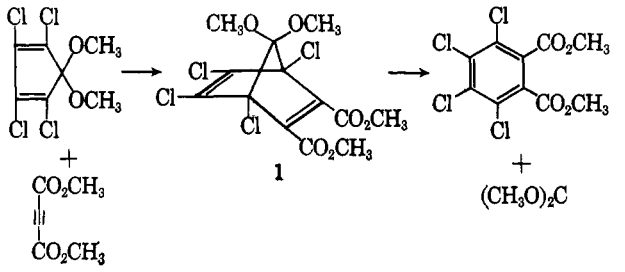
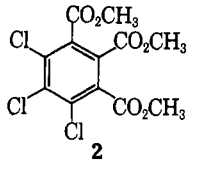
By an analogous scheme, we hoped to prepare the bicycloheptadiene **1**, a potential precursor to dimethoxycarbene, which can be considered the dimethyl ketal of carbon monoxide.



When equimolar amounts of 1,1-dimethoxytetrachlorocyclopentadiene and dimethyl acetylenedicarboxylate were heated to 150°, a product was obtained which was neither the expected bicycloheptadiene **1** nor dimethyl tetrachlorophthalate. Instead, the product had the composition of trimethyl trichlorohemimellitate **2**, another possible fragmentation product from **1**.



The structure assignment of **2** is supported by its n.m.r. spectrum which shows two unsplit peaks separated by 4 c.p.s. at 60 Mc. in a ratio of 2:1. Confirmation of the molecular weight came from the mass spectrum which showed the presence of the parent peak at $m/e = 354$; the observed isotope pattern confirms the presence of only three chlorine atoms.[4]

A similar fragmentation appears to be involved in the debromination of 1,2,3,4-tetrachloro-5,6-dibromo-7,7-dimethoxybicyclo[2.2.1]hept-2-ene with zinc in refluxing acetic acid to give methyl 2,3,4-trichlorobenzoate.[5]

Experimental

A mixture of 9.9 g. (0.037 mole) of 5,5-dimethoxytetrachlorocyclopentadiene and 5.3 g. (0.037 mole) of dimethyl acetylenedicarboxylate was heated to 150° at which temperature an exothermic reaction set in. Heating was continued for 10 min. On cooling, the brown mixture solidified. Recrystallization of the crude product from ethanol gave 8.2 g. (62%) of trimethyl trichlorohemimellitate as colorless crystals, m.p. 93–94°; $\lambda_{max}^{CH_3CN}$ 222 (41,600), 292 (754), and 302 mμ (ε 704).

Anal. Calcd. for $C_{12}H_9Cl_3O_6$ (355.56): C, 40.54; H, 2.55; Cl, 29.93. Found: C, 40.54; H, 2.40; Cl, 30.37.

When the Diels–Alder components were heated in refluxing xylene or toluene, **2** was formed in 75% yield.

(4) Independently of us, Professor Lemal of the University of Wisconsin has attempted preparation of dimethoxycarbene by the same route. His findings agree with ours. Furthermore, he has also identified methyl chloride as the other fragmentation product. We wish to thank Professor Lemal for communication of his results prior to publication.

(5) K. Mackenzie, *J. Chem. Soc.*, 457 (1962).

Ionization Constants of Some *N*-Aryl-D-glucosylammonium Ions

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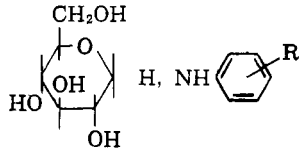
During the course of work in our laboratory on the hydrolysis rates of glucosylamines, it became necessary to investigate the ionization constants of certain glucosylammonium ions. Six glucosylamines (I) were selected for this study: (a) *N*-phenyl-, (b) *N*-*m*-tolyl- (c) *N*-*p*-tolyl-, (d) *N*-*p*-anisyl-, (e) *N*-*p*-chlorophenyl-, and (f) *N*-*p*-fluorophenyl-D-glucosylamine. Each of these compounds was prepared from the corresponding aromatic amine and glucose. The pK_a values for the glucosylamines were determined spectrophotometrically by a modification of the method described by Flexser, Hammett and Dingwall.[1]



I

Ia, R = H
b, R = *m*-CH_3
c, R = *p*-CH_3
d, R = *p*-OCH_3
e, R = *p*-Cl
f, R = *p*-F

The aryl-D-glucosylamines are stable in basic solution but undergo rapid hydrolysis in acid media.[2a,b] This hydrolysis makes the direct determination of pK_a very difficult and limits the experimental techniques which can be used. This paper describes an attempt to estimate the pK_a of some glucosylamines by a back-extrapolation method through which some of the difficulties associated with the instability of the aryl-D-glucosylamines in acid solution have been overcome.

The ultraviolet spectra of all glucosylamines studied were similar to those of the corresponding aromatic amine, and the absorptivity of the solutions decreased with increasing acidity. Therefore, it should be possible to determine the molar absorptivity of the glucosylammonium ion and the glucosylamine by measuring the absorbance of solutions at sufficiently high and low acidity, respectively. The molar absorptivity of the glucosylamines was readily measured in solutions that were 10^{-4} *M* in sodium hydroxide. The rapid hydrolysis of glucosylamines[2a,b] in acidic solutions makes the direct determination of the molar absorptivity of the protonated glucosylamines impossible. Because of the similarities of the glucosylamines to the anilines, we assumed that the molar absorptivity of the glucosylammonium ion would be small and that little error would be introduced by neglecting the absorptivity of this species. Other methods of determining pK_a when

(1) L. A. Flexser, L. P. Hammett, and A. Dingwall, *J. Am. Chem. Soc.* **57**, 2103 (1935).

(2) (a) S. Holton and O. Runquist, *J. Org. Chem.*, **26**, 5193 (1961); (b) W. W. Pigman, E. A. Cleveland, D. H. Couch, and J. H. Cleveland, *J. Am. Chem. Soc.*, **73**, 1976 (1951).

TABLE I

ACID DISSOCIATION CONSTANTS OF SOME *N*-ARYL-D-GLUCOSYLAMMONIUM IONS IN WATER AND 41% (BY WEIGHT) ETHANOL, 25°[a]

Glucosylamine	max, mμ	pH	pK_a (water) 25°	pK_a (41% ethanol), 25°
N-*p*-Anisyl (Id)	300	1.6	0.99 ± 0.07 (8)	0.97 ± 0.07 (6)
		1.1	1.05 ± 0.02 (3)	0.90 ± 0.02 (5)
N-*p*-Tolyl (Ic)	290	1.6	0.85 ± 0.10 (8)	0.91 ± 0.02 (5)
		1.1	0.88 ± 0.02 (4)	0.85 ± 0.02 (5)
N-*m*-Tolyl (Ib)	285	1.1		0.29 ± 0.08 (11)
		0.8	0.36 ± 0.05 (5)	
		0.3	0.30 ± 0.02 (3)	
N-Phenyl (Ia)	285	1.1		0.30 ± 0.08 (8)
		0.3	0.42 ± 0.05 (4)	
N-*p*-Fluorophenyl (If)	290	0.8	0.41 ± 0.03 (4)	
		0.3	0.30 ± 0.04 (4)	
N-*p*-Chlorophenyl (Ie)	295	0.3	−0.26 ± 0.06 (4)	

[a] Number in parenthesis indicates the number of determinations used for the average given.

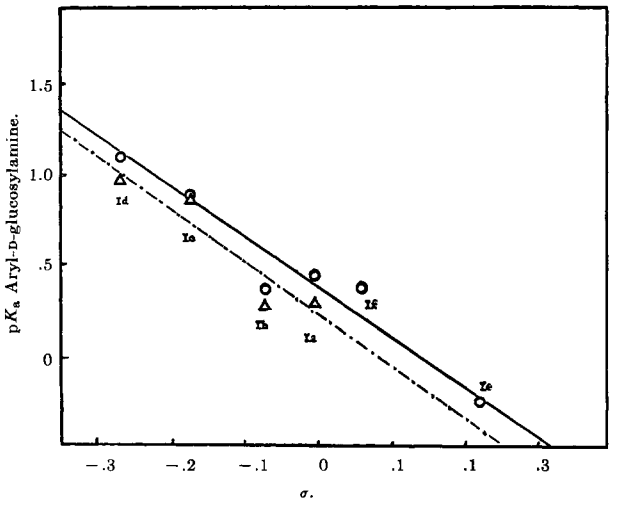


Fig. 1.—Variation of the pK_a of *N*-aryl-D-glucosylamines with the corresponding Hammett σ constants. Numbers refer to compounds in Table I: O ———, pK_a in water; △ — · —, pK_a in 41% ethanol.

the absorptivity of the protonated species is not known could not be used since all require measurements over a larger acidity range or more accurate determinations of absorptivity than the stability of the glucosylamines would allow.[1,3]

In acidic solutions containing both protonated and unprotonated glucosylamines, the hydrolysis reaction was 30–60% complete before absorbance measurements could be made. This difficulty was partially overcome by using the back-extrapolation method.[4] Linear plots of log absorbance against time were extrapolated to zero time to yield absorbance values. The rapid decrease in absorbance with time, however, limited the accuracy of the extrapolation.

pK_a of a base may be calculated from equation 1[1,5]

$$pK_a^{B} - pK_a^{In} = \log \frac{\epsilon_i - \epsilon_{InH^+}}{\epsilon_{In} - \epsilon_i} - \log \frac{\epsilon_b - \epsilon_{BH^+}}{\epsilon_B - \epsilon_b} \qquad (1)$$

where ϵ_{BH^+}, ϵ_B, ϵ_{InH^+}, and ϵ_{In} are the molar absorptivities of the base and indicator in strong acid and base; ϵ_b and ϵ_i are the apparent molar absorptivities of the base and indicator in solutions of intermediate acidity and pK_a^{In} is the dissociation constant for the indicator in the solvent. By assuming ϵ_{BH^+} was small as compared to ϵ_B and could be neglected, the pK_a of glucosylamines could be determined from equation (1). The values calculated for pK_a in 41% ethanol–water and water appear in Table I.

The relative order of base strengths of the substituted aryl-D-glucosylamines parallels that of the *meta* and *para* substituted anilines. A plot of glucosylamine pK_a against the respective Hammett σ constants gave reasonably linear relationships (Fig. 1). Thus, *meta* and *para* substitution in the aromatic ring appears to have only the expected resonance and inductive effect on the basic center of the glucosylamine. The greater part of the difference between base strength of a substituted aryl-D-glucosylamines and the corresponding aniline is most likely due to the polar influence of the C-1 ring oxygen system (C-1–O–C-5) of the glucopyranoside.

Experimental

Materials. *N*-Substituted Phenyl-D-glucosylamines (Ia–Ie).—*N*-Phenyl-(Ia) and *N*-*p*-anisyl-D-glucosylamine (Id) were prepared according to the method of Irvine and Gilmour,[6] *N*-*p*-chlorophenyl-(Ie) according to the method of Hanaoka[7] and *N*-*m*-tolyl-(Ib) and *N*-*p*-tolyl-D-glucosylamine (Ic) according to the method of Ellis and Honeyman.[8]

***N*-*p*-Fluorophenyl-D-glucosylamine (If).**—A mixture of *p*-fluoroaniline (25 g., 0.23 mole), anhydrous D-glucose (40.5 g., 0.23 mole) and 150 ml. of 83% ethanol was refluxed for 1 hr. The reaction mixture was cooled to −10° and the white crystals of *N*-*p*-fluorophenyl-D-glucosylamine collected. Recrystallization from hot acetone yielded 40.0 g. (61%) of the hemihydrate, m.p. 124–126°, $[\alpha]^{25}D$ −21.7° (*c* 1.15, in ethanol).

Anal. Calcd. for $C_{12}H_{16}O_5NF \cdot {}^1/_2H_2O$: C, 51.06; H, 6.07; N, 4.96. Found: C, 51.21; H, 6.18; N, 4.89.

Spectroscopic Measurements.—Stock solutions containing approximately 0.01 mole of glucosylamine per liter of 41% (by weight) ethanol–water were used to make up a series of acidic and basic 41% ethanol–water and water solutions in which the glucosylamine concentration was constant and approximately 1×10^{-4} *M*. The basic solutions were 10^{-4} *M* in sodium hydroxide while the acid solution varied from 0.01 to 0.5 *M* in hydrochloric acid. The absorption spectra of the glucosylamines in basic solution were determined with a Beckman DU line-powered spectrophotometer. The absorbance of each acidic solution was determined at the wave length of maximum absorbance (Table I) at timed intervals. The approximate values of the molar absorptivity of the acid solutions of glucosylamines were obtained by plotting log absorbance against time and extrapolating to zero time.

(3) C. T. Davis and T. A. Geissman, *J. Am. Chem. Soc.*, **76**, 3507 (1954).
(4) N. Naqvi and Q. Fernando, *J. Org. Chem.*, **25**, 551 (1960).
(5) L. P. Hammett and A. J. Deyrup, *J. Am. Chem. Soc.*, **54**, 2721 (1932).
(6) J. C. Irvine and R. Gilmour, *J. Chem. Soc.*, **95**, 1545 (1909).
(7) K. Hanaoka, *J. Biochem.* (Tokyo), **31**, 95 (1940).
(8) G. P. Ellis and J. Honeyman, *J. Chem. Soc.*, 1490 (1952).

Stock solutions containing approximately 0.01 mole of indicator per liter of 41% ethanol–water were used to prepare a series of acidic and basic 41% ethanol–water and water solutions in which the indicator concentration was constant and approximately 1×10^{-4} M. The solvents used to prepare the indicator solutions were identical to those used in preparing the glucosylamine solutions. An additional indicator solution was prepared in which the concentration of hydrochloric acid was 1 M or greater. The indicator methyl yellow (pK_a 2.04)[9] was used in the 41% ethanol–water solutions while the indicators thymol blue (pK_a 1.52 ± 0.02), *m*-cresol purple (pK_a 1.59 ± .02), *o*-cresol red (pK_a 1.26 ± .02), or diphenylamine (pK_a 0.89 ± .02),[10] were used in the water solutions.

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(9) From a large scale plot of values given by B. Gutbezahl and E. Grunwald, *J. Am. Chem. Soc.*, **75**, 559 (1953).

(10) These pK_a values were determined in our laboratories by the spectrophotometric method described by L. A. Fexser, L. P. Hammett, and A. Dingwall, *J. Am. Chem. Soc.*, **57**, 2103 (1935). Values previously reported are: thymol blue, pK_a 1.5 [W. C. Holmes and E. F. Snyder, *ibid.*, **47**, 221 (1925)]; *m*-cresol purple, pK_a 1.57 [B. Cohen, *Public Health Rept.* (U. S.), **32**, 3051 (1927)] and diphenylamine, pK_a 0.85 [N. F. Hall, *J. Am. Chem. Soc.*, **52**, 5124 (1930)].

Acid-Dissociations of 2-Hydroxypyridinium Ion

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During a discussion of Swain's evidence for polyfunctional catalysis, we became concerned about the difference in the order of acid-dissociation constants of 2-hydroxypyridine, implied by the presentation of the data,[1] and that inferred in an earlier paper[2] from data on pyridoxine (a 3-hydroxypyridine derivative).[3] A literature survey revealed that, in spite of extensive investigation by a number of authors, confusion about the correct assignments of pK_a' values for 2-hydroxypyridinium ion exists. The pK_b' values of 2-pyridone and its N-alkyl and O-alkyl derivatives are sometimes grouped together for comparison with no indication given that different functional groups are involved,[4] and some authors who seem to assign the lower pK_a' to O–H in one paper, or even in one section of a paper,[5] confuse the issue considerably by apparently attributing the higher pK_a' to O–H in a later paper or section.[6] Whereas controversy over the best structural representation for the neutral molecules is well resolved, the assignment of pK_a' values on the basis of quantitative data remains indefinite. Accordingly, we undertook a study of this system, confirming much of the published spectral data as well as obtaining some new data, and made a firm interpretation which is presented here.

Assignment of pK_a' Values.—The ultraviolet spectrum of 2-hydroxypyridine (2-pyridone),[7,8] like that of phenol, 3-hydroxypyridine,[2] and substituted 3-hydroxypyridines,[9,10] shows a single well resolved maximum in acid solution which is replaced by two maxima, one at a higher and the other at a lower wave length, in alkaline solution. The studies on 3-hydroxypyridine and its derivatives have established that the change in spectrum is almost entirely attributable to the phenol-to-phenolate transformation occurring as the pH is raised. The disappearance of the single "acid band" and the appearance of the two "alkaline bands" coincides with the change in the relative proportions of undissociated and dissociated groups as the pH approaches and passes the pK_a' for the phenolic hydroxyl. When neutral solutions of 2-hydroxypyridine, pyridoxine, and pyridoxine derivatives are made sufficiently basic to exceed the second pK_a' of the solute, the positions of the two bands shift slightly, but the spectra are essentially unchanged. Even benzene and cyclohexane solutions of 2-hydroxypyridine show similar spectra: one band in acidic solution, and two in neutral and basic solutions.[6,8,11,12]

The great similarity of these spectral data strongly suggests similar structural changes accompanying pH changes. There can be no doubt about the site of proton loss in phenol, and the assignment of the lower pK_a' to the O–H group in pyridoxine and its derivatives has not been disputed. The spectral changes for 2 hydroxypyridine solutions are essentially the same, and the situation (unlike that for 3-hydroxypyridine) is simplified by the absence of any detectible tautomeric equilibrium in neutral solution (99% amide form[13,14]).

The methiodides of both 2- and 3-hydroxypyridine exhibit a single pK_a' (<1.0 as estimated potentiometrically for *N*-methyl-2-hydroxypyridinium iodide[8] and 0.32 as measured spectrophotometrically for *N*-methyl-2-pyridone[5]; 4.96 for *N*-methyl-3-hydroxypyridinium iodide[14]). For the 3-hydroxy methiodide, a pK_a' of 4.96 establishes the enhanced acidic character of the phenolic O–H group when the ring can exist only in the

(1) C. G. Swain and J. F. Brown, Jr., *J. Am. Chem. Soc.*, **74**, 2534 (1952). The apparent assignment of acid-dissociation constants does not affect the authors' main conclusions regarding the significant polyfunctional catalysis by 2-hydroxypyridine.

(2) S. A. Harris, T. J. Webb, and K. Folkers, *J. Am. Chem. Soc.*, **62**, 3198 (1940).

(3) Although no species properly described as 2-hydroxypyridine actually exists in any significant amount in solid or solution, the name is nonetheless a convenient one, especially when comparisons of several hydroxypyridines or -quinolines are being made. The name 2-pyridone (or α-pyridone) is probably better otherwise.

(4) M. I. Kabachnik, S. T. Ioffe, and Yu. N. Sheinker, *J. Gen. Chem. USSR*, **26**, 2257 (1956).

(5) A. Albert and J. N. Phillips, *J. Chem. Soc.*, 1294 (1956).

(6) A. Albert, *ibid.*, 1020 (1960).

(7) H. Specker and H. Gawrosch, *Ber.*, **75**, 1338 (1942).

(8) This research.

(9) V. R. Williams and J. B. Neilands, *Arch. Biochem. Biophys.*, **53**, 56 (1954).

(10) D. Metzler and E. E. Snell, *J. Am. Chem. Soc.*, **77**, 2341 (1955).

(11) S. F. Mason, *J. Chem. Soc.*, 5010 (1957).

(12) Related data are obtained with 3-aminopyridine. In very strongly acidic solutions in which the solute exists as a dication, the single absorption maximum is near 260 mμ, and the spectrum is essentially that of pyridinium hydrochloride. The monocation, identified as 3-aminopyridinium ion, and the neutral molecule both display two maxima.[6]

(13) J. A. Berson, *J. Am. Chem. Soc.*, **75**, 3521 (1953).

(14) A. Albert, "Heterocyclic Chemistry," Essential Books, Fair Lawn, N. J., 1959, pp. 43–62.