Acidity in Nonaqueous Solvents. VI. Further Studies of Weak Acids in Dimethyl Sulfoxide Solution[1]

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Abstract: The potentiometric method, employing the glass electrode, has been applied to the determination of the acidities of a series of benzoic acids, several hydrocarbon acids, and some aniline indicators in pure dimethyl sulfoxide solution. The data provide evidence for an important effect of hydrogen bonding in protic solvents which decreases the effect of substituents on the acidities of benzoic acids. Studies of the hydrocarbon acids indicate that dispersion interactions of the conjugate bases with dimethyl sulfoxide cause a greater dissociation in this solvent than in protic solvents such as methanol. The data for the aniline indicators provide a partial check on the validity of the H_- function generated by their use.

In the two previous papers of this series[2,3] we have reported the development and application of a potentiometric method for the determination of ionization constants of acids having p*K*'s up to ~28 in pure dimethyl sulfoxide (DMSO) solution. Until recently, acidities of weak acids, such as fluorene, have been determined only on a relative scale, and absolute ionization constants could be assigned only by use of some acidity function assumption.[4]

The potentiometric method gives ionization constants relative to a standard state in the solvent in which the measurements are made and does not require assumptions concerning the activity coefficient behavior of the various acids studied. The method, therefore, furnishes an opportunity to check the validity of various acidity functions[5-7] and provides direct information as to the effect of solvent on ionization reactions.

In this paper we report the results of studies of a series of substituted benzoic acids, several hydrocarbon acids, and four of the aniline indicators used in the establishment of an H_- scale in aqueous DMSO solutions.

Results

The p*K* values determined in this study are reported in Table I. All of the data were obtained by the potentiometric titration of the acids with dimsylcesium solutions[2] at concentrations of $\sim 5 \times 10^{-4}$ to 10^{-3} *M*. The titrations gave plots of extent of neutralization *vs.* emf in good agreement with the Nernst equation. We estimate, as previously, that the accuracy of the reported values is ±0.3 p*K* unit. We believe that the relative acidities are accurate to better than ±0.2 p*K* unit.

In the titration of 2,4-dinitrodiphenylamine, an end point was observed, as expected, when 1 equiv of base had been added, but the "pH" of the solution then leveled out at ~17–18 shortly beyond the end point. This second buffer region continued until 1.35 equiv of base had been added, at which point a second break in the titration curve was observed. Up to the first end point the color of the solution was a reddish brown. In the second buffer region the color underwent little change, but then became bright red-orange after the second break. Multiple recrystallizations of the 2,4-dinitrophenylamine and repetition of the titration gave the same behavior. The titration curve up to the first break gave good agreement with the theoretically

Table I. Acidities in DMSO Solution at 25°

Acid	p*K* (DMSO)	p*K* (other)[a]
p-Nitrobenzoic acid	8.9	8.4 (MeOH)[b]
p-Chlorobenzoic acid	10.1	9.1 (MeOH)[b]
9-Carbomethoxyfluorene	10.3[c]	12.9 (H_-)[d]
Fluoradene	10.5	
Benzoic acid	11.0	9.4 (MeOH)[b]
m-Toluic acid	11.0	9.5 (MeOH)[b]
Malononitrile	11.0[c]	11.1 (H_-)[d]
m-Hydroxybenzoic acid	11.1	
p-Ethoxybenzoic acid	11.5	9.8 (MeOH)[b]
m-Aminobenzoic acid	11.6	
p-Hydroxybenzoic acid	11.8	
2,4-Dinitrodiphenylamine	12.4	13.8 (H_-)[e]
p-Aminobenzoic acid	12.7	
Acetylacetone	13.4[c]	9.0 (H_2O)[f]
Nitroethane	13.9	8.9 (H_2O)[f]
4-Nitrodiphenylamine	14.3	15.7 (H_-)[e]
1,12-*o*-Phenylenedihydropleiadene	14.4	
4-Chloro-2-nitroaniline	15.1	17.1 (H_-)[e]
Nitromethane	15.9[c]	10.2 (H_2O)[f]
9-Phenylfluorene	16.4[c]	18.6 (H_-)[d,g]
2,3,5,6-Tetrachloroaniline	17.1	19.2 (H_-)[e]
Indene	18.5[c]	
9-Methylfluorene	19.7[c]	21.8 (H_-)[g]
4,5-Methylenephenanthrene	20.0[c]	21.2 (H_-)[g]
Fluorene	20.5[c]	22.1 (H_-)[g]
Triphenylmethane	28.8[h]	

[a] The solvent shown in parentheses is that in which the p*K* was measured. H_- presumably refers to a standard state in water; see, however, ref 3. [b] Data taken from J. E. Leffler and E. Grunwald, "Rates and Equilibria of Organic Reactions," John Wiley and Sons, Inc., New York, N. Y., 1963, p 268. [c] These values were preliminarily reported in ref 3. [d] Data from ref 5. [e] Data from ref 7. [f] Data from ref 4. [g] Data from K. Bowden and A. F. Cockerill, *Chem. Commun.*, 989 (1967). These values are based on an assumed value of 18.6 for 9-phenylfluorene. [h] Data from C. D. Ritchie and R. E. Uschold, *J. Am. Chem. Soc.*, **89**, 2960 (1967).

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(1) This work was supported by Grants from the Public Health Service, National Institutes of Health (GM 12832), and the National Science Foundation (GP 5853).

(2) C. D. Ritchie and R. E. Uschold, *J. Am. Chem. Soc.*, **89**, 1721 (1967).

(3) C. D. Ritchie and R. E. Uschold, *ibid.*, **89**, 2752 (1967).

(4) See, for example: D. J. Cram, "Fundamentals of Carbanion Chemistry," Academic Press Inc., New York, N. Y., 1965.

(5) K. Bowden and R. Stewart, *Tetrahedron*, 21, 261 (1965).

(6) K. Bowden, *Chem. Rev.*, **66**, 119 (1966).

(7) D. Dolman and R. Stewart, *Can. J. Chem.*, **45**, 911 (1967).

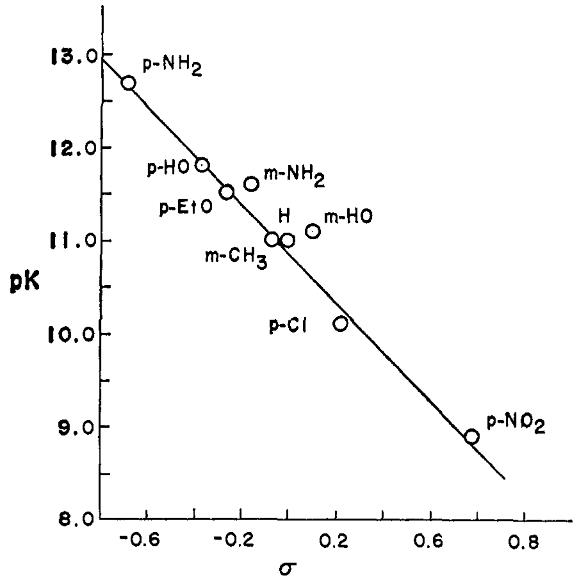


Figure 1. Hammett plot of acidities of substituted benzoic acids in DMSO solution at 25°.

expected behavior, and we assume that normal removal of a proton is occurring in this region of the titration.

In the titration of *m*-nitrobenzoic acid, addition of the first increment of dimsylcesium solution produced an orange color. A break in the titration curve was observed when 0.89 equiv of the base had been added, and the color of the solution turned yellow at this point. A second break in the titration curve was observed when 1 equiv of base had been added. In this case we believe that the reaction taking place during the first addition of base is not a proton transfer, and we have not included *m*-nitrobenzoic acid in the tabulation. The pH of the solution at the point where 0.45 equiv of base had been added was 8.6.

Discussion

Benzoic Acid Series. For some time it has been realized that hydrogen-bonding stabilization of anions in protic solvents has a pronounced effect on the acidity changes for uncharged acids on going from water, or alcohol, to dipolar aprotic solvents such as DMSO. It has also been realized that different extents of hydrogen-bonding stabilization for carboxylate ions and resonance-stabilized anions, such as *p*-nitrophenoxide ion, can lead to inversions in relative acidities of these acids on going from protic to aprotic solvents.[8] It has not generally been recognized, however, that hydrogen-bonding effects can have a large influence on substituent effects within a closely related series of acids. We have previously discussed this factor in connection with studies of phenols and picolinium ions in methanol and dimethylformamide solutions.[9] The effect is important in interpretations of the solvent dependence of the Hammett ρ values and the nature of transmission of substituent effects.[10]

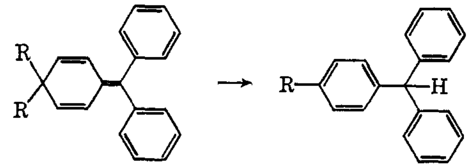
A Hammett plot of the acidities of the substituted benzoic acids in DMSO solution is shown in Figure 1. The ρ value for the reaction series is 2.6. ρ values for the ionizations of benzoic acids in other solvents are: water, 1.00; methanol, 1.54; ethanol, 1.65; acetonitrile, 2.8.[11,12] It is quite clear from these data that the *dielectric constant* of the solvent is, at most, a small factor, and that the most important factor is the possibility of hydrogen-bond donation by the solvent. Since the substituent effects on the stabilization of the benzoate ions by hydrogen bonds from solvent must show a negative ρ value, the observed ρ value for the over-all ionization will be diminished in those solvents capable of hydrogen bonding.

It is interesting to note that although all of the benzoic acids studied here are less ionized in DMSO than in methanol solution, an extrapolation of the above concept leads to the prediction that substituted benzoic acids much stronger than *p*-nitrobenzoic acid will be more ionized in DMSO than in methanol.

Hydrocarbon Acids. In the preliminary communication of this work[3] we pointed out that the data for the hydrocarbon acids clearly show the failure of the acidity function in ethanolic DMSO which was established by the use of these acids.[5] We shall, therefore, not dwell on this point. The important fact which was established is that the ionization behavior of hydrocarbon acids which have highly colored conjugate bases is not the same as that of acids whose conjugate bases are not highly delocalized. The relative acidities of malononitrile and 9-carbomethoxyfluorene, for example, change by 2.5 p*K* units on going from ethanol to pure DMSO solution. The importance of this behavior, which we believe to be due to strong dispersion interactions of the delocalized anions with DMSO solvent, is best illustrated by example.

In an earlier paper dealing with the rates of reaction of triphenylmethane with bases in DMSO solution[13] we arrived at the conclusion that the rate of proton transfer from triphenylmethane to alkoxide ions was increased by a larger factor than was the equilibrium constant for the reaction on going from methanol to DMSO solution. The conclusion was based on the assumption that the p*K* of triphenylmethane in methanol is the same as that in DMSO and that the equilibrium constant for the reaction with alkoxide was, therefore, changed only by the increase in basicity of the alkoxide on going from methanol to DMSO solution.

Long contemplation of the results of Cram's study[4,14] of the intramolecularity of the proton transfer involved in the methoxide ion catalyzed isomerization of triene I to the substituted triphenylmethane II caused us to question the above assumption.



I II

$R = C(CH_3)_2CO_2CH_3$

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[8] C. D. Ritchie and E. S. Lewis, *J. Am. Chem. Soc.*, **84**, 591 (1962).

[9] C. D. Ritchie and G. H. Megerle, *ibid.*, **89**, 1447 (1967).

[10] C. D. Ritchie and W. F. Sager, *Progr. Phys. Org. Chem.*, **2**, 323 (1964).

[11] J. E. Leffler and E. Grunwald, "Rates and Equilibria of Organic Reactions," John Wiley and Sons, Inc., New York, N. Y., 1963, p 268.

[12] J. F. Coetzee, *Progr. Phys. Org. Chem.*, **4**, 45 (1967).

[13] See Table I, footnote *h*.

[14] D. J. Cram, F. Willey, H. P. Fischer, and D. A. Scott, *J. Am. Chem. Soc.*, **86**, 5370 (1964).

Cram showed that the isomerization reaction proceeds in methanol-*d* with $\sim 50\%$ intramolecularity. This fact shows that the rate of proton donation from methanol to the substituted trityl anion is competitive with the rate of exchange of the initially produced methanol molecule with bulk solvent. Although the rate at which a methanol molecule associated with trityl anion exchanges with bulk solvent is not known, there is no reason to expect it to be any slower than the rate of exchange of methanol hydrogen bonded to an amine. This latter process has been shown[15] to have rate constants on the order of 10^9 sec^{-1}. Therefore, the rate constants for the reaction of methanol with the substituted trityl anion must be on the order of 10^8 M^{-1} sec^{-1}. Since the substituent is not likely to have any large effect, roughly the same rate constant must apply for the unsubstituted trityl anion.

Streitwieser has reported data[16] which allow an estimate[13] of 10^{-9} M^{-1} sec^{-1} for the rate constant of the reaction of methoxide ion with triphenylmethane-*t* in methanol solution. From the above estimate for the reverse rate constant, we may estimate an equilibrium constant for the reaction

$$(C_6H_5)_3CH + CH_3O^- \rightleftarrows (C_6H_5)_3C^- + CH_3OH$$

as 10^{-17}. Since methanol in methanol has a pK of 18.3,[13] then triphenylmethane must have a pK of ~ 35 in methanol. This is more than six units greater than the value in DMSO.

We reasoned that if the above value were correct for the pK of triphenylmethane in methanol, then a similar increase in pK for other hydrocarbon acids with highly colored conjugate bases should occur on going from DMSO to methanol. The reasoning was based on the fact that the *relative* acidities of such hydrocarbon acids appear to be the same in pure DMSO as in ethanolic DMSO.[3] For example, 9-carbomethoxyfluorene and 9-phenylfluorene have pK's which differ by 6.1 units in pure DMSO and by 5.9 units as determined on the H_- scale in ethanolic DMSO. Bowden's very recent data[17] on substituted fluorenes in aqueous DMSO also show reasonable agreement in *relative* acidities with those determined in pure DMSO.

In order to confirm our suspicions, we chose fluoradene[18] for study since it appeared that it might be acidic enough to allow pK measurements in both methanol and DMSO. As reported in Table I, the pK of fluoradene in DMSO is found to be 10.5. It has not proved possible to measure accurately the pK in methanol solution. We have found, however, that fluoradene is not completely ionized in the presence of 1 M potassium methoxide in methanol solution. A number of measurements allow us to estimate a pK of ~ 17 in methanol solution, and our suspicion is fully confirmed.[19]

We presently believe that all of the hydrocarbon acids with strongly colored conjugate bases will have pK's in methanol solution which are ~ 6.5 units greater than those measured in DMSO solution. The simplest explanation of this solvent effect is that the dispersion interactions of the delocalized anions with the highly polarizable DMSO solvent are more important than both dispersion and hydrogen-bonding stabilization in methanol. A part of the decrease in pK in DMSO solution, however, is probably due to the fact that DMSO is more basic than methanol.[2]

The importance of the above conclusions in interpretation of solvent effects on the rates of proton transfer reactions will be discussed in a separate paper.[20]

We may also note here that Stewart's recent report[21] of an estimated pK for DMSO in water which is the same as that found for pure DMSO solution[3,22] indicates that the ionization behavior of DMSO is similar to that of malononitrile and not to that of fluorenes.

Aniline-Type Indicators. The diphenylamine and aniline indicators used by Stewart[7] to establish an H_- acidity function in aqueous DMSO solutions might be expected, *a priori*, to exhibit both hydrogen-bonding and dispersion effects on their ionization behavior in mixed solvents. Either of these effects alone might lead to a breakdown in the acidity function. Stewart, however, has presented impressive evidence, in the form of overlap studies[7] and substituent effects,[23] to indicate that the acidity function is valid. In order to provide an independent check we have determined the pK's of four of the indicators in pure DMSO solution. If the acidity function is valid, of course, the *relative* acidities of the indicators must be independent of solvent composition.

The data reported in Table I show that all of the indicators have pK values in pure DMSO that are markedly lower than those determined by the H_- technique. The *relative* acidities in DMSO differ by slightly more than experimental error from those found by the H_- method, but the surprising fact is that the relative values change as little as they do. In fact, the relative acidities of 2,4-dinitrodiphenylamine and 4-nitrodiphenylamine, and of 4-chloro-2-nitroaniline and 2,3,5,6-tetrachloroaniline, are the same, to well within experimental error, in pure DMSO as on the H_- scale. The small discrepancy in relative acidities arises in the comparison of the anilines with the diphenylamines. The difference in pK between 4-chloro-2-nitroaniline and (4-nitrophenyl)phenylamine is 1.4 units on the H_- scale and only 0.8 in pure DMSO.

Apparently *p*-nitroaniline and 2,4-dinitroaniline behave quite differently from the anilines studied by Stewart in the most recent acidity function work.[7] We have previously reported[2] that the pK of 2,4-dinitroaniline in pure DMSO is the same as that determined by Steiner[24] by an acidity function technique employing

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(15) E. Grunwald and E. K. Ralph, *J. Am. Chem. Soc.*, **89**, 2963, 4405 (1967).

(16) A. Streitwieser and J. H. Hammons, *Progr. Phys. Org. Chem.*, **3**, 41 (1965). This estimate has been confirmed in private conversations with Professor Streitwieser. Data at 45°.

(17) See Table I, footnote *g*.

(18) H. Rappaport and G. Smolinsky, *J. Am. Chem. Soc.*, **82**, 934 (1960); G. Baum, R. Bernard, and H. Schecter, *ibid.*, **89**, 5308 (1967). Professor Schecter first suggested fluoradene to us for study. We are grateful to Professor Schecter for the suggestion and for furnishing us with an experimental procedure for the synthesis of this compound prior to publication.

(19) Two other results which were predicted on the basis of the reasoning presented earlier have also been confirmed. Professor Streitwieser has found that the isotope effect (k_D/k_T) for the reaction of triphenylmethane with methoxide is very small and that the Brønsted slope for acids close to triphenylmethane in strength is approaching unity.

(20) C. D. Ritchie and R. E. Uschold, *J. Am. Chem. Soc.*, in press.

(21) R. Stewart and J. R. Jones, *ibid.*, **89**, 5069 (1967).

(22) E. C. Steiner and J. D. Starkey, 153th National Meeting of the American Chemical Society, Miami Beach, Fla., April 1967, Abstracts, Q33.

(23) R. Stewart and D. Dolman, *Can. J. Chem.*, **45**, 925 (1967).

(24) E. C. Steiner and J. M. Gilbert, *J. Am. Chem. Soc.*, **87**, 382 (1965).

p-nitroaniline as the "anchor compound." Stewart[7] has found that *p*-nitroaniline gives an indicator slope of 0.91 on the H_- scale in aqueous DMSO, and Bowden[17] has suggested that this compound does not act as a Hammett indicator.

Comments on Intrinsic Acidities. The now generally accepted fact[4,5,7,13,21,23] that water and alcohols have acidities comparable to that of triphenylmethane in aprotic solvents has lead to some suggestions[25] that one is observing an "intrinsic" order of acidity in these solvents. We should like to point out that water and *methane* have comparable acidities in the gas phase, and that ammonia is slightly more acidic than either of these.[26]

It is quite clear, then, that acidity orders in DMSO, or probably in any other solvent, are not intrinsic in any sense. The intrinsic acidity of a compound is likely to be determined largely by the ability of the conjugate base to disperse negative charge. The more polarizable matter that is placed close to the center bearing charge, the more stable is likely to be the charged species. In solutions, the solvent can probably help greatly in dispersing charge of a solute by a variety of mechanisms including ion–dipole interaction, hydrogen bonding, and ion-induced dipole interactions, among others. The acidity of an acid in solution will then depend on the ability of the solvent to come close enough to the center of charge in the conjugate base to provide stabilization of various types.

Experimental Section

Materials. The purification of DMSO solvent and preparation of dimsylcesium solutions have been described previously.[2,13,27]

The substituted benzoic acids used in this study were obtained from commercial sources and were recrystallized from water. Melting points checked closely with literature values.

A sample of 1,12-*o*-phenylenedihydropleiadene was furnished by Professor P. T. Lansbury.

Fluoradene was prepared by the method described by Baum[18,28] and the melting point checked closely with that reported (130°).

Preparation of 9-phenylfluorene was accomplished by addition of phenyl-Grignard to fluorenone followed by reduction of the resulting carbinol with zinc in acetic acid.[29] The nmr spectrum of the compound in deuterated chloroform showed a complex aromatic pattern at 7.5 ppm and a singlet at 5.05 ppm, relative to internal TMS, and gave the proper integration for 9-phenylfluorene; mp 145–146°; lit.[29] mp 145°.

With the exception of 2,3,5,6-tetrachloroaniline, which was prepared as described by Stewart,[7] the other compounds studied were obtained from commercial sources. Melting points checked closely with literature values in all cases.

Methods. The methods used in the present study have been described in an earlier paper.[2] Titrations of the acids at concentrations of $\sim 5 \times 10^{-4}$ *M* in DMSO solution were carried out with solutions of dimsylcesium $\sim 10^{-2}$ *M*.

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[25] W. L. Jolly, *J. Chem. Educ.*, **44**, 304 (1967).

[26] C. D. Ritchie and H. F. King, *J. Am. Chem. Soc.*, **90**, 825, 833, 838 (1968).

[27] C. D. Ritchie, G. A. Skinner, and V. G. Badding, *ibid.*, **89**, 2063 (1967).

[28] G. Baum, Ph.D. Thesis, The Ohio State University, Columbus, Ohio, 1966.

[29] F. Ullman and R. VonWurstenberger, *Ber.*, **37**, 73 (1904).

Polyfunctional Catalysis. I. Activation Parameters for the Mutarotation of Tetramethyl-D-glucose in Benzene

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Abstract: A theoretical and experimental study of the mutarotation of 2,3,4,6-tetramethyl-D-glucose (TMG) in benzene has been performed. The kinetics are rigorously pseudo first order regardless of the substrate:catalyst ratio, a consequence of the presence of two anomeric forms of TMG which have nearly identical chemical characteristics. The rate laws and corresponding activation parameters, relative to the free species, for three catalyst systems that have been extensively studied as a function of temperature are: (1) benzoic acid, rate = $(k_1 + k_1')\cdot$[benzoic acid]$\{[\mathrm{TMG}] - [\mathrm{TMG}]_e\}$, $\Delta H^\ddagger = 10.8 \pm 1$ kcal/mol, $\Delta S^\ddagger = -21.5 \pm 3$ gibbs/mol at a standard state of 1 mol/l. at 25°, and $\Delta G^\ddagger = 17.2 \pm 0.4$ kcal/mol; (2) 2-pyridone, rate = $(k_1 + k_1')$[2-pyridone]$\{[\mathrm{TMG}] - [\mathrm{TMG}]_e\}$, $\Delta H^\ddagger = 10.8 \pm 1$, $\Delta S^\ddagger = -23.1 \pm 3$, and $\Delta G^\ddagger = 17.7 \pm 0.4$; and (3) pyridine–phenol mixtures, rate = $(k_2 + k_2')\cdot$[pyridine][phenol]$\{[\mathrm{TMG}] - [\mathrm{TMG}]_e\}$, $\Delta H^\ddagger = 8.7 \pm 1$, $\Delta S^\ddagger = -35.8 \pm 3$, and $\Delta G^\ddagger = 19.4 \pm 0.4$. Benzoic acid and 2-pyridone are *neutral tautomeric catalysts* that exhibit second-order kinetics in the mutarotation reaction. They derive their remarkable catalytic properties from the fact that they can exchange two protons without forming a high-energy dipolar ion.

Bifunctional catalysis, a term used when two catalytic groups present within the same molecule act on a substrate, continues to be one of the more appealing concepts for describing the mechanistic nature of enzyme-catalyzed reactions.[1] If the two groups act at the same time, such as in the simultaneous transfer of two protons proposed by Swain and Brown[2,3] for the mutarotation of 2,3,4,6-tetramethyl-D-glucose (TMG) in the presence of 2-hydroxypyridine (I and II), the process is called a concerted reaction.[2,4]

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[1] (a) F. M. Menger, *J. Am. Chem. Soc.*, **88**, 3081 (1966); (b) D. R. Robinson and W. P. Jencks, *ibid.*, **89**, 7096 (1967); (c) D. W. Tanner and T. C. Bruice, *ibid.*, **89**, 6954 (1967); (d) G. C. Overberger, T. St. Pierre, C. Yaroslavsky, and S. Yaroslavsky, *ibid.*, **88**, 1184 (1966); (e) J. C. Sheehan, G. B. Bennett, and J. A. Schneider, *ibid.*, **88**, 3455 (1966).

[2] C. G. Swain and J. F. Brown, Jr., *ibid.*, **74**, 2534 (1952).

[3] C. G. Swain and J. F. Brown, Jr., *ibid.*, **74**, 2538 (1952).

[4] (a) R. L. Schowen, H. Jayaraman, and L. Kershner, *ibid.*, **88**, 3373 (1966); (b) J. L. Kurz and J. I. Coburn, *ibid.*, **89**, 3528 (1967).