[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DUKE UNIVERSITY]

The Determination of the Association Constants of Some Acid Amides in Benzene Solution

BY MARCUS E. HOBBS AND W. W. BATES[1]

The monomer–dimer association constants of seven acid amides have been determined in benzene solution by dielectric constant measurements. The dipole moments of the monomers in benzene were well established as the amides are largely in the monomeric form in the accessible concentration range at 30°. The structure of the dimer was not defined but evidence is presented which indicates that the proposed hydrogen bonded ring structure has a center of symmetry as well as a small anomalous polarizability of about 15 cc. Comparison of the amide association with that of carboxylic acids leads to an estimated heat of hydrogen bonding in the amides of about 3.5 kcal. per bond. The amide structure present in natural and synthetic fibers as well as in physiological systems makes important the study of the factors influencing the association of this group.

The association of the amides has been studied[2] by a number of methods and in a variety of solvents, but definitive association constants, valid over a range of concentrations, have not been reported. Usually rather concentrated solutions were investigated so that many association products were formed. In the present work benzene was used as a solvent and because of limited solubility the concentration range was restricted to values less than about 5×10^{-3} mole fraction of solute. The dielectric constant data obtained from such solutions was analyzed by methods similar in principle to those previously reported[3] and from such an analysis the values of the monomer–dimer association constants for seven acid amides were established. The precision was somewhat limited because of the limited concentration range accessible and because, in the solutions used, the amides were largely in the monomeric form.

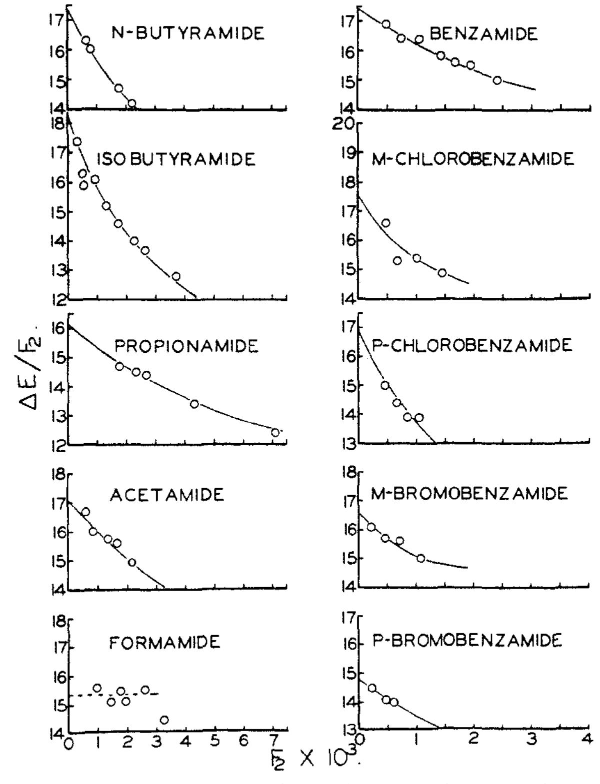

Fig. 1.—Experimental (points) and calculated (lines) $\Delta E/f_2$ data for some amides in benzene solution at 30°. The solid lines were calculated by equation (4) using the appropriate constants from Table I.

Method and Results

The purification procedures and physical constants of all compounds and the solvent have been previously reported as has a description of the method and equipment employed.[4] The experimental data[5] are shown graphically as points in Fig. 1. In this figure $\Delta E/f_2$ is plotted against mole fraction where $\Delta E/f_2$ is the ratio of the dielectric constant increment of the solution, ΔE, to the mole fraction of the solute, f_2, calculated as monomer.

In Table I are shown, among other things, the average value of $\Delta d/f_2$ for each of the amides in benzene solution along with the dipole moment, μ_M, in debyes, of the single molecule of the amides as calculated by the Hedestrand equation.[6] The term $\Delta d/f_2$ is the ratio of the density increment to the mole fraction of a particular solution. The other items listed in Table I are defined in the discussion section or in the table itself.

The limiting value of $\Delta E/f$ required in the Hedestrand equation was obtained from the analysis of the equilibrium between dimer and monomer amide molecules in terms of the dielectric measurements.

Discussion

It seems probable from the course of the data shown in Fig. 1 and the recognized nature of the amides that some type of association is responsible for the trend in the $\Delta E/f_2$ values with changing concentration. Possibly experimental peculiarities could be responsible for the observed trend, but no data similar to those presented are available so that direct comparison cannot be made with data from other sources. However, the authors have published data[4] on the same amides in dioxane solution and no such trend in $\Delta E/f_2$ was found.

Actually one can account quantitatively for the results by assuming an equilibrium between monomeric and dimeric forms of the amide. The analysis of the equilibrium was carried out as follows.

The equilibrium assumed is given by $2A_M \rightleftarrows A_D$ and in terms of mole fractions the equilibrium

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[1] Part of a thesis of W. W. Bates presented in partial fulfillment of the requirements for the Ph.D. degree in Chemistry at Duke University.

[2] (a) H. O. Chaplin and L. Hunter, *J. Chem. Soc.*, 1114 (1937); (b) A. N. Meldrum and W. E. S. Turner, *ibid.*, **93**, 876 (1908); **97**, 1605 (1910); **97**, 1805 (1910); (c) A. S. Dunstan and A. G. Mussell, *ibid.*, **97**, 1935 (1910); (d) W. E. S. Turner and E. W. Merry, *Proc. Chem. Soc.*, **26**, 128 (1910); (e) E. N. Lassettre, *Chem. Revs.*, **20**, 259 (1937); (f) M. J. Copley, G. F. Zellhoefer and C. S. Marvel, THIS JOURNAL, **60**, 2666 (1938).

[3] (a) H. A. Pohl, M. E. Hobbs and P. M. Gross, *J. Chem. Phys.*, **9**, 408 (1941); (b) A. A. Maryott, *J. Research Natl. Bur. Standards*, **41**, 1, 7 (1948).

[4] W. W. Bates and M. E. Hobbs, THIS JOURNAL, **73**, 2151 (1951).

[5] Mimeographed tables of data may be obtained from the authors.

[6] G. Hedestrand, *Z. physik. Chem.*, **B2**, 20 (1928).

TABLE I

SUMMARY OF RESULTS IN AMIDES (30.0°)

Substance	$\Delta d/f_2$	$\Delta E_M/f_M$	$\Delta E_D/f_D$[a]	μ_M	μ_M[b] (diox.)	P_{DAO}	$K_f \times 10^{-3}$
Formamide[c]	0.132	(15.3)	...	(3.37)	3.86	..	....
Acetamide	.124	17.1 ± 0.2	(0)	3.60	3.90	(3)	0.4 ± 0.1
Propionamide	.102	16.1 ± 0.1	(0)	3.47	3.85	(5)	.27 ± 0.05
n-Butyramide	.149	17.4 ± 0.1	(0)	3.59	3.86	(2)	.62 ± 0.05
i-Butyramide	.072	18.3 ± 0.1	0.6	3.70	3.88	16	.92 ± 0.06
Benzamide	.391	17.4 ± 0.1	(2)	3.55	3.84	(15)	.40 ± 0.06
m-Chlorobenzamide	.603	17.5 ± 0.3	20	3.57	3.67	288	2.9 ± 0.7
p-Chlorobenzamide	.663	16.9 ± 0.2	2	3.49	3.73	17	1.6 ± 0.2
m-Bromobenzamide	1.095	16.6 ± 0.2	21	3.40	3.66	297	2.2 ± 0.4
p-Bromobenzamide	1.11	14.8 ± 0.4	(2)	3.25	3.68	(14)	(0.6)

[a] The estimated uncertainty in this column is about one unit except for the case of isobutyramide where it is considered to be about 0.5 unit. [b] The dipole moments in Debyes of the amides in dioxane solution are taken from reference (4). The value of the molar refraction, R_D, required in the moment calculations are also given in this reference. [c] Data for this compound were not analyzed because of no clear evidence of association.

constant is expressed as $K_f = \frac{f_D}{f_M^2}$. Here the subscripts M and D refer to the monomer and dimer of the amide, respectively.

It is convenient to calculate the data in terms of f_2 and α which are defined by $f_2 = \frac{n_M + 2n_D}{n_M + 2n_D + n_S}$ and $\alpha = \frac{n_M}{n_M + 2n_D}$. In these expressions n is the number of moles and the subscript S refers to the solvent. With these definitions K_f is then given by

$$K_f = \left(\frac{1-\alpha}{2\alpha^2 f_2}\right)\left(\frac{1}{1 + \frac{n_D}{n_T}}\right) \qquad (1)$$

In equation (1) n_T is the total number of moles present in the solution and since the solute in all solutions used was of the order of 10^{-3} mole fraction and, as will be shown later, the amides were largely in the single molecule form it follows that, compared to unity, n_D/n_T can be neglected.

In order to relate α to the dielectric measurements use can be made of the observation by many investigators that $\Delta E/f_2$ for unassociated solutes is quite constant over a considerable range of concentrations. In view of this it is reasonable to assume that monomeric and dimeric amide molecules will each have characteristic values for this function, namely, $\Delta E_M/f_M$ and $\Delta E_D/f_D$, respectively. From the previous definition of α we may express $\Delta E/f_2$ as

$$\Delta E/f_2 = \alpha \Delta E_M/f_M + \left(\frac{1-\alpha}{2}\right) \Delta E_D/f_D$$

$$\alpha = \left(\frac{\Delta E/f_2 - \Delta E_D/2f_D}{\Delta E_M/f_M - \Delta E_D/2f_D}\right) \qquad (2)$$

Combination of equations (1) and (2), if n_D/n_T is neglected, gives after some rearrangement

$$Xf_2 = \frac{B^2}{2K_f}\left(\frac{1}{X}\right) - \frac{B}{2K_f} \qquad (3)$$

where $X = (\Delta E/f_2 - \Delta E_D/2f_D)$ and $B = (\Delta E_M/f_M - \Delta E_D/2f_D)$. Before equation (3) can be used for graphical purposes one must assign an approximate value to $\Delta E_D/2f_D$. The rough limits of the values which $\Delta E_D/2f_D$ may assume are from zero to the lowest value of $\Delta E/f_2$ found experimentally for a particular amide. Actually in this range it is of no great consequence what value of $\Delta E_D/2f_D$ is chosen in the present work since the amides are all largely dissociated into single molecules and the plot Xf_2 *vs.* $1/X$ can be rather unambiguously extrapolated to $Xf_2 = 0$. At $Xf_2 = 0$, $1/X = 1/B$ and from the definition of B one may obtain the value of $\Delta E_M/f_M$. The derived value of $\Delta E_M/f_M$ found above is rather insensitive to the value used for $\Delta E_D/2f_D$, *i.e.*, the value of $\Delta E_M/f_M$ differed only 0.1 unit in 17 when values of $\Delta E_D/2f_D$ from 0 to 10.5 were used in equation (3) to allow graphing of Xf_2 *vs.* $1/X$. Because of the insensitivity to the particular value of $\Delta E_D/f_2$ chosen the values of $\Delta E_M/f_M$ seem to be rather well established.

After evaluation of $\Delta E_M/f_M$, the value of $\Delta E_D/2f_D$ was rather easier defined by plotting another form of equation (3); *viz.*

$$\Delta E/f_2 = Z\left(\frac{B}{2K_f}\right)^{1/2} + \Delta E_D/2f_D \qquad (4)$$

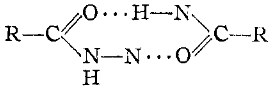
where $Z = \left(\frac{\Delta E_M/f_M - \Delta E/f_2}{f_2}\right)^{1/2}$. When $\Delta E/f_2$ is plotted against Z the intercept on the $\Delta E/f_2$ axis is $\Delta E_D/2f_D$. The value of Z is determinable from the well established value of $\Delta E_M/f_M$ and the experimental values of $\Delta E/f_2$.

Analysis of the data of Fig. 1 by the methods indicated yield the values of $\Delta E_M/f_M$, $\Delta E_D/f_D$ and K_f recorded in Table I. The solid lines of Fig. 1 are calculated from the derived values of K_f, $\Delta E_M/f_M$ and $\Delta E_D/f_D$. The fit of the line with the experimental points gives some indication of the precision of the analysis.

The values enclosed in parentheses in Table I are approximate and blanks indicate that the data was not analyzed. As shown, the values of $\Delta E_D/f_D$ were rather uncertain in many cases. Examination of the amides in a solvent in which more dimerization occurs would probably improve the accuracy of $\Delta E_D/f_D$.

The values of μ_M and $\mu_{M(\text{Diox})}$ listed in Table I for the single molecules in benzene and in dioxane, respectively, show a quite significant difference, about 0.2–0.3 debye, in solvent effect between these two solvents. This matter has been discussed briefly in a previous publication.[4] It appears that the much stronger donor property of dioxane as compared to benzene gives rise to this rather specific solvent effect difference. It may be noted that both of these solvents have about the same dielectric constant.

The existence of an apparent moment of the dimer molecule of the amide is indicated by the value of P_{DAO}, the molar atomic and orientation polarization of the dimer. The total molar polarization of the dimer was calculated from the Hedestrand equation by assuming that the value of $\Delta d/f$ for the dimer is two times the value of $\Delta d/f_2$ recorded in Table I. The value of P_{DAO} was taken as the difference between P_D and the molar refraction of the dimer. The large calculated value for the *m*-chlorobenzamide and *m*-bromobenzamide dimer molecule, corresponding to a dipole moment of about 3.8 debyes, suggests some kind of unsymmetrical structure for these dimers even after allowance for free rotation of the two phenyl groups. The data for these two cases is so limited that it should be taken primarily as an indication and certainly more work along these lines should be done to clarify the situation. The value of 16 cc. for P_{DAO} in the case of isobutyramide is reasonably well established and is about the same magnitude as is found for the dimer of carboxylic acids.[3a] One might picture the dimer of the amides as



The plane of the ring is not well defined but the data on *p*-chlorobenzamide and *p*-bromobenzamide seem to indicate that in these cases, at least, the C–Cl and C–Br bond moments nearly cancel each other. Thus one has some basis for thinking of the ring as nearly in a plane and that probably there is a center of symmetry.

The uncertainty in the association constants, K_f, given in Table I is caused chiefly by the limited precision of the available equipment and technique coupled with the fact that measurements were restricted to rather small concentrations of solute because of limited solubility. The estimates of uncertainty in K_f are in all cases several times the average deviation of a single observation. The recorded average value of K_f was obtained by calculating the constant for each of the experimental points and then taking the mean value of K_f in the usual way. In the case of isobutyramide the K_f values for measurements at $f_2/10^{-3} = 0.491$ and 0.516 were omitted from the averaging as these points had deviations considerably beyond reasonable expectation as determined by Chauvenet's criterion.[7]

The general trend of the association constants seems to be toward increasing association with increasing size of the grouping to which the $-CONH_2$ group is attached. Benzamide is apparently a well established exception to this trend and at present the authors can suggest no simple explanation for this exception that is consistent with the rest of the data. The case of *p*-bromobenzamide also appears to be an exception but the data in this case are quite limited. A detailed discussion of the association constants does not seem warranted in view of their limited precision and the fact that there is no experimental information as to the proportions in which entropy and energy terms contribute to the magnitude of the constants.

A study of the heat of reaction for the amide monomer–dimer system projects some experimental difficulties as the fraction of dimers present in benzene solution is not large. Thus, with a rather limited precision in the $\Delta E/f$ values, one can expect from the small changes in this quantity a seriously limited precision in the heat values as determined from the change of K_f with temperature. By way of comparison the range of values of $\Delta E/f_2$ readily accessible with carboxylic acids in benzene can be varied over threefold or 300% whereas with the amides in this solvent the range is about 130% in the best cases. The limited association of the amides may be illustrated as follows. The fraction, α, for a particular solution is given by

$$\alpha = \frac{1}{y}\left[(1 + 2y)^{1/2} - 1\right]$$

where $y = 4K_f f_2$. For the cases $y = 0.1$, 0.5, 1.0 and 2.0 the values of α are 0.97, 0.83, 0.73 and 0.62, respectively. The values of the parameter $K_f f_2$ for the amide solutions reported in this investigation are such that $\alpha > 0.70$ in all cases. In order to obtain values of $\alpha < 0.7$ it will probably be necessary to work at rather low temperatures and/or change the solvent to a less basic one than benzene.

In the absence of other data the heat of formation of the N–H- -O hydrogen bond can be estimated in the following way. The heat and entropy of dimerization of the carboxylic acids in benzene solution have been found to be about 9 kcal. and 15 entropy units, respectively, per mole of dimer. If one assumes that the entropy of dimerization of the amides is about the same as for the acids the calculated heat of dimerization for isobutyramide is about 7 kcal. per mole of dimer or approximately 3.5 kcal. per hydrogen bond between amides. From this estimate it appears that the heat of the N–H- -O bond in amides may be about 1 kcal. per mole less than for the O–H—O bond in acids. In order to obtain precise experimental values for the heat of formation of the N–H—O bridge in benzene solution a considerable range in temperature would be necessary since the association heat is apparently relatively small.

It seems appropriate to emphasize that values of equilibrium constants and heats for hydrogen bonding determined in solutions may be related to the dimerization reaction in a rather complicated fashion. By way of illustrating this, consider the dimerization reaction of the amides in benzene solutions. The appropriate reactions would be

$$\begin{array}{l} \Delta H_1 + 2\mathrm{A_M}\cdot\mathrm{Bz} \overset{K_1}{\longleftrightarrow} 2\mathrm{A_M} + 2\mathrm{Bz} \\ \qquad\qquad\qquad\qquad\qquad \uparrow\!\underset{K_2}{\longrightarrow} \mathrm{A_D} + \Delta H_2 \end{array} \qquad (5)$$

We may reasonably assume that forming the amide–benzene complex, $\mathrm{A_M{\cdot}B_Z}$, has only a small influence on the amide moment and in making dielectric measurements on solutions of amides in benzene, the single amide molecules and the benzene amide complex both are counted as monomeric units. The appropriate equilibrium constants for the above reactions are

$$K_1 = \frac{[\mathrm{Bz}]^2[\mathrm{A_M}]^2}{[\mathrm{A_M}\cdot\mathrm{Bz}]^2};\ K_2 = \frac{\mathrm{A_D}}{(\mathrm{A_M})^2} \qquad (6)$$

but the experimentally determined constant is

$$K_{\mathrm{exp.}} = \frac{\mathrm{A_D}}{[\mathrm{A_M} + \mathrm{A_M}\cdot\mathrm{Bz}]^2} = \frac{K_2K_1}{[\sqrt{K_1} + \mathrm{Bz}]^2} \qquad (7)$$

Since ΔH_1 and ΔH_2 in reactions (5) probably have the same sign it is apparent that the plot of $-\ln K_{\mathrm{exp.}}$ *vs.* $1/T$ will give a line of smaller slope, *viz.*, smaller heat than would be obtained if $-\ln K_2$ *vs.* $1/T$ had been plotted. In two cases the actual heat of dimerization would be obtained. These are for the condition $K_1 \gg [\mathrm{Bz}]$ or for the case $\Delta H_1 = 0$ over the temperature interval examined. In any case it does appear that heats obtained from solution measurements will gener-

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[7] A. G. Worthing and J. Geffner, "Treatment of Experimental Data," John Wiley and Sons, Inc., New York, N. Y., 1943, p. 170.

ally have a somewhat lower value than that appropriate to the actual dimerization reaction. By the same reasoning it appears that $K_{\text{exp.}}$ will always be less than K_2 but will approach K_2 as K_1 becomes very much larger than [Bz]. The influence of the dielectric constant of the medium represents an additional complicating factor in solution measurements but such factors are probably not first order if a substance of reasonably low dielectric constant, <3, is used as a medium. If the preceding discussion is correct one may expect different values of K and ΔH in media with the same dielectric constant but with different basicities such as say benzene and carbon tetrachloride.

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES, K-25 PLANT, CARBIDE AND CARBON CHEMICALS COMPANY]

Reactions of Polyfluoro Olefins. V.[1] Chemical Properties of Anionic Addition Products[2]

BY KARL E. RAPP, JOHN T. BARR, ROY L. PRUETT, CARL T. BAHNER, J. DONALD GIBSON AND ROBERT H. LAFFERTY, JR.

A variety of chemical reactions which normally involve the functional linkages of organic sulfides, ethers, and amines were investigated using the products of anionic addition of thiols, alcohols, and amines to polyfluoro olefins. The results of these reactions, in a number of cases negative results, established the strong influence exerted by fluorine upon neighboring functional groups of organic, fluorine-containing compounds. Thus the theory is supported that fluorine, in transmitting an extremely electronegative force through the C–F covalent bond, so distorts the electronic field of a neighboring functional group that chemical reaction involving the electrons of this group is virtually prevented except under the most rigorous conditions; and, conversely, the less electronegative nature the central atom of a functional group possesses the less resistance it offers to field distortion allowing the adjacent C–F bonds to become more polar, less covalent, and more susceptible to chemical attack.

Previous reports of this series have described the reactions of certain polyfluoro olefins with thiols,[3] alcohols[4] and amines.[5] The chemical properties of the products of these anionic addition reactions have been studied in an effort to elucidate the role played by fluorine in the chemistry of organic compounds of this type.

Sulfides

Attempts to form sulfoxides from polyfluoroalkyl sulfides, such as those obtained by the addition of thiols to chlorotrifluoroethylene and *unsym*-dichlorodifluoroethylene, by a standard procedure using hydrogen peroxide[6] were unsatisfactory. Experimental evidence indicated initial formation of a sulfoxide which decomposed during purification to revert to the original sulfide. Bromine also proved ineffective as a means of oxidation for subsequent hydrolysis to the sulfoxides. This is significant since the addition of bromine to form the dibromide has been reported to occur readily with organic sulfides.[7] Addition of methyl iodide[8] failed to take place to give the expected sulfonium salts. Although the reaction of alkyl sulfides in adding heavy metal salts qualifies as a test for the C–S–C linkage,[9] its failure to occur in the case of polyfluoroalkyl sulfides has been reported.[3] These examples of the retiring nature assumed by the sulfur atom attest to the strong influence a pair of fluorine atoms bonded to the same carbon exerts upon the reactivity of the neighboring atoms. The strong electronegativity of the fluorine atoms, by drawing electrons from the carbon atom, causes the normal electronic fields of the neighboring atoms to become so distorted that these electrons are available for sharing or transfer only under much more strenuous conditions than are normally necessary. Since all reactions designed to attack these fluorinated molecules near the "fluorine center" would have involved sharing or transfer of electrons, a lack of reaction at this point should not be entirely unexpected.

By way of contrast, however, a more vigorous oxidation of these sulfides with potassium permanganate gave good yields of the corresponding sulfones.[3] The increases of molecular refraction produced by these oxidations (1.70–1.75) are greater by about one unit than that produced by oxidation of diethyl sulfide to diethyl sulfone.[10] According to the theory of Fajans,[11] this indicates that the electronic system undergoes more loosening, or less tightening, in the oxidation of the polyfluoroalkyl sulfides than in the oxidation of the unhalogenated sulfides.

Although sulfones are the normal products of a vigorous oxidation of organic sulfides, such treatment of bis-(alkyl- and arylthio)-tetrafluorocyclo-

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[1] The previous paper in this series is: K. E. Rapp, THIS JOURNAL, **73**, 5901 (1951).

[2] This document is based on work performed for the Atomic Energy Commission by Carbide and Carbon Chemicals Company, a Division of Union Carbide and Carbon Corporation, at Oak Ridge, Tennessee.

[3] K. E. Rapp, R. L. Pruett, J. T. Barr, C. T. Bahner, J. D. Gibson and R. H. Lafferty, Jr., THIS JOURNAL, **72**, 3642 (1950).

[4] J. T. Barr, K. E. Rapp, R. L. Pruett, C. T. Bahner, J. D. Gibson and R. H. Lafferty, Jr., *ibid.*, **72**, 4480 (1950).

[5] R. L. Pruett, J. T. Barr, K. E. Rapp, C. T. Bahner, J. D. Gibson and R. H. Lafferty, Jr., *ibid.*, **72**, 3646 (1950).

[6] M. Gazdar and S. Smiles, *J. Chem. Soc.*, **93**, 1833 (1908;) O. Hinsberg, *Ber.*, **43**, 289 (1910).

[7] J. R. Sampey, K. H. Slagle and E. E. Reid, THIS JOURNAL, **54**, 3401 (1932).

[8] A. von Oefele, *Ann.*, **132**, 82 (1864); A. Cahours, *ibid.*, **135**, 352 (1865).

[9] R. Connor, "Organic Chemistry, An Advanced Treatise," H. Gilman, ed., 2nd ed., John Wiley and Sons, Inc., New York, N. Y., Vol. I, 1943, p. 858.

[10] W. Strecker and R. Spitaler, *Ber.*, **59B**, 1754 (1926).

[11] K. Fajans, "Physical Methods of Organic Chemistry," A. Weissberger, ed., 2nd ed., Interscience Publishers, Inc., New York, N. Y., 1949, Vol. I, Part II, p. 1171.