[CONTRIBUTION FROM THE DEPARTMENT OF PHYSIOLOGICAL CHEMISTRY, THE JOHNS HOPKINS UNIVERSITY, SCHOOL OF MEDICINE]

Ionization Exponents of Homologs of Quinacrine in the Extended pH Range[1]

BY J. LOGAN IRVIN, RICHARD W. MCQUAID AND ELINOR MOORE IRVIN

In the preceding paper[2] apparent ionization exponents were reported for various homologs of quinacrine [2-methoxy-6-chloro-9-(4′-diethylamino-1′-methylbutylamino)-acridine]. The exponents previously determined were concerned with the two proton-exchanges which are exhibited by these compounds in dilute aqueous solutions, the proton-acceptors for these exchanges being the diethylamino nitrogen and the ring-nitrogen, respectively. The proton-donor (cationic) species resulting from the acceptance of a proton by the ring-nitrogen is considered to be a resonance-hybrid which receives contributions from Kekulé or benzenoid structures and from a quinonoid structure (see Fig. 1 and the preceding paper).[2] Albert, *et al.*,[3] have presented evidence for this special resonance of the cationic species of the 9-aminoacridines (5-amino in the system of numbering used by Albert). The formation of this resonance-hybrid requires that the proton be accepted by the ring-nitrogen rather than by the 9-amino nitrogen atom. Evidence that the ring-nitrogen is the acceptor for this proton was presented in the preceding paper.[2] No evidence was obtained for the addition of a third proton to the quinacrine homologs in dilute aqueous solutions. It was anticipated that the energy required for the addition of a third proton would be very great since the addition of this third proton would be opposed by the powerful benzenoid–quinonoid resonance of the divalent cationic species and by the electrostatic repulsion exerted by the two positive charges already attached to the molecule (see Fig. 1).

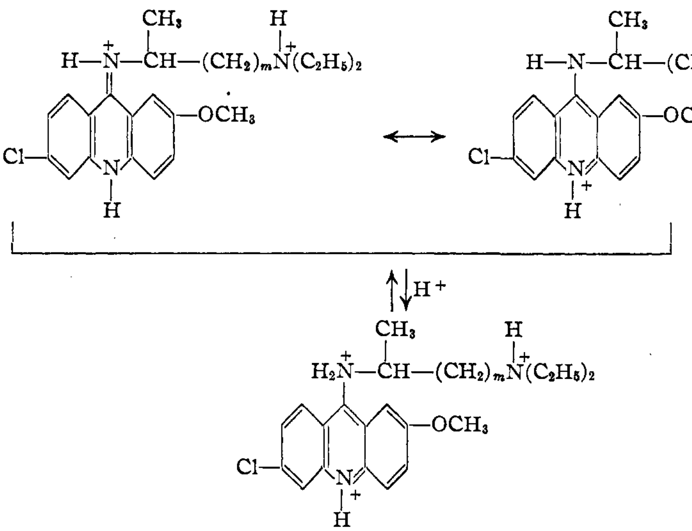

Fig. 1.—The proton-exchange involving quinacrine and its homologs in concentrated solutions of sulfuric acid. $m + 1$ is the number of carbon atoms separating the 9-amino nitrogen from the diethylamino nitrogen. The values of m are 1, 3, and 7 for SN-12867, SN-390, and SN-12868, respectively.

In the present paper spectrophotometric evidence is presented which demonstrates that a third proton is accepted by these quinacrine homologs in concentrated solutions of sulfuric acid. This proton-exchange has been evaluated for a few of the homologs in terms of the extended pH scale of Michaelis and Granick.[4]

Formulation of the Equilibrium.—The proton-exchange exhibited by the quinacrine homologs in concentrated solutions of sulfuric acid as solvent and involving the secondary amino group at position-9 as acceptor can be represented as

$$^{++}H_2B—B'H^+ \rightleftarrows {}^{+}HB—B'H^+ + H^+ \quad (1)$$

in which B refers to the aromatic nucleus with two proton-acceptors (ring-nitrogen and 9-amino nitrogen) and B′ represents the proton-acceptor (diethylamino nitrogen) located on the side-chain. The ionization exponent for this process is defined by means of the equation

$$pK_{(H_2SO_4)} = pH_{(H_2SO_4)} - \log\frac{[^{+}HB—B'H^+]}{[^{++}H_2B—B'H^+]} = pH_{(H_2SO_4)} - \log\frac{\alpha}{1-\alpha} \quad (2)$$

in which brackets represent concentrations, $pH_{(H_2SO_4)}$ refers to the extended pH scale of Michaelis and Granick, and α is the degree of dissociation of $^{++}H_2B—B'H^+$ into $^{+}HB—B'H^+$ and H^+. The data for the present compounds conformed more closely to the pH scale of Michaelis and Granick than to the H_0 acidity function scale of Hammett, *et al.*[5-10] This was anticipated

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[1] The work reported in this paper was aided by a grant from the Penrose Fund of the American Philosophical Society.

[2] Irvin and Irvin, THIS JOURNAL, **72**, 2745 (1950).

[3] Albert, Rubbo and Goldacre, *Nature*, **147**, 332 (1941); Albert and Goldacre, *ibid.*, **153**, 467 (1944).

[4] Michaelis and Granick, THIS JOURNAL, **64**, 1861 (1942).

[5] Hammett and Deyrup, *ibid.*, **54**, 2721, 4239 (1932); **55**, 1900 (1933).

[6] Hammett and Paul, *ibid.*, **56**, 827, 830 (1934); **58**, 2182 (1936).

[7] Hammett, *Chem. Rev.*, **13**, 61 (1933); **16**, 67 (1935).

[8] Hammett, Dingwall and Flexser, THIS JOURNAL, **56**, 2010 (1934).

[9] Flexser, Hammett and Dingwall, *ibid.*, **57**, 2103 (1935).

[10] Flexser and Hammett, *ibid.*, **60**, 885 (1938).

inasmuch as these acridine derivatives correspond more closely to the charge-type of the indicators used by Michaelis and Granick in evaluating their extended scale than to the simpler charge-type of the series employed by Hammett. Hammett and Deyrup emphasized clearly that several acidity functions (H_-, H_0, H_+, H_{++}, etc.) would be expected on the basis of the charge-types of the indicators. The scale which we have used with these homologs of quinacrine should correspond to the H_{++} scale in the notation of Hammett, and in the present case

$$pH_{(H_2SO_4)} = H_{++} = -\log(H^+)f_1/f_2 \quad (3)$$

in which (H^+) is the hydrogen ion activity and f_1 and f_2 are the activity coefficients of the ^+HB—$B'H^+$ and $^{++}H_2B$—$B'H^+$ species, respectively.

Experimental

The sources of the 9-aminoacridine derivatives used in this work were acknowledged in the preceding paper.[2] Values of $pK_{(H_2SO_4)}$ were determined spectrophotometrically by a procedure similar to that of Flexser, Hammett and Dingwall[9] and identical with that described in previous papers on quinoline derivatives.[11] Optical densities of a series of solutions of an acridine derivative in various concentrations of sulfuric acid were determined with a Beckman spectrophotometer, model DU, with 1-cm. fused silica cuvettes. The nominal spectral interval isolated, which was evaluated from the data for dispersion and slit widths, was maintained at 2 mμ. Sulfuric acid solutions of concentrations identical with the corresponding principal solutions were used as blanks. Absorption data were calculated as molecular absorption coefficients, ε, which are defined by the equation $-\log T = D = \epsilon cl$, in which T is the transmittancy, D is the optical density, c is the concentration of the compound in moles per liter, and l is the length in cm. of the light path through the solution. All equilibrium measurements were made at 30°. The concentrations of sulfuric acid in the series of solutions were determined by titrations with standard 1 M sodium hydroxide. Values of $pH_{(H_2SO_4)}$, were calculated from the molar concentrations of sulfuric acid by means of the scale of Michaelis and Granick. For the evaluation of $pK_{(H_2SO_4)}$, the data for $pH_{(H_2SO_4)}$, and the corresponding absorption coefficients at some selected wave-length were rectified by the general method of Reed and Berkson[12] with the adaptation of Clark[13] applied essentially as described previously[11] in connection with spectrophotometric evaluation of ionization exponents of 4-aminoquinolines. Corrections for "medium effects," as defined by Flexser, Hammett and Dingwall,[9] were made essentially as described by these authors.

Discussion

The absorption spectra of quinacrine (SN-390)[14] in 0.1 M and in 17.5 M sulfuric acid are presented in Fig. 2. The absorption spectrum of SN-12868 [2-methoxy-6-chloro-9-(8′-diethylamino-1′-methyl-octylamino)-acridine] in 17.5 M sulfuric acid is almost identical with that of quinacrine in this solvent except for a slight shift in the wave lengths of the maxima of the absorption bands as follows: from 448 mμ for quinacrine to 442 mμ for SN-12868; from 380 mμ to 378 mμ; from 364 mμ to 362 mμ. In the

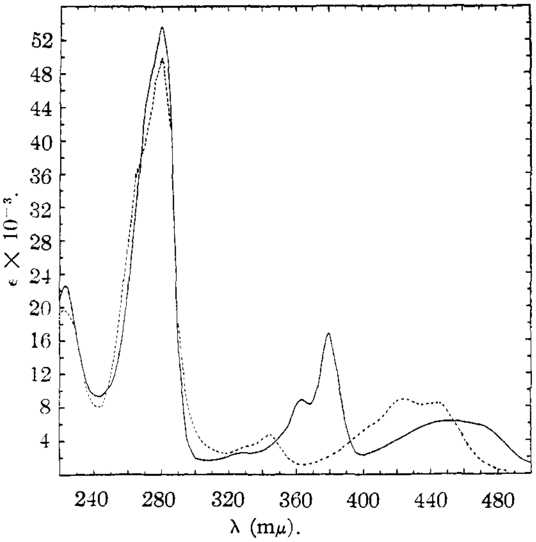

Fig. 2.—Absorption spectra for quinacrine: ---- 0.1 M sulfuric acid; — 17.5 M sulfuric acid.

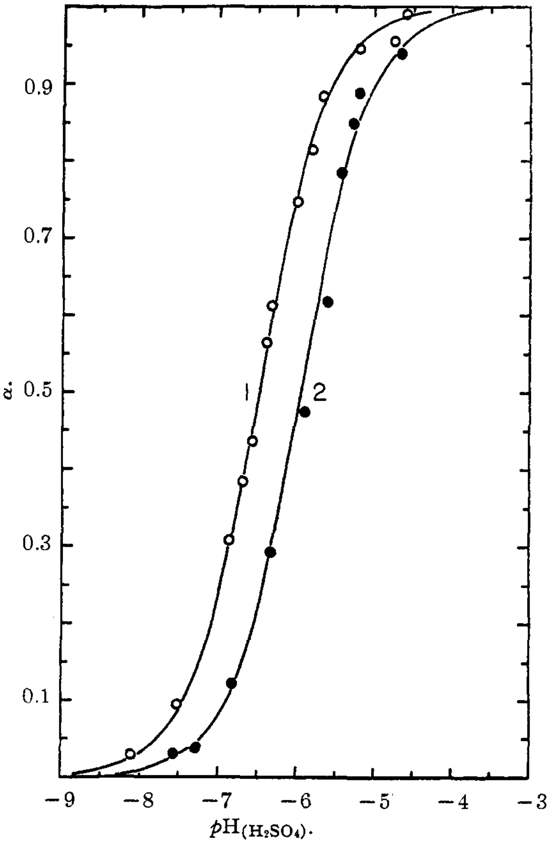

Fig. 3.—○ data for quinacrine (SN-390); ● data for SN-12868. Lines 1 and 2 are the theoretical curves drawn according to equation 2, the values of $pK_{(H_2SO_4)}$ being −6.49 and −5.95, respectively.

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[11] Irvin and Irvin, THIS JOURNAL, **69**, 1091 (1947); *J. Biol. Chem.*, **174**, 577 (1948).

[12] Reed and Berkson, *J. Phys. Chem.*, **33**, 760 (1929).

[13] Clark, Taylor, Davies and Vestling, *J. Biol. Chem.*, **135**, 543 (1940).

[14] This is the code number assigned to this compound in the monograph edited by Wiselogle, "A Survey of Antimalarial Drugs, 1941–1945," Edwards Bros., Ann Arbor, Mich., 1947.

case of SN-12867 the proton-exchange was incomplete even in 18 *M* sulfuric acid, but the change in spectrophotometric absorption was in the direction of that exhibited by the other compounds. The addition of a third proton to these 9-aminoacridine derivatives is a reversible process as demonstrated by the complete reversal of the spectrophotometric changes by dilution of the sulfuric acid solutions with water. A "medium effect," consisting principally of a small increase in the molecular absorption coefficients at all wave lengths, was observed at the lower range of sulfuric acid concentrations (0.1 to 5 *M*), below the range of the proton-exchange. Another medium effect, consisting of a slight, progressive shift to lower wave lengths (the maximum shift being 3 mμ) of the peaks of the absorption band of the species $^+$HB—B'H$^+$ in the visible range of the absorption spectrum, was observed throughout the range from 6 *M* to 17 *M* sulfuric acid. Corrections for these medium effects in the evaluation of $pK_{(\mathrm{H_2SO_4})}$ were made essentially as described by Flexser, *et al.*[9]

The agreement of the experimental data for SN-390 and SN-12868 with the theoretical relationship of equation 2 is shown in Fig. 3. The values of $pK_{(\mathrm{H_2SO_4})}$ determined for these compounds are -6.49 and -5.95, respectively. An accurate evaluation of $pK_{(\mathrm{H_2SO_4})}$ for SN-12867 [2 - methoxy - 6 - chloro - 9 - (2' - diethylamino-1'-methyl-ethylamino)-acridine] was not feasible inasmuch as the proton-exchange for this compound was incomplete even in 17.5 *M* sulfuric acid. However, an approximate value of -9.2 was calculated from the spectrophotometric data for solutions of the compound in sulfuric acid of concentrations ranging to 17.5 *M* by rectification of the data by the logistic analysis of Reed and Berkson.[12,13] The progressive decrease in $pK_{(\mathrm{H_2SO_4})}$ with shortening of the side-chain in this series of compounds can be attributed to the increase in the electrostatic repulsion of the third proton by the positive charge on the diethylamino group of the side-chain as the distance of separation is shortened. No attempt has been made to analyze quantitatively the increase in the electrostatic effect, which accompanies the shortening of the side-chain, in terms of the extended theory of Bjerrum.[15] The lack of accurate data on the dielectric constant of sulfuric acid and of concentrated solutions of sulfuric acid in water prevents quantitative application of the Bjerrum theory to the present case, but the semi-quantitative aspects of the effect are in agreement with the theory.

Summary

In concentrated aqueous solutions of sulfuric acid a reversible proton-exchange involving the 9-amino nitrogen atom of quinacrine, and of two homologs of this compound, has been studied, and the ionization exponents have been evaluated spectrophotometrically in terms of the extended *p*H scale of Michaelis and Granick. The difficulty in adding the third proton to these molecules is attributed to electrostatic and resonance effects.

[15] Bjerrum, *Z. physik. Chem.*, **106**, 219 (1923).

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[CONTRIBUTION FROM THE WILLIAM H. CHANDLER CHEMISTRY LABORATORY OF LEHIGH UNIVERSITY]

Sorption by Organic Substances. I. Krypton and Nitrogen on Polyethylene, Nylon and Collagen[1]

BY A. C. ZETTLEMOYER, AMIR CHAND AND ERNEST GAMBLE

The adsorption of non-polar gases on organic solids presents a field that has been little developed. This situation contrasts sharply with the field of the adsorption of gases on inorganic solids. In the latter case considerable progress has been made in developing a fundamental understanding of the adsorption phenomenon, and a large body of data is available in the literature.

Previous adsorption work on organic solids reported in the literature includes a few exploratory measurements of nitrogen adsorption by Emmett and co-workers on dried bacteria[2a] and on paper[2b]; the point B method was employed for the first and the BET equation for the second to estimate the surface areas. The BET method was also used by Shaw[3] on egg albumen, by Benson and Ellis[4] on various proteins, by Assaf, Haas and Purves[5] on cellulose, by Palmer, Shaw and Ballantyne[6] on sodium pectate and by Zettlemoyer, Schweitzer and Walker[7] on hide powder.

These few studies have not demonstrated thoroughly that the BET method is applicable to organic surfaces. In this study adsorption isotherms on polyethylene, nylon and collagen were measured with both krypton and nitrogen so that

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[1] Presented before the 116th meeting of the American Chemical Society in Atlantic City, N. J., September, 1949.

[2] (a) S. Brunauer and P. H. Emmett, THIS JOURNAL, **59**, 2682 (1937); (b) P. H. Emmett and T. DeWitt, *I. E. C., Anal. Ed.*, **13**, 28 (1941).

[3] T. M. Shaw, *J. Chem. Phys.*, **12**, 391 (1944).

[4] S. W. Benson and D. A. Ellis, THIS JOURNAL, **70**, 3563 (1948).

[5] A. G. Assaf, R. H. Haas and C. B. Purves, *ibid.*, **66**, 66 (1944).

[6] K. J. Palmer, T. M. Shaw and M. Ballantyne, *J. Polymer Science*, **2**, 318 (1947).

[7] A. C. Zettlemoyer, E. Schweitzer and W. C. Walker, *J. Am. Leather Chem. Assoc.*, **41**, 253 (1946).