociated acid was obtained in 1.2 *M* hydrochloric acid and the rotation of the anion in 0.1 *M* sodium hydroxide. Sodium chloride-hydrochloric acid buffers of ionic strength (μ) 0.10 were used for the measurements between pH 1.2 and 2.1. All measurements were made in a 5-cm. cell and the solution scanned from 250 to 220 $m\mu$. In any pK_a' determination the concentration of the betaine was kept constant.

RESULTS AND DISCUSSION

These betaine salts form micelles (the critical micelle concentration is estimated to be 1×10^{-2} moles/l. from Reference 3), and it has been found (5) that the degree of ionization changes abruptly on micelle formation, and in the investigations reported here betaine concentrations of approximately 2×10^{-3} moles/l. were used to avoid this complication. A typical set of ORD curves is shown in Fig. 1 using *N*-decyl-*N*, *N*-dimethyl alanine hydrobromide. The molecular rotation of the undissociated acid at 225.5 $m\mu$ is seen to be approximately 1,000 while its anion has a value of approximately 90. The pK_a' can be calculated when the rotations of the two species as well as the rotations in several buffers are known at any wavelength, in the same manner as is used with spectrophotometric data (6). Let α_{HA} be the observed rotation of the unionized moiety, $[\alpha]_{HA}$ its specific rotation and C_{HA} its concentration. Then $\alpha_{HA} = KC_{HA}[\alpha]_{HA}$ where $K = 0.01$ (path-length in decimeters). Similarly for the anion (A) $\alpha_A = KC_A[\alpha]_A$ for a mixture of the two species the

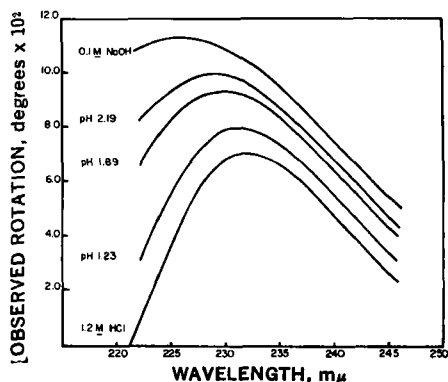


Fig. 1—Typical set of ORD curves.

observed rotation is the sum of the above at the same wavelength

$$\alpha = \alpha_{HA} + \alpha_A = K_{CH_A}[\alpha]_{HA} + K_{C_A}[\alpha]_A \quad (\text{Eq. 1})$$

$$\alpha = KC[\alpha] = K(CH_A + C_A)[\alpha] \quad (\text{Eq. 2})$$

where C is the total concentration of the compound and $[\alpha]$ its specific rotation. Combining Eqs. 1 and 2 gives

$$\frac{C_A}{C_{HA}} = \frac{[\alpha] - [\alpha]_{HA}}{[\alpha]_A - [\alpha]}$$

In any pK_a' determination the concentration of the compound is kept constant and observed rotations can be substituted for specific rotations and the pK_a' 's are given by (6).

$$pK_a' = pH - \log \left(\frac{[\alpha] - [\alpha]_{HA}}{[\alpha]_A - [\alpha]} \right)$$

Measurements were made in at least eight buffers and the pK_a' 's were calculated from the rotations at several wavelengths. The results are summarized below.

Betaine	pK_a' ($\mu = 0.10$)
L chloride	1.75 ± 0.02
L bromide	1.75 ± 0.02

D chloride	1.76 ± 0.03
D bromide	1.73 ± 0.02

The results show the pK_a' to be independent of the configuration of the betaine and the nature of the anions investigated.

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Keyphrases

Betaine salts
Dissociation constants—betaine salts
Spectropolarimetry—dissociation constants

Improved Method for Preparing 3-Azabicyclo[3.2.1]octane Hydrochloride and the Synthesis of its Phenothiazine Derivatives

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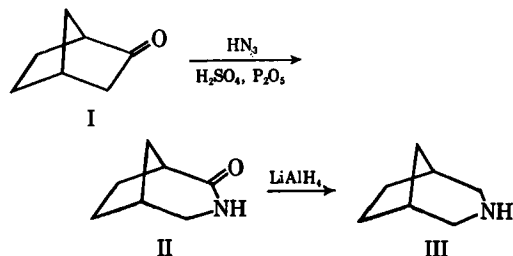
Hydrazoic acid in the presence of concentrated sulfuric acid and phosphorus pentoxide has improved the yield of the lactam in the Schmidt reaction of norcamphor. Reduction of the lactam with lithium aluminum hydride gives 3-azabicyclo[3.2.1]octane in good yields. The synthesis of two new phenothiazine derivatives of this complex amine is reported.

SEVERAL COMPOUNDS derived from azabicyclic amines were reported to possess useful and interesting pharmacodynamic and chemotherapeutic properties (1-3). The primary purpose of this study was to elaborate an easier method for the preparation of 3-azabicyclo[3.2.1]octane (III). A few methods have been reported in the literature (2, 4-7) for the synthesis of this compound or its derivatives; however, these methods either are time-consuming and laborious or they make use of special equipment. The synthesis of two new phenothiazine derivatives of this complex amine is also reported.

The Schmidt reaction of norcamphor (I) was reported (7) to yield 10-28% of the lactam (II), which on reduction gave the desired amine (III). (Scheme I.)

The reaction was repeated under different conditions in order to account for the unusually low yield of the lactam (II). It was noted that by using sodium azide at a temperature of -10° ,

approximately 40% of the norcamphor remained unreacted. Furthermore, the presence of unused sodium azide was noted. On repeating the reaction with hydrazoic acid instead of sodium azide, the yield of the lactam was found to increase up to 34%. Several attempted changes in the reaction conditions did not noticeably improve the yield. Nevertheless, an overall yield of 40-45% of the lactam (II) was obtained when the reaction was carried out in the presence of phosphorus pentoxide. The method of Blicke and Doorenbos



Scheme I