Ionization Constants of Mandelic Acid Derivatives

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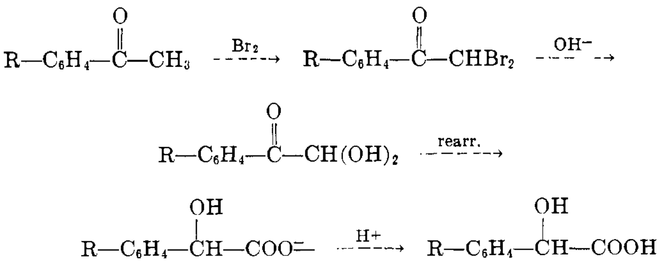
The ionization constants of thirteen mandelic acid derivatives were measured in aqueous solution at 25° C. using the potentiometric method described by Albert and Serjeant.

DATA on the ionization constants of mandelic acid derivatives are limited. Besides mandelic acid (*11*), values appear to be available only for the *m*-halo (*5, 11*), *o*-, *m*-, and *p*-nitro (*6*), and *p*-bromo (*2*) mandelic acids. The ionization constants of additional mandelic acid derivatives have now been obtained.

EXPERIMENTAL

The acids used in this work were prepared and purified by the methods indicated in Table I. The keto-aldehyde synthesis consists of alkaline hydrolysis and rearrangement of the appropriate ω,ω-dibromoacetophenone



$$R{-}C_6H_4{-}\overset{\overset{\displaystyle O}{\|}}{C}{-}CH_3 \xrightarrow{Br_2} R{-}C_6H_4{-}\overset{\overset{\displaystyle O}{\|}}{C}{-}CHBr_2 \xrightarrow{OH^-}$$

$$R{-}C_6H_4{-}\overset{\overset{\displaystyle O}{\|}}{C}{-}CH(OH)_2 \xrightarrow{\text{rearr.}}$$

$$R{-}C_6H_4{-}\overset{\overset{\displaystyle OH}{|}}{C}H{-}COO^- \xrightarrow{H+} R{-}C_6H_4{-}\overset{\overset{\displaystyle OH}{|}}{C}H{-}COOH$$

The cyanohydrin synthesis consists of hydrolysis of the cyanohydrin obtained by the addition of hydrogen cyanide to the aldehyde.

$$R{-}C_6H_4{-}CHO \xrightarrow{HCN} R{-}C_6H_4{-}CHOH{-}CN \xrightarrow[HOH]{H+} R{-}C_6H_4{-}CHOH{-}COOH$$

In the case of the *o*-methoxy and *p*-methoxy mandelic acids, the cyanohydrin was first converted into an imido ester before hydrolysis to the acid via the ester. This is the first reported instance of the preparation of *o*-bromo and *o*-methoxy mandelic acids. Considerable difficulty was experienced in the purification of the *o*-methoxymandelic acid and the melting point range could not be narrowed any further than indicated.

Ionization constants were measured potentiometrically by the method of Albert and Serjeant (*1*). This consists essentially in the measurement of the pH of a solution of a known con-

Table I. Preparation and Melting Points of Mandelic Acid Derivatives

Mandelic Acid Derivative	Method of Preparation	Reference to Preparation	Melting Point, °C.		
			Liter.	Ref.	Exper.
p-Fluoro	keto-aldehyde	(*4, 10*)	137.0	(*7*)	138.5
p-Chloro	keto-aldehyde	(*10*)	120–121	(*8*)	120.0
p-Bromo	keto-aldehyde	(*10*)	117–119	(*10*)	121.5
p-Iodo	keto-aldehyde	(*10*)	135–136	(*14*)	139.5
2,5-Dimethyl	keto-aldehyde	(*9*)	116–117	(*16*)	116.0
p-Ethyl	keto-aldehyde	(*9*)	141–142	(*15*)	145.5
p-Isopropyl	keto-aldehyde	(*9*)	159–160	(*15*)	160.0
p-*n*-Butyl	keto-aldehyde	(*9*)	116–117	(*14*)	119.0
o-Fluoro	cyanohydrin	(*4, 7*)	116.5	(*7*)	117.0
o-Chloro	cyanohydrin	(*8*)	85–85.5	(*8*)	87.0
o-Bromo[a]	cyanohydrin	(*13*)	...	...	88.0[b]
o-Methoxy[c]	cyanohydrin	(*12*)	...	...	42–47
p-Methoxy	cyanohydrin	(*12*)	108.0	(*3*)	108.0

[a] Analysis. Calcd. for $C_9H_{10}O_4$: C, 59.33; H, 5.53. Found: C, 59.32; H, 5.43.
[b] Perry obtained a value of 89–90 (*13*).
[c] Analysis. Calcd. for $C_8H_7O_3Br$. C, 41.60; H, 3.05, Br, 34.6. Found: C, 41.90, H, 3.39; Br, 34.8.

Table II. Ionization Constants of Mandelic Acid Derivatives at 25° C.

Acid[a]	pK_a	K_a
o-Fluoromandelic	3.30 ± .04[b]	5.0×10^{-4}
o-Chloromandelic	3.31 ± .06	4.9×10^{-4}
o-Bromomandelic	3.32 ± .06	4.8×10^{-4}
p-Fluoromandelic	3.19 ± .06	6.5×10^{-4}
p-Chloromandelic	3.15 ± .05	7.1×10^{-4}
p-Bromomandelic[c]	3.15 ± .04	7.1×10^{-4}
p-Iodomandelic	3.14 ± .04	7.2×10^{-4}
p-Ethylmandelic	3.55 ± .06	2.8×10^{-4}
p-Isopropylmandelic	3.64 ± .05	2.3×10^{-4}
p-*n*-Butylmandelic	3.58 ± .05	2.6×10^{-4}
2,5-Dimethylmandelic	3.57 ± .06	2.7×10^{-4}
o-Methoxymandelic	3.64 ± .03	2.3×10^{-4}
p-Methoxymandelic	3.42 ± .07	3.8×10^{-4}

[a] Concentration 0.01*M*.
[b] Obtained by taking antilogarithms of each pK_a value in the set of results, averaging these, and writing down the logarithm of the average as pK_a. The largest deviation between this value and any value in the set is written after the pK_a as its scatter (*1*).
[c] Alimarin and Hang-Shi (*2*) reported a pK_a of 3.07 for *p*-bromomandelic acid at 18° C.

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centration of the test acid after the addition of successive increments of standard base until the equivalence point is reached. The pK_a is calculated from the equation:

$$pK_a = pH + \log \frac{[HA] - \{H^+\}}{[A^-] + \{H^+\}}$$

where [HA] is the stoichiometric concentration of the undissociated acid molecule, $[A^-]$ is the stoichiometric concentration of the anion and $[H^+]$ is the activity of the hydrogen ion as calculated from the pH. The results are tabulated in Table II.

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Compound Formation in the Chloroform-Triethylamine System

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The phase diagram for the chloroform-triethylamine system has been determined from the results of cooling-curve experiments. Evidence has been found for a 1 to 1 compound which melts at 191° K. Eutectic compositions are at 0.38 and 0.78 mole fractions of triethylamine and 180° and 142° K.

RECENT equilibrium measurements (*1*) of the effect of chloroform on the mutual solubility of water and triethylamine have indicated strong interaction between chloroform and triethylamine. A variety of earlier investigations by others have also provided evidence for strong interactions of chloroform with triethylamine in all-liquid systems. Although there is general agreement that the observed deviations from ideal behavior can be attributed to hydrogen bonding and resulting formation of a complex or addition compound, no direct evidence for the existence of the proposed compound is available. This investigation was undertaken to provide direct evidence for or against the proposed compound.

EXPERIMENTAL

Cooling curves over the whole composition range from pure chloroform to pure triethylamine were determined with apparatus consisting of an evacuable Dewar, motor-driven stirring device, electric timer, calibrated platinum resistance thermometer, and Leeds and Northrup Type G-2 Mueller Bridge with Type HS galvanometer. Provision was made for passing a slow stream of dry air over the sample in the Dewar while measurements were being made. Cooling rates were controlled by adjusting the vacuum in the Dewar. The vacuum flask containing the sample to be investigated was immersed in a bath of liquid nitrogen.

Both chloroform and triethylamine were purified by distillation under reduced pressure. Boiling point and HCl titration measurements (*1*), as well as the freezing point data obtained in this investigation, confirm the purity of the triethylamine.

Because of the high viscosity of solutions containing more than about 60 mole % triethylamine, it was necessary to introduce seed crystals to prevent considerable supercooling. Several measurements made without the use of seed crystals indicated supercooling of more than 10° C., and in one experiment a temperature lower than the eutectic temperature was

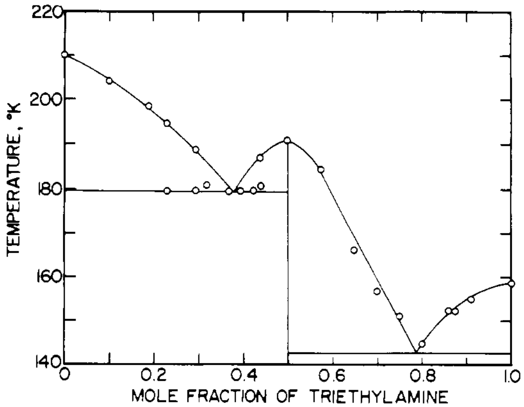

Figure 1. Phase diagram of chloroform and trimethylamine

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