pohalite.[14] The only apparent difference between these two types of reaction is that, whereas in one the phenol is condensed with a simple amine (or ammonia) under the influence of hypohalite,[15] it is condensed with a guanido group in the other. It may thus be speculated that perhaps their products also parallel each other in structure, although it must be remembered that the indophenols and indamines as a class (blue, green or purple) differ appreciably from the products of Sakaguchi reaction (yellow to red) in being more intensely colored.

Incidentally, thymol, 5-quinolinol and 5-chloro-7-iodo-8-quinolinol (the latter in ethyl acetate solution), besides 8-quinolinol, gave sufficiently intense color to be of possible use as substitutes for 1-naphthol in the estimation of arginine by Sakaguchi reaction; 1-naphthol is known to have several disadvantages in this respect.[5b,6,10] With thymol, moreover, blank coloration was practically absent.

EXPERIMENTAL

Arginine and glycocyamine[2,3a] were employed as the guanidine compounds. Because of the advantage of a clear contrast between the color of the spot and that of the surrounding areas, the reactions were carried out on filter paper[9a] rather than in solution. Briefly, spots of arginine (or glycocyamine) were treated first with 2.5% potassium hydroxide in ethanol, then with a 0.1–0.2% solution of the phenol[16] in a suitable solvent, and finally with aqueous hypobromite solution (0.1–2 g. % bromine in 1*N* potassium hydroxide).

Note added in proof: After this note went to the press, a copy of the paper of Kraut *et al.*[6] has been procured. It has been noted that these workers, while selecting a suitable naphtholsulfonic acid for the method, found 1-naphthol-4-sulfonic acid to be ineffective in producing color by this reaction and so concluded that a free 4-position in 1-naphthol was apparently essential for Sakaguchi reaction.

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(14) A. P. Orr, *Biochem. J.*, **18**, 806 (1924); J. A. Russell, *J. Biol. Chem.*, **156**, 457 (1944).

(15) It is noteworthy that the 2,6-dibromoquinonechlorimine of Gibbs is itself prepared by the action of hypochlorite on 2,6-dibromo-*p*-aminophenol.[11a]

(16) We wish to express our appreciation to Prof. B. D. Tilak of the Department of Chemical Technology, University of Bombay, for generous gifts of 1-naphthol-4-sulfonic acid and 2-naphthol-6-sulfonic acid.

Isolation and Characterization of a Phenol Half-Salt

A. T. SHULGIN AND H. O. KERLINGER

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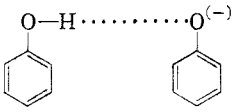
Many observations have been made of anomalous behavior at or near the half neutralization point in the nonaqueous titration of weak acids. In conductometric titration[1] conductivity maxima have frequently been recorded, whereas in potentiometric titration[2] there have been observed corresponding inflections or distortions in the titration curve.

These anomalies have been explained[2a] by the generation, during titration, of an association species in which the generated anion (of either a

R—O—H . . . . . O⁻—R

carboxylic acid or a phenol) protects an equivalent amount of acid, the association being stoichiometric at the half-titration point. This new species is then the acidic participant for the remainder of the titration. The evidence for such a material has been entirely physical and predominately spectroscopic. Pool[3] and Kaufman[4] have presented cryoscopic evidence for the formation of a solid compound composed of one molecule of a base and two molecules of a carboxylic acid, the latter preparing several half-salts between fatty acids and tertiary amines. Analysis of the infrared spectra of dilute solutions of carboxylic acids and tertiary amines[5] has yielded support for this same 2:1 relationship. Recently the alkali half-salts of several carboxylic peptide precursors have been described.[6] In the case of phenols, the evidence for this relationship with bases has been heretofore titrimetric The structural requirements of an unhindered —OH group,[1b,2a,b] and for the exclusion of appreciable amounts of polar solvents (as hydrogen bonding competitors)[1b] imply that the acid-anion structure is a dimer as shown:



We have found that the inclusion of a sterically hindered formamido group *para* to the phenolic —OH group greatly increases the stability of these half-salts, permitting their isolation and manipulation as discrete chemical substances.

When a solution of 4-formamido-3,5-xylenol in methyl isobutyl ketone is titrated with tetrabutylammonium hydroxide in solution in a mixture of methanol and isopropanol, there is obtained a titration curve typical of those described earlier.[2a] In addition, however, there is the generation of a

(1) (a) A. A. Maryott, *Journ. of Res. Nat. Bureau. Standards*, **38**, 527 (1947). (b) D. B. Bruss and G. A. Harlow, *Anal. Chem.*, **30**, 1836 (1958).

(2) (a) G. A. Harlow, and D. B. Bruss, *Anal. Chem.*, **30**, 1833 (1958). (b) H. B. van der Heijde, *Anal. Chem. Acta*, **16**, 392 (1957).

(3) W. O. Pool, H. J. Harwood, and A. W. Ralston, *J. Am. Chem. Soc.*, **67**, 775 (1945).

(4) S. Kaufman, and C. R. Singleterry, *J. Phys. Chem.*, **56**, 604 (1952).

(5) G. M. Barrow, *et al.*, *J. Am. Chem. Soc.*, **76**, 5211 (1954). *J. Am. Chem. Soc.* **77**, 4475 (1955). *J. Am. Chem. Soc.*, **78**, 5802 (1956).

(6) M. Goodman, and K. C. Stueben, *J. Org. Chem.*, **24**, 112 (1959).

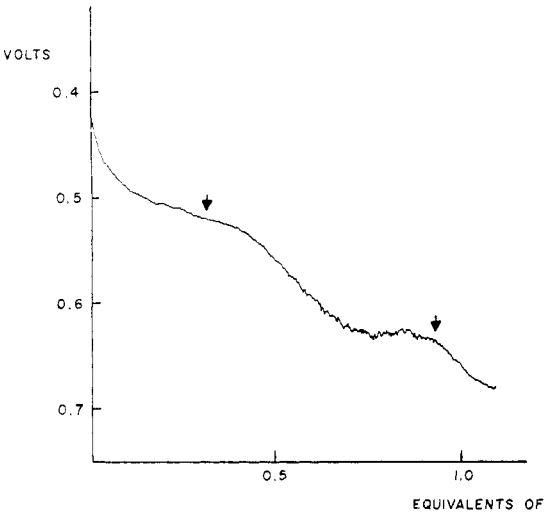


Fig. 1. Titration curve of 4-formamido-3,5-xylenol with tetrabutylammonium hydroxide. The arrows indicate the point of first appearance and of final disappearance of the crystalline half-salt

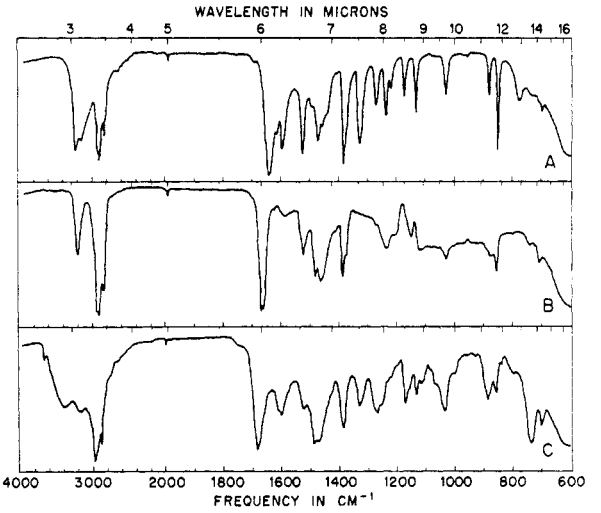


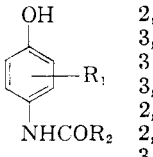
Fig. 2. Spectra of: a) 4-Formamido xylenol (mineral oil mull). b) 4-formamido xylenol·tetrabutylammonium 4-formamido xylenate (mineral oil mull). c) Tetrabutylammonium 4-formamido xylenate (smear). All from a Beckman prism-grating IR-7 spectrophotometer

crystalline product prior to the half-neutralization point, which redissolves prior to the final endpoint (see Fig. 1).

This material may be filtered free of the solvent and recrystallized as required. If the titration is continued to the full 1:1 endpoint, the normal salt is formed (in solution) from which the half-salt may be regenerated by the introduction of an additional mole of phenol. The normal salt cannot be isolated from this ketone medium, however.

As to the structural requirements permitting formation of an isolatable half-salt under these conditions, it appears that both a hindered formamido group and an unhindered —OH group are necessary. The acetamido homolog yielded no such precipitate.

The following table summarizes the structural requirements permitting the formation of a stable, insoluble half-salt with tetrabutylammonium hydroxide under the experimental conditions mentioned below.



R_1	R_2	Formulation of Half-Salt
H	H	−
2,6-CH_3	H	−
3,5 CH_3	H	+
3 CH_3,5 C_2H_5	H	+
3,5-C_2H_5	H	+
2,3,5-CH_3	H	+
2,3,5,6-CH_3	H	−
3,5-CH_3	CH_3	−

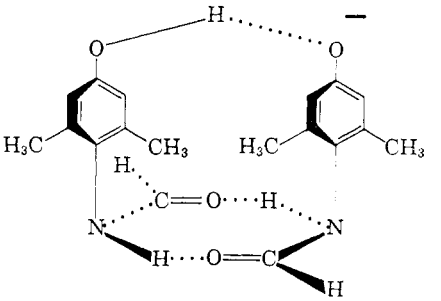
The solvent employed in the titration is not critical. Various diethers of ethylene glycol and diethylene glycol all yielded an insoluble half-salt and a redissolved normal salt. However, dioxane yielded a dark solution at the endpoint and lower ketones (acetone) were unsatisfactory.

When the tetrabutyl ammonium hydroxide was in water solution, apparently any solvent may be used in which both the phenol and water are soluble. Dimethyl formamide and diethylene glycol dimethyl ether were satisfactory.

The only other base employed was trimethylbenzylammonium hydroxide in methanol (with the phenol in methyl isobutyl ketone). The half-salt was a gummy solid, and was not further pursued.

Structure of the half-salt. Infrared spectra of the free phenol, the half-salt, and the normal salt of 4-formamido-3,5-xylenol and tetrabutylammonium hydroxide are shown in Fig. 2.

The unexpected stability of this half-salt, demonstrated by its formation in water and its insolubility, suggests a more strongly bonded dimer than one associated by the phenolic —OH alone. In the structure below these arguments are



achieved. Infrared spectra of dilute solutions (saturated in methylene chloride solution, 1 cm. cells) show no unbonded —OH in the half-salt, whereas the free phenol contains such an —OH (at 3595 cm.$^{-1}$).[7] Any attempt to provide a quinone-like structure for the anionic portion of the half-

salt must allow for the complete absence of color in all the half-salts observed so far.

EXPERIMENTAL

Acylamido phenols. All formulations and acetylations were performed as described by Smith, *et al.*[8] for the formation of 4-formamido-2,3,5-trimethylphenol from the aminophenol. It was desirable, however, to employ boiling water or a water–formic acid mixture as a recrystallization solvent, after prior treatment of the crude reaction product with charcoal.

4-Formamido phenol melted at 137.5–139° (from water).

4-Formamido-2,6-xylenol melted at 159–160° (from water).

4-Formamido-3,5-xylenol melted at 233° (from water).

5-Ethyl-4-formamido-m-cresol melted at 185–186° (from formic acid-water).

3,5-Diethyl-4-formamido phenol melted at 208–209° (from formic acid–water).

4-Formamido-2,3,5-trimethylphenol melted at 215° (from water).

4-Formamido-2,3,5,6-tetramethylphenol melted at 298° dec. (from formic acid–water).

4-Acetamido-3,5-xylenol was obtained as the monohydrate from water; m.p., 179–180.5°, with sintering at 90°. The anhydrous form may be obtained by dehydration with boiling benzene and recrystallization from ether-pentane.

4-Formamido-3,5-xylenol tetrabutylammonium 4-formamido-3,5-xylenate. Preparation in nonaqueous medium. A solution of 1.0 g. of 4-formamido-3,5-xylenol in a minimum amount of methyl isobutyl ketone was titrated to its normal endpoint with a full equivalent of 0.2*M* tetrabutylammonium hydroxide[2a] in isopropyl alcohol methanol (5:1 V/V). To this solution of the normal salt was then added an additional 1.0 g. of the parent phenol in a minimum amount of solvent. The mixture was stirred for 2 hr. during which time the half-salt was deposited as a white, crystalline solid. It was removed by filtration and washed sparingly with methyl isobutyl ketone. Recrystallization from acetonitrile yielded 2.5 g. (72%) of a fine, white microcrystalline product; m.p. 189° dec.

Anal. Calcd. for $C_{34}H_{57}N_3O_4$: C, 71.41%; H, 10.05%; N, 7.35%; neut. equiv. ($HClO_4$) 571. Found: C, 71.08%; H, 9.96%; N, 7.28%; neut. equiv. 560.

Preparation in aqueous medium. To a solution of 4-formamido-3,5-xylenol in three times its weight of dimethylformamide there was added exactly 0.5 equivalent to a 1*M* solution of tetrabutylammonium hydroxide in water (Southwestern Analytical Chemical Co.). Crystallization of the half-salt started immediately and was essentially complete in 10 min. Filtration and recrystallization yielded a product identical with that formed in preparation in nonaqueous medium, above.

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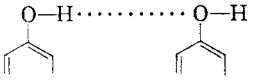
(7) This does not exclude a dimeric form for the free phenol, as a normal —OH group would still be expected for the unbonded form, and the bonded —OH may well lie outside of the narrow, transparent region available in methylene chloride.



Unfortunately, neither the free phenol nor the half-salt was sufficiently soluble in carbon tetrachloride or carbon disulfide to permit their use as solvents.

(8) L. I. Smith, H. H. Hoehn, and A. G. Whitney, *J. Am. Chem. Soc.*, **62**, 1867 (1940).

The Preparation of Tetrahydro-3,3,5,5-tetrakis(hydroxymethyl)pyran

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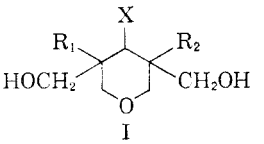
Limited evidence found in the literature indicates that the base catalyzed, exhaustive hydroxymethylation of ketones in which the carbonyl group is flanked by methylene groups gives rise to substituted tetrahydropyran-4-ols. Thus, the reaction of acetone and formaldehyde gives anhydroenneaheptitol (Ia),[1] whereas methyl ethyl ketone and diethyl ketone are reported to give tetra-

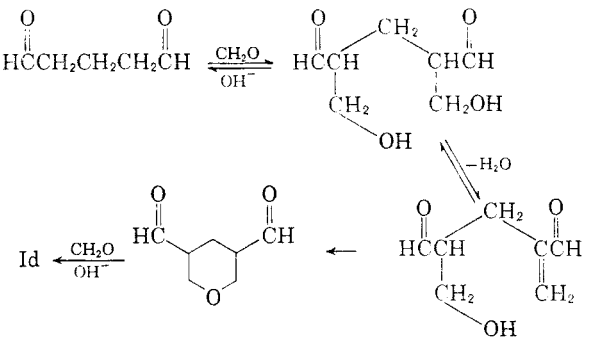


I

a) $R_1 = R_2 = CH_2OH$; X = OH
b) $R_1 = CH_2OH$; $R_2 = CH_3$; X = OH
c) $R_1 = R_2 = CH_3$; X = OH
d) $R_1 = R_2 = CH_2OH$; X = H

hydro-3,3,5-tris(hydroxymethyl)-5-methylpyran-4-ol (Ib) and tetrahydro-3,5-bis(hydroxymethyl)-3,5-dimethylpyran-4-ol (Ic), respectively.[2]

It has now been found that a similar reaction takes place in a 1,3-bis(methylene) system activated by terminal aldehyde groups rather than by a central ketone function. The exhaustive hydroxymethylation of glutaraldehyde gives the previously unreported tetrahydro-3,3,5,5-tetrakis(hydroxymethyl)pyran (Id). A general reaction mechanism would seem to apply to all of the above cases. The following scheme is proposed for the glutaraldehyde-formaldehyde reaction and is analogous to that suggested for the formation of dipentaerythritol in the preparation of pentaerythritol from acetaldehyde and formaldehyde.[3]



The tetraacetate, dibenzylidene acetal, and diisopropylidene ketal derivatives of Id were prepared.

(1) M. Apel and B. Tollens, *Ber.*, **27**, 1089 (1894), *Ann.*, **289**, 46 (1896); C. Mannich and W. Brose, *Ber.*, **55**, 3155 (1922).

(2) I. R. Roach, H. Wittcoff, and S. E. Miller, *J. Am. Chem. Soc.*, **69**, 2651 (1947).

(3) S. Wawzonek and D. A. Rees, *J. Am. Chem. Soc.*, **70**, 2433 (1948).