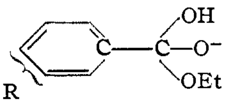
terms in the above equation can be defined from the structure of the intermediate ionic complex involved in the saponification.



The charge on the reactive ester function is represented by e_ρ, the charge induced by the group R on the nuclear carbon holding the functional group by e_σ. The distance separating these two charges in the transition complex is r and the effective dielectric between them is D.

If the PZ factors for the rates with and without a substituent R are the same and if the only additional factor in the energy of activation is the simple coulombic interaction described in the added electrical potential term involving the charges e_σ and e_ρ, then Hammett's equation will be an accurate estimate of the charge e_σ. In fact, under these circumstances, Hammett's σ-value will be directly related to the magnitude of this charge.

However, if any other important energy factor differs in going from unsubstituted to substituted benzene reactant, then the σ-value calculated from Hammett's equation will not be an accurate representation of e_σ. It is suggested that this may be the explanation of the anomalous values for the *t*-butyl group. In the process whereby saponification occurs, a neutral ester molecule is converted to a negatively charged transition complex. In a polar solvent such as aqueous acetone, the charged transition complex will be appreciably stabilized by solvation and, to whatever extent this stabilization can occur, the activation energy will be decreased. Replacing a methyl group by a *t*-butyl group on the ring, *even in the para position*, will prevent solvent dipoles from orienting in this region and will thus, to a greater or lesser degree, decrease the solvation energy. This will in effect further increase the activation energy, already raised by the negative e_σ induced by the alkyl group, and will therefore give a σ-value disproportionately more negative than e_σ. As expected for such an effect, it is evidently of considerably greater magnitude in the meta position, closer to the polar reactive center. This is apparent from the much greater difference between methyl and *t*-butyl in the meta position as compared to the para (Tables II and III).

It is suggested that this sort of steric effect on solvation energy, which is quite distinct from the direct steric influences commonly recognized, be distinguished from these usual steric effects by the name "bulk effect."

It is perhaps appropriate to point out that the similar influence of *t*-butyl and neopentyl groups on the rates of bromination of alkyl benzenes, quite unexpected on the basis of hyperconjugation effects,[14] is not nearly so surprising if one of the important effects of varying alkyl groups is a "bulk effect" on the solvation stabilization of the polar transition complex for the bromination process.

(14) Berliner and Berliner, THIS JOURNAL, **71**, 1195 (1949).

NOTRE DAME, INDIANA RECEIVED MARCH 22, 1950

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF NOTRE DAME]

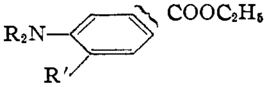
The Rates of Saponification of Some Ortho-substituted Ethyl *m*- and *p*-Aminobenzoates

BY CHARLES C. PRICE AND DWIGHT C. LINCOLN[1,2]

Steric inhibition of resonance between a dimethylamino group and a benzene ring has been measured by studying the rates of saponification of ethyl 3-dimethylamino-4-methylbenzoate and 4-dimethylamino-3-methylbenzoate. The inhibition of resonance by one ortho-methyl group markedly affects the electrical influence of the dimethylamino group in either the para or meta position to the reactive ester group, although quantitatively the influence is greater in the para position. A second order inductive or field effect is necessary to account for such a resonance influence on the meta position.

Westheimer and Metcalf[3] have shown that the influence of a dimethylamino group markedly decreasing the rate of saponification of an ethyl ester in the para position is almost completely damped by the presence of two methyl groups flanking the dimethylamino group. This evidence was interpreted as indicating a marked steric inhibition by the two *ortho*-methyl groups of resonance donation of electrons by the dimethylamino group to the para (and ortho) positions of the ring.

The purpose of the work reported herein was to use the same general experimental measurement, the rate of saponification, to estimate the effect of damped resonance on the position meta as well as para to the dimethylamino group. In order to avoid direct steric effects from a substituent ortho to the carbethoxyl group, it was possible to incorporate only one ortho-methyl group to hinder the amino group.



R and R′ = H or CH_3

Experimental[4]

***m*-Dimethylaminobenzoic acid** was prepared through methylation of the amino acid to the hydriodide of trimethyl-*m*-benzobetaine, pyrolysis to the dimethylamino methyl ester followed by saponification, essentially according to the directions of Cumming.[5] The product melted at 150.5–151.3° (lit.[5] m.p. 151°).

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(1) Eastman Kodak Fellow, 1947–1948. Hercules Powder Company, Wilmington, Delaware.

(2) Abstracted from a portion of the Ph.D. dissertation submitted to the University of Notre Dame by Dwight C. Lincoln.

(3) Westheimer and Metcalf, THIS JOURNAL, **63**, 1339 (1941).

(4) Melting points are corrected. Analyses by Micro-Tech Laboratories, Skokie, Ill.

(5) Cumming, *Proc. Roy. Soc.* (*London*), **A78**, 103 (1906).

***p*-Dimethylaminobenzoic acid** was prepared by methylation of the amino acid according to Willstätter and Kahn.[6] It formed heavy white needles, m.p. 237–238° (lit.[6b] m.p.'s from 234 to 240°).

3-Amino-4-methylbenzoic acid was prepared from *p*-toluic acid by nitration[7] and reduction,[8] m.p. 163–163.5° (lit.[9] 164–165°).

3-Dimethylamino-4-methylbenzoic acid was prepared from the preceding acid by methylation with methyl sulfate. In a 1-l. round-bottomed flask equipped with stirrer, dropping funnel and air condenser were placed 150 ml. of water and 41.0 g. (0.272 mole) of 3-amino-*p*-toluic acid and the mixture was stirred to a uniform slurry. To the stirred mixture, 137 g. (103 ml., 1.09 moles) of dimethyl sulfate was added in four portions, each portion being added dropwise over a period of 30 minutes and being followed by neutralization with an exactly equivalent quantity of concentrated potassium carbonate solution. After the final addition, the solution was stirred for one-half hour and then made strongly ammoniacal to destroy any unreacted dimethyl sulfate. The ammoniacal solution was extracted with ether to remove base-insoluble materials and the layers were further treated as follows.

Aqueous Layer.—The aqueous solution was boiled with decolorizing charcoal, filtered, cooled and barely acidified with acetic acid. The clear acidic solution was extracted with several portions of ether and the combined ether extracts were evaporated to dryness to yield 14.0 g. of slightly yellow needles. This product was further purified by recrystallization from "Skellysolve L" and from cyclohexane, giving fine white needles melting at 124.0–126.0°.

Ether Layer.—The ether extract was evaporated and the oily residue was refluxed for one hour with 150 ml. of 6 *N* hydrochloric acid. The resulting clear solution was then made basic with potassium carbonate, extracted with ether and the ether discarded. The aqueous solution was treated in exactly the same manner as the aqueous layer described above and yielded 16.0 g. of product which proved to be identical with the product obtained above.

The two portions were combined and, after two more recrystallizations from "Skellysolve L" and two from cyclohexane, employing decolorizing charcoal in each case, there was obtained fine white needles melting at 125.6–126.6°. A neutralization equivalent obtained by titration with sodium hydroxide solution to a phenolphthalein end-point gave an equivalent weight of 178 compared with the value of 179 calculated for 3-dimethylamino-*p*-toluic acid.

Anal. Calcd. for $C_{10}H_{13}O_2N$: C, 67.02; H, 7.31; N, 7.82. Found: C, 66.90; H. 7.33; N, 7.77.

4-Dimethylamino-3-methylbenzoic Acid.—N,N-Dimethyl-4-bromo-*o*-toluidine, b.p. 105–107° (7 mm.); $n^{20}D$ 1.5645 (lit.[10] b.p. 246°), was prepared by bromination of acet-*o*-toluidide, hydrolysis and methylation with methyl sulfate.

Lithium metal was cut into thin slices and 3.1 g. (0.44 mole) was placed along with 70 ml. of dry ether into a 1-l., three-necked flask equipped with a mercury-sealed stirrer, reflux condenser, and dropping funnel. As the mixture was stirred vigorously, 42.8 g. (0.2 mole) of N,N-dimethyl-4-bromo-*o*-toluidine was added dropwise at such a rate as to maintain gentle refluxing. Following the final addition, the mixture was stirred for four hours and then poured onto a large excess of pulverized Dry Ice with vigorous stirring. After evaporation of the Dry Ice, water was added, the mixture was just acidified with dilute hydrochloric acid and extracted several times with ether. The combined ether extracts were extracted with saturated sodium carbonate solution and the resulting aqueous layer was boiled with decolorizing charcoal, filtered, cooled and barely acidified with dilute hydrochloric acid. The light tan granular precipitate was filtered, washed with water, and dried in air to yield 8.3 g. (22%) of a product melting at 129–130°. Upon recrystallization from "Skellysolve L," it formed white monoclinic crystals, and from hot water containing a little ethanol it came down in the form of white scales melting at 131.0–131.6°.

Anal. Calcd. for $C_{10}H_{13}O_2N$: C, 67.02; H, 7.31; N, 7.82. Found: C, 67.10; H, 7.20; N, 7.94.

Ethyl esters were prepared by Fischer esterification and purified by fractional distillation under reduced pressure through a 90 × 1.2 cm. column containing three 25-cm. sections of double glass spiral surrounded by an electrically heated jacket. Large foreruns and residues were discarded, close-boiling center fractions being taken for the kinetic measurements. The properties of the esters are summarized in Table I.

Ethyl *p*-dimethylaminobenzoate crystallized after one distillation and was further purified by recrystallization from aqueous ethanol, m.p. 63.5–64° (lit.[3] 63–63.5°).

TABLE I

PHYSICAL PROPERTIES OF SUBSTITUTED ETHYL BENZOATES

Substituent	Boiling point °C.	Mm.	$n^{20}D$
m-$N(CH_3)_2$	124.5 ± 0.3	3.0	1.5475
3-NH_2-4-CH_3[a]	154.6–155	6.0	[a]
3-$N(CH_3)_2$-4-CH_3[b]	98.0 ± 0.5	0.8	1.5270
4-$N(CH_3)_2$-3-CH_3[c]	156.0 ± 0.3	12	1.5438

[a] M.p. 48.6–50.1°. *Anal.* Calcd. for $C_{10}H_{13}O_2N$: C, 67.02; H, 7.31; N, 7.82. Found: C, 67.22; H, 7.31; N, 7.88. [b] *Anal.* Calcd. for $C_{12}H_{17}O_2N$: C, 69.54; H, 8.27; N, 6.76. Found: C, 69.60; H, 8.17; N, 6.58. [c] Found: C, 69.60; H, 8.20; N, 6.61.

The rate measurements and the calculation of the rate constants and the σ values were carried out as described in the previous communication.[11] The results are summarized in Table II.

Discussion

In discussing the nature of the electrical effects capable of influencing reactive groups on the benzene ring (or any double bond or conjugate system of double bonds) it seems clear that there are two different types of effects which must be considered. One is a type of effect which is present even in saturated compounds and which decreases steadily with the separation of the reactive group from the polar or dipolar substituent. One theory as to the nature of this effect has been described in terms of the so-called "inductive" effect. On the basis of this explanation, a portion of the charge on any particular carbon atom, by influencing the electron affinity of that atom, allows a portion of that charge to be passed on to adjoining atoms by influencing the degree of sharing of electrons in the covalent bonds to adjoining atoms. It has been proposed that this effect damps out exponentially as the number of bonds through which it is passed increases.

An alternate explanation for a similar type of steadily decreasing effect is by direct electrostatic interaction between polar or dipolar charges in the reactive group with polar or dipolar charges in a substituent group elsewhere in the reactant molecule. For many years this theory had been considered only with considerable reservation because the two approximations utilized for estimating its magnitude either ignored the dielectric medium entirely or greatly overemphasized it. Recently Kirkwood and Westheimer[12] have developed equations

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[6] (a) Willstätter and Kahn, *Ber.*, **37**, 411 (1904); (b) Bischoff, *ibid.*, **22**, 341 (1889); Michler, *ibid.*, **9**, 40 (1876); Houben and Schottmuller, *ibid.*, **42**, 3736 (1909).

[7] Kloeppel, *ibid.*, **26**, 1733 (1893).

[8] Jacobs and Heidelberger, THIS JOURNAL, **39**, 1435 (1917).

[9] Kunckell, *Chem. Zentr.*, **83**, I, 136 (1912).

[10] Fries, *Ann.*, **346**, 201 (1906).

[11] Price and Lincoln, THIS JOURNAL, **73**, 5836 (1951).

[12] (a) Kirkwood and Westheimer, *J. Chem. Phys.*, **6**, 506 (1938); (b) Westheimer and Shookoff, THIS JOURNAL, **61**, 555 (1939); Westheimer, *ibid.*, **61**, 1977 (1939); (c) Westheimer and Shookoff, *ibid.*, **62**, 269 (1940); Westheimer, *ibid.*, **62**, 1893 (1940).

TABLE II

RATE CONSTANTS, ACTIVATION ENERGY, *PZ* VALUES AND σ-VALUES[a] FOR SAPONIFICATION OF SOME SUBSTITUTED ETHYL BENZOATES

Substituent	$k_{25} \times 10^3$	$k_{40} \times 10^3$	ΔH_{act}, kcal./mole	log *PZ*	σ[a]
3-$N(CH_3)_2$	1.27 ± 0.01	3.97 ± 0.04	14.06 ± 0.25	7.41 ± 0.18	−0.160
4-$N(CH_3)_2$	0.060 ± 0.0006	0.236 ± 0.0024	16.92 ± .25	8.18 ± .18	− .720
3-NH_2-4-CH_3	0.91 ± 0.01	2.90 ± 0.03	14.32 ± .25	7.47 ± .18	− .222
3-$N(CH_3)_2$-4-CH_3	1.10 ± 0.02	3.42 ± 0.03	14.07 ± .25	7.36 ± .18	− .188
4-$N(CH_3)_2$-3-CH_3	0.428 ± 0.004	1.37 ± 0.14	14.39 ± .25	7.18 ± .18	− .360

[a] $\sigma = (\log k_{25} + 2.513)/2.373$ (Hammett, "Physical Organic Chemistry," McGraw-Hill, Book Co., Inc., New York, N. Y., 1940).

for correcting the dielectric constant of the solvent for the low-dielectric of the "hole" created by the reactant molecules. Using these equations Westheimer has shown that by simple electrostatic influence alone one can make reasonably satisfactory approximations for the influence of dipolar substituents on the dissociation constants of paraffinic and aromatic acids[12b] and on the saponification constants of esters.[12c]

No experimental procedure for distinguishing these two influences has been suggested. The calculations of Westheimer at least suggest that the simple electrostatic (or "field") effect must be important. How important the "inductive" effect may be in supplementing the "field" effect does not seem readily ascertainable.

In olefins, conjugate olefins and aromatic systems, it is necessary to consider a second type of effect, superimposed on the first, which has the character of alternating the polarity of atoms in the conjugate system. For example, although a methyl group should decrease and a nitro group increase the dissociation constant of benzoic acid by a simple "field" or inductive effect, this type of effect alone would certainly predict that the influence of the methyl or nitro group should, because of the shorter distance, be larger in the meta than in the para position, quite contrary to the experimental facts.

Again there seem to be two different theories able to account qualitatively for these and related observations. The well-established concept of resonance interaction (or "mesomerism") involves an overlap of electron orbitals between the substituent and the olefin, conjugated olefin or aromatic system and a shift of electrons in this hybridized orbital either to or from the substituent group. This shift of electrons involves decreasing or increasing the electron density on alternate carbon atoms in a conjugate or aromatic system (see Figs. 1 and 2). This type of interaction involves double bond character between the substituent and the unsaturated system and generates a dipole moment between the unsaturated system and the substituent.

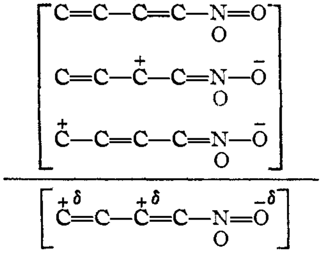

Fig. 1

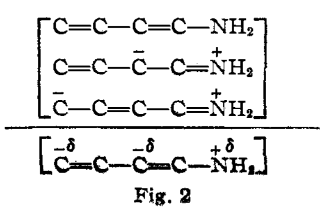

Fig. 2

Alternatively (or complementarily), it has been suggested[13] that a similar type of influence may be generated in an unsaturated system through electrical polarization of the unsaturation electrons by poles or dipoles in the substituent (see Fig. 3). In Figs. 1, 2 and 3, the fractional charges indicated by ±δ are of course not necessarily equal.

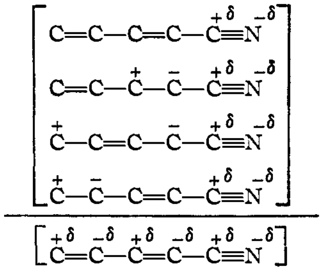

Fig. 3.

This type of effect involves no double bond character between the substituent and the unsaturated system but does generate a dipole moment within the unsaturated system.

When the unsaturated system is the benzene ring, information concerning the total electrical effect of a substituent group may be derived from a study of a reactive group in the meta or para position. The difference between effects in the meta and para positions may give some indication of the second type ("mesomeric" or "electrical polarization") effect, although this interpretation is accurate only if the "field" and "inductive" effects do not vary appreciably for the meta and para positions. Further, if we may take the meta–para difference as an approximate indication of the sum of the "mesomeric" and "electrical polarization" effects, we may derive further information on the relative magnitudes of these two factors since the former requires double bond character between the unsaturated system and the substituent and is therefore sensitive to steric inhibition.

Westheimer and Metcalf[8] have already shown that the influence of a dimethylamino group on the

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(13) C. C. Price, *Chem. Revs.*, **29**, 37 (1941); THIS JOURNAL, **73**, 5833 (1951).

rate of saponification of an ester group in the para position is markedly reduced when the dimethylamino group is flanked by a methyl group on each side. This is unquestionably properly interpreted as the result of steric inhibition by the two ortho methyl groups of resonance donation of electrons to the ring.

It seemed of interest, however, to extend the investigation to ascertain the nature of the steric inhibition of resonance on the position meta to the dimethylamino group, since this position is not subject to any direct influence by a resonance effect. In order to accomplish this without having a substituent ortho to the reactive ester group, it was necessary to use only one hindering methyl group, even though this would decrease the effectiveness of the hindering.

If we compare the $\Delta \log k$ resulting from the introduction of the *p*-dimethylamino group in ethyl benzoate ($\Delta \log k = \log k_S/k_H = -1.53$[3]) and in ethyl 3,5-dimethylbenzoate ($\Delta \log k = -0.26$)[3] with that for its introduction into *m*-toluate ($\Delta \log k = -0.61$), it is evident that the single methyl group is effective but not as effective as two.

The over-all negative electrical effect of the *m*-dimethylamino group ($\sigma = -0.161$) cannot be ascribed directly to any of the four basic electrical effects between a substituent and an unsaturated system. The inductive, field and electrical polarization effects all predict small positive values for σ, the resonance effect cannot directly influence the meta position. However, the negative value may be a second-order field effect, arising from the negative charges placed on the adjoining ortho and para carbon atoms by resonance. One could also account for a resonance influence to the meta position as an inductive effect sharing with the intermediate meta atoms charge placed on the ortho and para carbon atoms by resonance.

An approximate comparison of the influence of the ortho-methyl group on the electrical effect of the dimethylamino group may be obtained by subtracting the σ-constant of the methyl group from the σ-constant for the doubly-substituted esters. If we subtract the σ-value for a meta-methyl group, $\sigma = -0.102$, from that for the 4-dimethylamino-3-methylbenzoate, $\sigma = -0.360$, the contribution of the *p*-dimethylamino group in the latter corresponds to $\sigma = -0.258$, much less than the unhindered value, $\sigma = -0.720$. For the hindered *m*-dimethylamino group, the contribution corresponds to $\sigma = -0.188 (-0.170) = -0.018$, considerably less than the unhindered value, $\sigma = -0.160$.

NOTRE DAME, INDIANA RECEIVED MARCH 22, 1950

[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

The Diacylation of Amides by Acyl Chloride–Pyridine Compounds

BY QUENTIN E. THOMPSON

A novel acylation of amides has been reported in which amides of the type $RCONH_2$ react with two molecules of acyl chloride–pyridine addition compound at low temperatures to give the corresponding triacylated ammonias in good yields. Evidence is presented which indicates that this acylation is a true "diacylation" and does not involve the intermediate formation of a secondary amide. Some fourteen amides have been diacylated in this manner. Seventeen acid chlorides have been investigated to determine their relative ability to diacylate amides. Using acetamide as a standard amide, diacylation occurred with the following acid chlorides in order of increasing yield: cinnamoyl, anisoyl < *p*-toluyl, 3-methoxybenzoyl < 2-naphthoyl, 4-bromobenzoyl, benzoyl, diphenylacetyl, 4-chlorobenzoyl, 4-iodobenzoyl and 3-bromobenzoyl. Of the remaining six acid chlorides, 2-furoyl, propionyl and isocaproyl chlorides gave monoacylation while ortho-, meta- and para-nitrobenzoyl chlorides gave dehydration of the amide as the principal reaction.

A recent paper[1] from this Laboratory has described the preparation of anhydrides and diacyl sulfides by the diacylation of water and hydrogen sulfide by acyl chloride–pyridine compounds. The reaction unexpectedly appeared to be a one-step acylation without the intermediate formation of the acid. Minnuni,[2] who discovered the diacylation reaction with water, suggested without supporting evidence, a mechanism which was in effect termolecular. In the present paper, the extension of the diacylation reaction to some compounds of the ammonia system is reported and evidence supporting the premise of a one-step diacylation mechanism is presented.

Certain acyl chloride–pyridine compounds were found to diacylate primary amides (*i.e.* $RCONH_2$) very readily to give good yields of the corresponding tertiary amides. In all, the reactions between seventeen acid chlorides and some twenty-three amides have been investigated. Generally, it was found that any or all of the following reactions could occur: (a) diacylation (b) monoacylation, and (c) dehydration of the amide to a nitrile. The factors determining the reaction or reactions occurring were the experimental conditions, the effect of substituents on the acyl–chlorine bond and to a lesser extent, the structure of the amide being acylated.

$$RCONH_2 + 2R'COCl\cdot C_5H_5H \longrightarrow RCO(COR')_2 + 2C_5H_5N\cdot HCl$$

A striking characteristic of these diacylation reactions was the remarkable facility with which they occurred at low temperatures. For example, optimum conditions for the preparation of tribenzamide involved the reaction of essentially equivalent quantities of benzoyl chloride and pyridine with one equivalent (one-half mole) of benzamide in a chloroform solution at temperatures around −60°. The diacylation of acetamide by such powerful diacylating agents as diphenylacetyl chloride, 3-bromobenzoyl chloride or 4-bromobenzoyl chloride occurred most readily in more dilute solutions and at even lower temperatures. Low tempera-

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(1) H. Adkins and Q. E. Thompson, THIS JOURNAL, **71**, 2242 (1949).

(2) G. Minunni, *Gazz. chim. ital.*, **22**, 213 (1892).