from one another to avoid interaction with the solvent or other reacting molecules. This has been accomplished in gas-phase reactions. $\sigma_o{}^0$ substituent constants obtained in the gas-phase pyrolysis of isopropyl benzoates[2] correlate very well with other polar *ortho*-substituent constants obtained from Davis and Hetzer's work on the reaction of benzoic acid with 1,3-diphenylguanidine in benzene.[24] This correlation is shown in Figure 6.

As solvent molecules apparently play a major role in proximity effects, it is not surprising that *ortho*-substituent effects in one gas-phase reaction correlate with *ortho*-substituent effects in another, particularly if the reactions both utilize a similar pathway. Unimolecular gas phase reactions correlated by σ^+ substituent constants, therefore, afford an approach to establishing σ^+ substituent constants for *ortho* substituents free from solvent participation and, of course, primary steric effects. Apparently the secondary steric effects for such reactions are negligible or similar and cancel out. Earlier studies[17a] showed that two methyl groups, flanking a *p*-methoxy substituent, exhibited steric inhibition of resonance in the gas-phase pyrolysis of 1-arylethyl acetates.

The general applicability of these *ortho*-substituent constants will be shown as other similar systems are studied where different bonds are broken such as in the thermolysis of 1-arylethyl methyl xanthates, amine oxides, and β-hydroxy olefins ($CH_2{=}C(Ar)CH_2CH_2OH$, $ArCHOHCH_2CH{=}CH_2$).

Strong support has already been obtained for these *ortho*-substituent constants in an electron-impact study of substituted benzophenones. Mass spectral data for *ortho*-, *meta*-, and *para*-substituted benzophenones, log (Z/Z_0) ($Z = [C_6H_5CO^+]/[XC_6H_4COC_6H_5{}^+]$, $Z_0 = [C_6H_5CO^+]/2X[C_6H_5COC_6H_5{}^+]$) were plotted *vs.* σ^+ constants for *meta* and *para* substituents, and for the *ortho* σ^+ constants reported from this study. The correlation coefficient in this study, which is reported elsewhere,[25] is 0.984.

Acknowledgment.—This work was supported in part by two National Science Foundation Grants, GP 2940 and GP 6006. Grateful acknowledgment is given for this support.

---

[24] M. M. Davis and H. B. Hetzer, *J. Res. Natl. Bur. Std.*, **60**, 569 (1958).

[25] K. K. Lum and G. G. Smith, *J. Org. Chem.*, **34**, 2095 (1969).

Linear Free-Energy Relationship Involving *ortho* Substituents in Mass Spectrometry

KIN K. LUM AND GRANT GILL SMITH

Department of Chemistry, Utah State University, Logan, Utah 84321

Received November 12, 1968

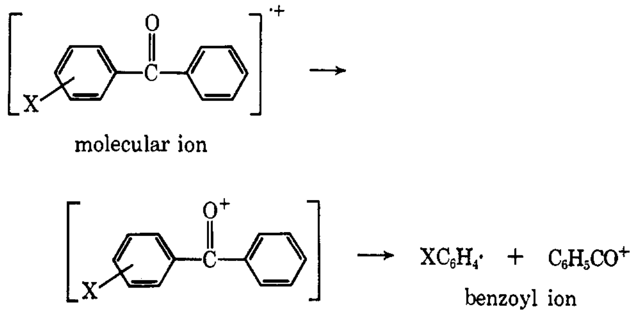
A linear free-energy relationship involving *ortho* substituents has been found between the benzoyl ion intensities in the mass spectra of substituted benzophenones and σ^+ substituent constants. This good correlation indicates that proximity effects are equivalent or negligible in gas-phase electron-impact reactions of benzophenones.

The evaluation of *ortho* σ^0 [1] and σ^+ constants[2] has been carried out in this laboratory by studying the gas-phase pyrolysis of esters which is a unimolecular, homogeneous reaction. The correlation of the $\sigma_o{}^0$ constants with the ion-pair formation of benzoic acid in benzene[3] is remarkable.[2] The present study was designed to test whether $\sigma_o{}^+$ constants previously obtained from kinetic data of pyrolysis of various esters[2] could be correlated in another gas-phase reaction which is unimolecular and homogeneous.

Mass spectrometry provides a system for this purpose. Lossing, *et al.*,[4] have shown that the ionization potentials of benzyl radicals, eq 1, can be correlated in a linear free-energy relationship involving σ^+ substituent

$$XC_6H_4CH_2I \xrightarrow{\Delta} XC_6H_4CH_2\cdot \xrightarrow{e^-} XC_6H_4CH_2{}^+ + 2e^- \quad (1)$$

constants. They limited their study to *meta* and *para* substituents. McLafferty, *et al.*,[5] have investigated substituent effects in benzophenones and acetophenones by studying the ratio of ion intensities in mass spectrometry. They also limited their study to *meta* and *para* substituents. In the present investigation the method of McLafferty, *et al.*, of correlating relative ion intensities with σ^+ substituent constants was adopted. Mass spectral data for *ortho*-, *meta*-, and *para*-substituted benzophenones, log (Z/Z_0), ($Z = [C_6H_5CO^+]/[XC_6H_4COC_6H_5{}^+]$, $Z_0 = [C_6H_5CO^+]/2[C_6H_5COC_6H_5{}^+]$) were plotted *vs.* σ^+ constants for *meta* and *para* substituents, and the recently reported *ortho* σ^+ constants were determined from pyrolysis of esters.[2]



Experimental Section

Preparation of Benzophenones.—Substituted benzophenones commercially available were recrystallized two or three times from spectral grade methanol or fractionally redistilled at reduced pressure. *o*-Hydroxy, *m*-chloro-, and *m*- and *o*-bromobenzophenones were prepared by a Friedel–Craft reaction with the

---

[1] D. A. K. Jones and G. G. Smith, *J. Org. Chem.*, **29**, 3531 (1964).

[2] G. G. Smith, K. K. Lum, J. A. Kirby, and J. Pospisil, *ibid.*, **34**, 2090 (1969).

[3] M. M. Davis and H. B. Hetzer, *J. Res. Natl. Bur. Std.*, **60**, 569 (1958); G. G. Smith and K. K. Lum, *Chem. Commun.*, 1208 (1968).

[4] A. G. Harrison, P. Kebarle, and F. P. Lossing, *J. Am. Chem. Soc.*, **83**, 777 (1961).

[5] (a) M. M. Bursey and F. W. McLafferty, *ibid.*, **88**, 529 (1966); (b) F. W. McLafferty, *Chem. Commun.*, 956 (1968), and references therein.

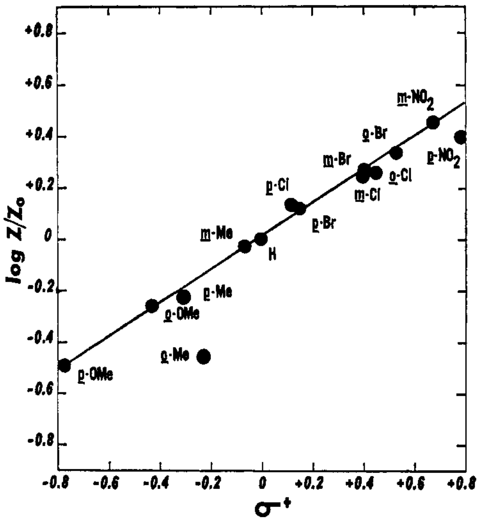


Figure 1.—Linear free-energy correlation of the benzoyl ion intensity, $Z = [C_6H_5CO^+]/[C_6H_5COC_6H_4Y]^+$ in the mass spectra of *ortho-*, *meta-*, and *para*-substituted benzophenones with σ^+ constants. $\rho = +0.619$; linear correlation coefficient = 0.984.

corresponding benzoyl chloride, benzene, and aluminum chloride. *o*-Methoxybenzophenone was prepared by methylation of *o*-hydroxybenzophenone with dimethyl sulfate in alcoholic sodium hydroxide solution. No indication of appreciable impurities was detected in the mass spectrum of any compound.

Mass Spectra.—All the mass spectra were recorded on a Hitachi RMU-6E single-focusing instrument using 80-eV electrons at an emission current of 80 μA. All solid samples were introduced at a suitable temperature inside the sample heater (25–45°) to give enough vapor pressure for recording. Liquid samples were injected at 170°. The source temperature was maintained at 175 ± 2°. It has been reported that benzophenones do not undergo thermal decomposition under 185°.[5] The standard deviation for four to eight replicate recordings of the same sample was, on the average, 2.5%; ratios of fragment ion intensities to molecular ion intensities were constant to within 3% from day to day for all the compounds except *p*-nitrobenzophenone, a phenomenon also observed by McLafferty, *et al.*[5]

Results and Discussion

The application of the kinetic approach to mass spectra has been discussed in detail by McLafferty, *et al.*[5] The decomposition of the molecular ion in the gas phase is a unimolecular, homogeneous reaction. Table I shows the data for substituted benzophenones in which Z equals the ratio of the intensity of the m/e 105 ion ($C_7H_5O^+$) to that of the molecular ion as stated above. When log (Z/Z_0) was plotted against σ^+ constants, including those for *ortho* substituents previously determined, a straight line was obtained ($\rho = 0.619$); the linear correlation coefficient equals 0.984 as shown in Figure 1.

Table I

Substituent	Log (Z/Z_0)
p-NO₂	0.40 (0.35–0.45)
m-NO₂	0.46
p-Br	0.12
m-Br	0.37
o-Br	0.34
p-Cl	0.135
m-Cl	0.25
o-Cl	0.26
H	0.00
m-Me	−0.03
p-Me	−0.22
o-MeO	−0.26
o-Me	−0.46
p-MeO	−0.50

The fact that a good correlation of $\sigma_o{}^+$ constants was obtained with the ion intensities in mass spectra of benzophenones indicated that proximity effects are equivalent or negligible in gas-phase pyrolysis of esters and gas-phase electron-impact reactions of benzophenones. These results are surprising considering the complexity of the factors which affect ion abundance.[5b] An explanation for the failure of the *o*-Me substituent to correlate in this study is given in a recent paper by Ballantine and Pillinger[6a] who have studied the mass spectra of *ortho*-substituted benzophenones. Based on their paper the *o*-OH substituent would also show a marked deviation. With *o*-Me and *o*-OH substituents a hydrogen migration occurs and a large M − 1 peak appears as the base peak. Meyerson, *et al.*, discussed the mass spectra of *ortho*-substituted diarylmethanes.[6b] This proximity effect causes a marked deviation as shown in the figure. The result of this investigation, however, supports the suggestion that $\sigma_o{}^+$ constants are obtainable for gas-phase, unimolecular, homogeneous reactions. One of the differences between these two reactions is that the reactant of the latter is an unsolvated cation, whereas in pyrolysis the reactant is an unsolvated molecule.

It has often been emphasized that reactions which follow a $\rho\sigma^+$ relationship involve a negative ρ value. This is because the reaction involves an electron-deficient intermediate, transient or otherwise, which can be stabilized in the rate-determining transition state by electron release from an aromatic ring. Examples of this are cumyl chloride solvolyses,[7] the pyrolysis of 1-arylethyl acetates,[8] and the appearance potential studies in mass spectroscopy of benzyl radicals.[4]

The ρ value in this mass spectral study, however, is positive even though it too follows a σ^+ correlation. An explanation for this is that the positive charge which is stabilized by the electron-releasing substituent is located on the starting material, $[ArCOPh]\cdot^+$. Hence, these substituents stabilize these species and decrease the reaction rate. To our knowledge this reaction is the only reported example where this point has been observed. The ρ value reported by McLafferty, *et al.*,[5a] was also positive (0.66 linear correlation coefficient = 0.963); they proposed a different explanation for the positive ρ value and found as good a correlation using σ as σ^+.

The fact that proximity effects are equivalent or reduced to a minimum in gas-phase reactions may be mainly because the transition state is unsolvated as compared with reactions in the condensed phase. The steric effect of the *ortho* substituent, which contributes greatly to the proximity effects, may be overcome in the transition state by lack of solvation.[9] Based on this

---

(6) (a) J. A. Ballantine and C. T. Pillinger, *Org. Mass Spectrmy.*, **1**, 425 (1968); (b) S. Meyerson, H. Drews, and E. K. Fields, *J. Amer. Chem. Soc.*, **86**, 4964 (1964).

(7) H. C. Brown and Y. Okamoto, *ibid.*, **80**, 4979 (1958).

(8) R. Taylor, G. G. Smith, and W. H. Wetzel, *ibid.*, **84**, 4817 (1962).

(9) It has been reported that the anomalous influence of *ortho* substituents in the condensed phase is partially due to its steric interference with solvation of the transition state [C. C. Price and D. C. Lincoln, *ibid.*, **73**, 5836 (1951); J. B. Hyne and R. Wills, *ibid.*, **85**, 3650 (1963); J. G. Watkinson, W. Watson, and B. L. Yates, *J. Chem. Soc.*, 5437 (1963)].

reasoning, McLafferty, *et al.*,[5] explained their data of *p*-phenylbenzophenone from electron-impact reactions. In their case, the transition state also receives excess vibrational energy from electron impact to overcome the steric strain. The suggestion that proximity effects can be reduced by overcoming steric strain in the transition state is also revealed in Weale's[10] study of the reaction between *o*-methyl-N,N-dimethylaniline and methyl iodide in dry methanol. He found that the "*ortho* effect" is decreased by increasing the pressure on the system. He explained this observation as due to the contribution from compression energy which overcomes the steric strain in the transition state. Certainly this study and other gas-phase studies[2] demonstrate the advantages of gas-phase studies when relating structure to chemical reactivity.

Acknowledgment.—This work was supported in part by two National Science Foundation Grants, GP 6006 and an equipment grant for the purchase of the mass spectrometer. The Utah State University Research Council also supported this study. We wish to express our appreciation for these generous supports.

(10) K. E. Weale, *J. Phys. Soc.*, 2959 (1954).

Carboxylate-Facilitated Acetylation of Hydroxy Acids in Aqueous Solution

ROLF B. PAULSSEN, IAN H. PITMAN, AND TAKERU HIGUCHI

Department of Pharmaceutical Analytical Chemistry and Pharmaceutics, University of Kansas, Lawrence, Kansas 66044

Received October 16, 1968

Interactions of acetic anhydride with glycolate, malate, salicylate, and similar hydroxy acid anions in dilute aqueous solutions have been shown to lead to significant formation of corresponding acetyl esters. Thus, when acetic anhydride (initial concentration 0.02 *M*) was added to 0.5 *M* solutions of sodium salicylate or sodium glycolate, 22.6% of the acetic anhydride reacted to form aspirin (acetylsalicylic acid) and 48.4% to form acetylglycolic acid, respectively. The reactions which take place competitively with the hydrolysis of the acetic anhydride are believed to be mediated by initial attack of the carboxylate function followed by an O (carboxyl) to O (hydroxy) transacetylation reaction. Salicylate ions, for example, appear to form mixed salicylic acetic acid anhydride species, which preferentially undergo rearrangement to aspirin rather than hydrolysis. These mechanisms appear to play a part in the slow hydrolysis of the corresponding acetyl esters.

In an earlier paper[1] we reported that small amounts of acetylmalate ion were obtained when acetic anhydride was added to dilute aqueous solutions of sodium malate. Further investigation of this reaction and studies on similar acetylations of other hydroxy acid anions strongly indicate that the responsible mechanism involved an O to O transacetylation process mediated by the carboxylate function. Relevant data on these systems are presented in this article.

Although unsubstituted alcohols and phenols can be acetylated by acetic anhydride in inert solvents, or in the absence of solvents, the acetylation of the hydroxy group normally competes unsuccessfully with the hydrolysis of acetic anhydride in water. For example, when acetic anhydride (0.02 *M*) was added to a solution of ethanol (0.50 *M*) in water, more than 99% of the acetic anhydride was hydrolyzed to acetic acid.

The present investigation was undertaken to examine what role a carboxylate group in the alcohol or phenol molecule played in the reaction sequence which led to the significant acetylation of these molecules by acetic anhydride in water.

Results and Discussion

Formation of Ester.—One of the simpler indications of rapid concomitant ester formation during apparent hydrolysis of acetic anhydride in, for example, aqueous sodium glycolate, is the observed reduction in the amount of acetic acid found. Thus the solution obtained 1 hr after adding acetic anhydride (0.02 *M*) to aqueous solutions of sodium glycolate (0.5 *M*) at 25° (solution 1) required a 24% smaller titer of standard sodium hydroxide solution to raise its pH to the phenolphthalein end point than did a solution obtained 1 hr after adding acetic anhydride (0.02 *M*) to water (solution 2).

When solution 1 was acidified with mineral acid and chromatographed on a silicic acid column, it was found to contain the ester, acetylglycolic acid, together with acetic and glycolic acids. The composition of solution 1 did not change appreciably between 30 min and 2 hr after mixing acetic anhydride with the sodium glycolate solution. The slow hydrolysis of acetylglycolic acid in neutral solutions has been investigated by Senter and Ward.[2]

Similar behavior was observed following addition of acetic anhydride to aqueous solutions of other hydroxy acid anions. Errors in the titration of the salicylic acid reaction mixture due to the hydrolysis of acetylsalicylic acid proved to be within the experimental error.

The per cent yield of ester, relative to moles of added acetic anhydride (relative yield, R), was calculated from the titration data on the assumption that the lower titer of sodium hydroxide against the reaction mixture (solution 1) was due to the fact that some of the acetic acid, which would result from the hydrolysis of acetic anhydride, was tied up as an acetyl group in the ester. Results in Table I show the per cent relative yield of ester obtained following the addition of acetic anhydride to aqueous solutions of hydroxy acid anions and alcohols at 25°. The importance of a carboxylate group in the molecules is evident in the fact that the un-ionized hydroxy acids and simple alcohols and phenol were not acetylated to an appreciable extent under the experimental conditions. The failure of tri-

---

(1) I. H. Pitman, R. B. Paulssen, and T. Higuchi, *J. Pharm. Sci.*, **57**, 239 (1968).

(2) G. Senter and T. J. Ward, *J. Chem. Soc.*, 2535 (1912).