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Dissociation Constants of the Conjugate Acids of Substituted Benzyl Phenyl Ketones and of Alkyl-substituted Benzophenones

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The dissociation constants of the conjugate acids of a number of substituted benzyl phenyl ketones have been measured. Unlike the acetophenone and benzaldehyde series, there is no resonance exaltation of the effective σ -values, and inductive substituent constants (σ^0) are applicable. Similar measurements have also been made on 4-alkyl-substituted benzophenones and 2,6-dimethylbenzophenones. With the benzophenones, $\log K$ values decrease in the order $H > 4-t-C_6H_9 > 4-CH_3$, but the accuracy of measurement with the 2,6-dimethylbenzophenones did not allow detection of the expected effect, on hyperconjugation, of the *ortho* methyl groups.

Stewart and Yates¹ measured the dissociation constants of the conjugate acids of an extensive series of substituted acetophenones,^{1a} benzaldehydes^{1b} and benzoic acids.^{1c} In these reactions *para* substituents, capable of electron-donating resonance interaction with the benzene ring (+M), had considerably exalted effects (their effective Hammett σ -values, $(1/\rho) \log (K/K_0)$, were σ^+ -values). In the present paper we report the dissociation constants of the conjugate acids of substituted benzyl phenyl ketones, a reaction to which σ^0 , the inductive substituent constant,² should apply since direct conjugative interaction between substituent and reaction center is prevented by the interposed methylene group.

In addition, we report the dissociation constants of the conjugate acids of some *para* alkyl-substituted benzophenones and 2,6-dimethylbenzophenones. Ionization of these conjugate acids would be expected to be a highly electron-demanding reaction as found for the acetophenone conjugate acids. For the 2,6-dimethylbenzophenones, extended conjugation between the *p*-substituent and the protonated carbonyl group should be greatly reduced owing to the out-of-plane nature of the carbonyl group,³ and it was thought that examination of these series might yield some indication of the hyperconjugative factor operating in the electron release by alkyl groups⁴ in an electron-demanding reaction.

Experimental and Results

Ketones. *m*-Fluorobenzyl Phenyl Ketone.—Redistilled thionyl chloride (30 ml.) was added to *m*-fluorophenylacetic acid⁶ (15.4 g., 0.1 mole) and the mixture heated under reflux on the steam-bath for 0.75 hr. The excess thionyl chloride was then removed under vacuum and dry (sodium) AnalaR benzene (100 ml.) added. Crushed anhydrous aluminum chloride (16 g., 0.12 mole) was added in small portions to the stirred reaction mixture over 0.75 hr. The mixture was then heated under reflux in the steam-bath for 1 hr. and poured onto a mixture of crushed ice (100 g.) and concentrated hydrochloric acid (40 ml.). The benzene layer was separated and the aqueous layer extracted (2X) with a mixture of benzene (25 ml.) and ether (25 ml.). The combined organic layers were washed successively with water, sodium carbonate solution (2.5%), and water. The solution was

then dried (magnesium sulfate) and distilled under vacuum. The *m*-fluorobenzyl phenyl ketone (17.2 g., 0.08 mole) was obtained as a pale yellow oil, b.p. 167–172° (5 mm.) which subsequently solidified. After recrystallization from methanol, the white crystals had m.p. 47°. *Anal.* Calcd. for $C_{14}H_{11}OF$: C, 78.5; H, 5.2. Found: C, 78.0; H, 5.5.

Similarly were prepared benzyl phenyl ketone, m.p. 56°; *m*-chlorobenzyl phenyl ketone, m.p. 43°; *p*-chlorobenzyl phenyl ketone, m.p. 136.5°; *p*-fluorobenzyl phenyl ketone, 74% yield, white plates (ethanol), m.p. 111° (*Anal.* Calcd. for $C_{14}H_{11}OF$: C, 78.5; H, 5.2. Found: C, 78.0; H, 5.2.; *m*-methylbenzyl phenyl ketone, yield 70%, liquid at room temperature, but recrystallized from methanol using a solid carbon dioxide-acetone bath, then redistilled, b.p. 126° (0.5 mm.), n_D^{25} 1.5865 (*Anal.* Calcd. for $C_{15}H_{14}O$: C, 85.7; H, 6.7. Found: C, 85.4; H, 6.6); *p*-methylbenzyl phenyl ketone, m.p. 95.5°; *m*-nitrobenzyl phenyl ketone, m.p. 82°; *p*-nitrobenzyl phenyl ketone, m.p. 144°. In the case of the nitro ketones the amount of aluminum chloride was raised to 0.22 mole and the solid ketone isolated by steam distilling the excess benzene from the decomposed Friedel-Crafts reaction mixture.

Benzophenone, m.p. 48°, and *p*-methylbenzophenone, m.p. 57°, were commercial samples, recrystallized from methanol and petroleum ether. 4-*t*-Butylbenzophenone,^{6,7} b.p. 189° (4 mm.), m.p. 31.5–35° from ethanol (reduced) to 4-*t*-butylbenzhydrol,⁸ m.p. 82°; 4-*t*-butyl-2,6-dimethylbenzophenone, m.p. 106–106.5°; 2,4,6-trimethylbenzophenone b.p. 136–139° (0.5 mm.), were obtained by conventional Friedel-Crafts procedures. 2,6-Dimethylbenzophenone was prepared in the following manner. 2,6-Dimethylphenylmagnesium iodide from 1 g. of magnesium and 10 g. of 2,6-dimethyliodobenzene,⁸ b.p. 46° (0.2 mm.), n_D^{25} 1.5969, in ether (75 ml.) was slowly added (0.5 hr.) with stirring⁹ to excess benzoyl chloride (9 g.) in dry ether (30 ml.), the reaction mixture being then refluxed for 14 hr. and decomposed by refluxing (0.5 hr.) with 10% acetic acid (70 ml.). The ether layer was separated, combined with ether extracts of the aqueous layer, washed with 5% sodium hydroxide and then with water, dried (magnesium sulfate) and distilled to give unreacted iodoxylylene (1.5 g.) and 2,6-dimethylbenzophenone, b.p. 150–160° (3.5 mm.) (0.55 g., 5% based on initial iodoxylylene). After recrystallization from petroleum ether the white needles had m.p. 64–64.5°. ¹⁰ *Anal.* Calcd. for $C_{15}H_{14}O$: C, 85.68; H, 6.71. Found: C, 85.70; H, 6.75. Contributing to the inherent low yield for this Grignard reaction⁹ was the low yield for the Grignard reagent (28% based on carbonation to give 2,6-dimethylbenzoic acid). The de-*t*-butylation of 4-*t*-butyl-2,6-dimethylbenzophenone used by Hofmann, *et al.*,¹⁰ would seem to be a more acceptable route to 2,6-dimethylbenzophenone.

Sulfuric Acid Solutions.—Fuming sulfuric acid was prepared by distilling sulfur trioxide from commercial 20% fuming acid (1.5 l.) into AnalaR sulfuric acid. The first

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150 ml. of the distillate was rejected and the second 150 ml. collected in 1 l. of the AnalaR acid.¹¹

Sulfuric acid (100.0%) was prepared from the fuming sulfuric acid and AnalaR acid by the "fair and foggy" method.¹¹

Constant boiling sulfuric acid was prepared by adding AnalaR sulfuric acid (2.5 l.) to distilled water (90 ml.) and distilling off 500 ml. The acid remaining in the distilling flask was constant boiling acid of composition 98.5%.¹¹

Standard sulfuric acid solutions of composition 98.5–100% were prepared by weight dilution of the 100% acid, and those of composition less than 98.5% by dilution of the constant boiling acid.

Solutions of 20 (volume %) ethanol–80 (volume %) sulfuric acid–water were made by a method similar to that of Jaffé.¹² Reagent grade 1,4-dioxane was refluxed over sodium and fractionated; b.p. 101° (760 mm.).

Dissociation constants were obtained by the method of Davis¹³ and Geissman using the H_0 values of Paul and Long.¹⁴ Optical densities were measured with a Hilger Uvispek spectrophotometer fitted with a water-jacketed cell holder. The cell and contents were maintained at 25.0 ± 0.2°.

Solutions of ketone (8–12 μ moles l.⁻¹) in aqueous sulfuric acid (ca. 15 ml.) were prepared by weight. The small amounts of ketones required were obtained by weighing out 0.1–0.15-ml. samples of standard solution of the ketone (ca. 5 mg.) in dioxane (ca. 20 g.). The dioxane was then removed under vacuum and the sulfuric acid added. Molar concentrations of the ketone solutions were evaluated from the molar concentrations and the densities of the sulfuric acid solutions at 25°, obtained, by interpolation, from the density-composition data listed in the "International Critical Tables." For each ketone, optical densities (4-cm. cells, acid solution used as blank) of a range of acid solutions in which the ketone was "completely" non-protonated, partially protonated and "completely" protonated were measured at wave lengths ($m\mu$) 249, 250.5, 252, 253.5, 255, 256.5, 258, 289, 290.5, 292, 293.5, 295, 296.5, 298; λ_{max} for (unprotonated) benzyl phenyl ketone in 50% acid was 249 $m\mu$ and for the protonated ketone, in 95% acid, it was 298 $m\mu$. The first set of seven wave lengths above correspond to the carbonyl peak and the second set to the protonated carbonyl peak. For each ketone plots were made of ($\epsilon_{289} - \epsilon_{249}$) vs. H_0 , ($\epsilon_{290.5} - \epsilon_{250.5}$) vs. H_0 etc., and the inflection point of each curve determined by the graphical method in which the approximately linear plots at the beginning and end of the sigmoid curve are extended to meet the straight line which takes in the approximately linear portion about the inflection point. This point was then taken as the point mid-way between the two intersections of the three straight lines. The value of H_0 at the inflection point is the pK . Wave lengths used for the benzophenones were those at λ_{max} for the unprotonated ketone, λ_{max} for the protonated ketone, together with wave lengths 5 $m\mu$ either side of these values.

Results for substituted benzyl phenyl ketones are given in Table I and for substituted benzophenones in Table II.

TABLE I
LOG K_a VALUES OF CONJUGATE ACIDS OF X-BENZYL PHENYL KETONES AT 25°^a

Wave length pairs, $m\mu$	p .	m .		p .	p .	m .	m .	m .
	CH ₃	CH ₃	H	F	Cl	F	Cl	NO ₂
249, 289	6.77	6.80	6.85	6.96	6.98	6.98	7.01	7.29
250.5, 290.5	6.80	6.82	6.87	6.99	7.01	7.01	7.04	7.33
252, 292	6.82	6.86	6.89	7.02	7.04	7.04	7.07	7.35
253.5, 293.5	6.87	6.89	6.91	7.04	7.07	7.06	7.12	7.39
255, 295	6.89	6.92	6.94	7.07	7.10	7.09	7.15	7.43
256.5, 296.5	6.92	6.96	6.98	7.10	7.13	7.12	7.18	7.46
258, 298	6.95	6.98	7.01	7.12	7.15	7.16	7.20	7.50
Mean	6.86	6.89	6.92	7.04	7.07	7.07	7.11	7.39

^a Relative log K values are estimated to be accurate to ±0.06 unit.

m-Methylbenzyl phenyl ketone (which would be expected to be the most activated of the benzyl phenyl ketones toward electrophilic substitution), 2,4,6-trimethylbenzophenone, and 4-*t*-butyl-2,6-dimethylbenzophenone underwent reac-

tion, presumably deacylation and/or sulfonation, at "high" acid concentrations (>95%, >75%, >65% sulfuric acid, respectively). The extinction coefficients of these solutions were obtained by (linear) extrapolation, to zero time, of plots of optical density versus time.

p-Nitrobenzyl phenyl ketone proved to be too insoluble in acid solutions in which it is "completely" non-protonated for the Geissman method to be applied. For 2,4,6-trimethylbenzophenone (in <60% sulfuric acid) and 4-*t*-butyl-2,6-dimethylbenzophenone (in <80% acid), the dioxane standard solution was weighed directly into the sulfuric acid-water solvent to ensure complete solution, the concentration of dioxane being less than 0.1% by weight. Equivalent amounts of dioxane were added to the solvent blank. 4-*t*-Butyl-2,6-dimethylbenzophenone proved insufficiently soluble in <70% sulfuric acid, recourse being made to the 20 volume % ethanol–80 volume % sulfuric acid solvent used by Jaffé.¹² Optical densities in this solvent were necessary only to define the "unprotonated line" for the Geissman plot where the ketone is less than 5% protonated.

The nitro ketones showed no change in extinction coefficient in the 350 $m\mu$ region (where the protonated nitrophenyl group absorbs¹⁵) as the acid solution was varied from 98.5% ($-H_0 = 9.54$) through to 99.5% ($-H_0 = 10.03$). This indicates that, at these acid concentrations, there is no significant protonation of the nitro group in these ketones, presumably because of the deactivating influence of the protonated carbonyl group.

Our mean dissociation constant for the conjugate acid of benzophenone (log K 6.1₈) is in agreement with the value reported earlier¹⁶ (log K 6.0) when the latter figure is corrected for the revision in the H_0 scale¹⁴ by the addition of 0.12 unit to the log K value.

Discussion of Results

Benzyl Phenyl Ketones.—For each pair of wave lengths the dissociation constants of benzyl phenyl ketones were fitted to the Hammett equation in the form $\log K = \rho\sigma^0 + \log K_0$. It is noteworthy that whereas there is a rather large variation in individual log K values with wave length, the derived ρ -values vary only slightly, ranging from +0.57 (for wave lengths 249, 289, $m\mu$) to +0.61 (258, 298 $m\mu$). The mean ρ is +0.59. The range of variation of ρ with wave length is equivalent to a maximum variation (for the *m*-nitro compound) of 0.03 (= 0.04 × 0.70) in log K . In contrast, the range of variation of the experimental log K values is 0.21. Thus in spite of the rather large variation of the dissociation constants the mean reaction constant does provide an accurate measure of the susceptibility of the dissociation reaction to substituent effects.

The variation of log K with wave length may be in part a result of evaluating the log K values from optical densities at a set of fixed wave lengths, rather than at similar positions in the spectrum of each of the compounds. However, in general the spectra of the "completely" unprotonated benzyl phenyl ketones were closely similar; this was also the case with the series of conjugate acids. Only for the nitro compounds were there noteworthy differences in the spectra. Thus for *p*-nitrobenzyl phenyl ketone λ_{max} was shifted to 254 $m\mu$ (in 55% acid), and for its conjugate acid to 305 $m\mu$ (99.5% acid).

For the dissociation of the conjugate acids of acetophenones,^{1a} ρ (+2.17) is considerably greater than that for benzyl phenyl ketones (+0.59). The interposition of the methylene group between the reaction center and aromatic ring makes the

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TABLE II

LOG K_a VALUES OF CONJUGATE ACIDS OF ALKYL-BENZOPHENONES AT 25°						
H	4-CH ₃	4-C(CH ₃) ₂	2,6-(CH ₃) ₂	2,4,6-(CH ₃) ₃	4- <i>t</i> -Bu-2,6-(CH ₃) ₂	
6.09	($\frac{335}{255}$) ^a	5.78 ($\frac{355}{270}$)	5.97 ($\frac{355}{270}$)	6.31 ($\frac{295}{255}$)	5.88 ($\frac{295}{255}$)	6.14 ($\frac{295}{255}$)
6.20	($\frac{340}{260}$) ^b	5.93 ($\frac{360}{275}$)	6.02 ($\frac{360}{275}$)	6.56 ($\frac{300}{260}$)	6.20 ($\frac{300}{260}$)	6.35 ($\frac{300}{260}$)
6.25	($\frac{345}{265}$)	6.03 ($\frac{365}{280}$)	6.08 ($\frac{365}{280}$)	6.74 ($\frac{305}{265}$)	6.38 ($\frac{305}{265}$)	6.58 ($\frac{305}{265}$)
Mean	6.18	5.91	6.02	6.57	6.15	6.36

^a Wave length pairs, (m μ). ^b Wave length pairs in this row are λ_{\max} values.

reaction less sensitive to the polar effects of substituents because such effects must now be relayed through an additional bond. Similarly, ρ for ionization of phenylacetic acids¹⁷ (+0.47) is substantially smaller than that for benzoic acids (+1.00). As expected, in the dissociation of the conjugate acids of benzyl phenyl ketones, the σ -values for *p*-substituents show no resonance exaltation. In contrast, dissociation constants of the conjugate acids of acetophenones (and benzaldehydes) correlate well with σ^+ -values.¹

Benzophenones.—Variation of dissociation constant with wave length for the *p*-alkylbenzophenones is of similar order to that found for the benzyl phenyl ketones and relative log K values may have an accuracy close to that estimated for the latter ketones. Despite the variation with wave length, the results indicate an expected "hyperconjugative order" (log $K = H > 4-t$ -butyl $>$ 4-methyl) for each set of wave lengths which are similarly related to the λ_{\max} values for the ketone and the conjugate acid at the 1% and 99% protonated levels, respectively.

A much larger variation of dissociation constant with wave length is found with the 4-alkyl-2,6-dimethylbenzophenone series, a variation of magnitude precluding the placing of any significance on the "hyperconjugation order" found with each wave length set.

Absolute log K Values.—If there is no opportunity for the operation of the conjugative mechanism, a phenyl substituent is weakly electron withdrawing. For this reason it would be anticipated that benzyl phenyl ketone should be a weaker

base than acetophenone. The steric effect of the substituted phenyl group (presumably steric inhibition of solvation and possibly steric inhibition of the phenylcarbonyl conjugation) and the loss of some of the greater hyperconjugative stabilization of the protonated carbonyl group should lead to the same effect. Thus log K for the conjugate acid of benzyl phenyl ketone (6.9) is greater than that for acetophenone (6.15).^{1a,14,18} Replacement of the methyl group of acetophenone by the greater (conjugatively) electron-donating phenyl group should increase the basicity of the ketone. In fact, log K for the conjugate acid of benzophenone (6.2) is approximately the same as that of acetophenone. It is likely, therefore, that either or both of the base-weakening effects, *viz.* steric inhibition of mesomerism and steric inhibition of solvation, are present in the benzophenone system.

The large "ortho-effect" reflected in the increase in log K from benzophenone to 2,6-dimethylbenzophenone (6.6) supports the ultraviolet evidence³ that conjugation is decreased on substitution of the two *o*-methyl groups in benzophenone. That the difference found is less than that for the acetophenones (acetophenone log $K = 6.15$, 2,6-dimethylacetophenone log $K = 7.9$ ¹⁹ using the revised H_0 scale¹⁴) is evidence for a leveling effect caused by a second conjugated ring in the benzophenones.

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