benzophenone fraction was converted to its 2,4-dinitrophenylhydrazone. From the yield of derivative it was calculated that the over-all yield of benzophenone from 1,2,2-triphenylethanol was 90%. Radioactivity assay of benzoic acid, 1.200 ± 0.014 mc./mole. Radioactivity assay of purified benzophenone 2,4-dinitrophenylhydrazone, 0.5125 ± 0.0027 mc./mole. These two assays total 1.713 ± 0.017 mc./mole (compared with a calculated value of 1.739 mc./mole for the doubly-labeled amine). According to Pearson and Greer,[11] 2.20 g. of benzophenone hydrazone prepared from the foregoing benzophenone was dissolved in 45 ml. of concd. H_2SO_4. The solution was cooled to 5°, and 820 mg. of $NaNO_2$ was slowly added, the mixture being stirred all the while. After about one hour all of the $NaNO_2$ had been added during which time the temperature had been maintained below 8°. The solution was poured onto ice, and the resulting mixture was neutralized with ammonium hydroxide. The crude benzanilide was filtered to yield 2.08 g. of product after desiccation. A portion of this benzanilide (1.5 g.) was boiled for 30 minutes with 20 ml. of 50% (by volume) sulfuric acid. The cooled mixture was extracted with ether. The aqueous layers were carefully and slowly neutralized with sodium hydroxide, and then extracted with ether. The fraction containing the aniline was concentrated, then acetylated by boiling with acetic anhydride to yield 683 mg. (66%) of acetanilide. The benzoic acid fraction weighed 613 mg. (66%). Radioactivity assay of acetanilide, purified by repeated crystallization from benzene, 0.09625 ± 0.00025.

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[11] D. E. Pearson and C. M. Greer, *ibid.*, **71**, 1895 (1949).

[CONTRIBUTION FROM ROHM AND HAAS CO., REDSTONE ARSENAL RESEARCH DIVISION]

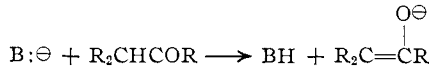
Primary and Secondary Isotope Effects in the Enolization of Ketones

BY WILLIAM D. EMMONS AND M. FREDERICK HAWTHORNE

RECEIVED FEBRUARY 13, 1956

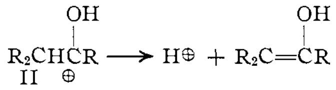
Primary and secondary isotope effects have been determined for the acid- and base-catalyzed rates of enolization of phenyl cyclopentyl and phenyl cyclohexyl ketones. The α-deutero and the $\beta,\beta,\beta',\beta'$-tetradeuteroketones were prepared by standard methods and their enolization rates were determined by using a spectrophotometric bromination procedure. The rates were all obtained in an acetic acid–water solution using sodium acetate as the catalyst for the base-catalyzed rates and hydrochloric acid as catalyst for the acid-catalyzed rates. The observed isotope effects are discussed in terms of previous work on secondary isotope effects in chlorosulfite solvolysis and offer rather striking evidence that Swain's termolecular picture of ketone enolization is correct. The importance of a steric factor in ketone enolization is also pointed out and the Hughes–Ingold picture of ketone enolization is refuted in part.

In recent years two somewhat different pictures of acid- and base-catalyzed enolization of ketones have been presented. Thus the Hughes–Ingold school[1] has proposed that the base-catalyzed enolization of a ketone proceeds through the enolate anion I whose formation is controlled largely by inductive effects of the alkyl groups. The acid-catalyzed enolization is believed by this group to involve the removal of a proton from the conjugate acid of the ketone II and this process is dependent chiefly on hyperconjugation by the alkyl groups in the transition state for the formation of the carbon–carbon double bond. Evidence cited in favor of these concepts is that alkyl groups depress the base-catalyzed enolization rate of ketones. Furthermore, striking differences are often observed during preparative experiments in acid- and base-catalyzed halogenation of the same ketone. Thus while methyl alkyl ketones undergo base-catalyzed iodination almost exclusively in the methyl group (iodoform reaction), acid-catalyzed halogenation generally takes place in the alkyl group.



$$\mathrm{B{:}^{\ominus} + R_2CHCOR \longrightarrow BH + R_2C{=}\overset{O^{\ominus}}{C}R}$$

I

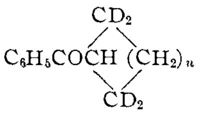


$$\mathrm{R_2CH\overset{OH}{C}R^{\oplus} \longrightarrow H^{\oplus} + R_2C{=}\overset{OH}{C}R}$$

II

In contrast to the above theory of ketone enolization, Swain[2] has presented rather convincing evidence that both the acid- and base-catalyzed enolization of acetone are termolecular reactions involving a nucleophile and an electrophile. Swain analyzed the rather complete rate data on acetone iodination and showed quite clearly that these data were acceptably explained by a termolecular transition state for ketone enolization. Swain did not, however, attempt to present a complete picture of ketone enolization or to explain many of the facts which the Ingold school had utilized in developing their concepts.

In order to obtain a more detailed picture of ketone enolization, it was decided to determine the secondary deuterium isotope effects in the enolization of cyclopentyl-2,2,5,5-d_4 phenyl ketone (IIIa) and cyclohexyl-2,2,6,6-d_4 phenyl ketone (IIIb). Recently the use of secondary hydrogen isotope effects has been developed as a potentially useful tool for studying hyperconjugation so the knowledge of these effects in the above systems conceivably would be of some value in formulating a more complete picture of ketone enolization. In examination of the solvolysis of secondary chlorosulfites Lewis and Boozer initially observed that when β-deuterium was substituted for β-protium, these esters solvolyzed at a considerably slower rate.[3] The transition state for this reaction has a great deal of carbonium ion character so the observed isotope effect is best explained by weakening



IIIa, $n = 2$; IIIb, $n = 3$

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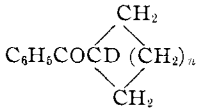
[1] C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell Univ. Press, Ithaca, N. Y., 1953, pp. 557–559; see also R. P. Bell and P. Jones, *J. Chem. Soc.*, 88 (1953).

[2] C. G. Swain, THIS JOURNAL, **72**, 4578 (1950).

[3] E. S. Lewis and C. E. Boozer, *ibid.*, **76**, 791 (1954).

of the β-hydrogen and β-deuterium bonds by hyperconjugation in this carbonium ion. As a result of this bond weakening a portion of the difference in zero point energy between the protium and deuterium chlorosulfites is lost in the transition state for the solvolysis reaction; hence the protium compound solvolyzes at a more rapid rate. Further work has also indicated the possible utility of secondary deuterium isotope effects as a tool for studying hyperconjugation.[4,5] It should, of course, be pointed out that the exact nature of secondary isotope effects and their relationship to hyperconjugation is not fully understood. However, these effects which have been observed in reactions having a considerable amount of carbonium ion character appear to be best correlated by the concept of hyperconjugation in the carbonium ion and the transition state leading to it.

The two tetradeuteroketones were synthesized by conventional methods starting from cyclopentanone and cyclohexanone, respectively. These ketones were exchanged with deuterium oxide and reduced to the alcohols, which were in turn converted to the chlorides. The corresponding Grignard reagents were then prepared and carbonated yielding the acids from which the acid chlorides were obtained. A Friedel–Crafts reaction with benzene gave in each case the final product. In order to present as complete a picture as possible of the deuterium isotope effects in these systems the α-deuteroketones IVa and IVb were also prepared by direct exchange of the corresponding ketones with deuterium oxide.



$C_6H_5COCD(CH_2)_n$ with CH_2 above and below

IVa, $n = 2$; IVb, $n = 3$

Since it was initially anticipated that the secondary deuterium isotope effects would be small, it was first necessary to develop a satisfactory method for accurate measurement of enolization rates of the ketones. Accordingly, a spectrophotometric method for following the bromination of the ketones on a semimicro scale was worked out. This method was greatly superior to titrimetric procedures previously used both in accuracy and in the fact that it could be utilized with very small samples of ketones. Bromine was determined by reading the optical density at 390 mμ in a Beckman DU spectrophotometer. The extinction coefficient of bromine was around 250, the exact value depending on the particular solution employed, and the bromine absorption followed Beer's law at the concentrations employed.

The bromination rates were all determined at 26.70° under zero order conditions with a large excess of ketone. The plots of optical density *vs.* time were linear, and the assembled rate data are summarized in Table I. In general, the rate constants were reproducible to within ±5%, the principal uncertainty being temperature control since the rates were run in stoppered cells inside a thermostated cell compartment of the spectrophotometer. Cyclohexyl phenyl ketone could not be brominated at a measurable rate in the acetate-acetic acid solvent and hence base-catalyzed rates could not be obtained with this ketone. The k_H/k_D ratios obtained from Table I were calculated and are summarized in Table II.

TABLE I

BROMINATION OF KETONES IN AQUEOUS ACETIC ACID

Phenyl ketone	Ketone molarity	Catalyst	Catalyst molarity	First-order rate constant, sec.$^{-1}$ × 10^{-8}	No. of runs
Cyclopentyl	0.611	CH_3CO_2Na	1.83	9.35 ± 0.3	4
Cyclopentyl-2,2,5,5-d_4	.667	CH_3CO_2Na	1.83	7.52 ± .1	2
Cyclopentyl-1-d_1	.602	CH_3CO_2Na	1.83	1.54 ± .1	2
Cyclopentyl	.0579	HCl	0.0722	1300 ± 30	2
Cyclopentyl-2,2,5,5-d_4	.0601	HCl	.0722	1007 ± 50	2
Cyclopentyl-1-d_1	.294	HCl	.0722	328 ± 10	2
Cyclohexyl	.0695	HCl	.722	2520 ± 90	3
Cyclohexyl	.311	HCl	.0722	90.2 ± 3	3
Cyclohexyl-2,2,6,6-d_1	.0427	HCl	.722	1780 ± 50	2
Cyclohexyl-2,2,6,6-d_1	.293	HCl	.0722	64.2 ± 15	2
Cyclohexyl-1-d_1	.398	HCl	.0722	13.4	1

TABLE II

RATIOS OF RATE CONSTANTS FOR HYDROGEN AND DEUTERIUM KETONES IN ENOLIZATION

Phenyl ketone	Aqueous solvent	k_H/k_D (primary)	k_H/k_D (secondary)
Cyclopentyl	CH_3CO_2H, CH_3CO_2Na	6.17	1.24
Cyclopentyl	CH_3CO_2H, HCl	3.96	1.21
Cyclohexyl	CH_3CO_2H, HCl	6.72	1.41[a]

[a] This value was obtained at two acid concentrations and was identical in each case.

Several interesting deductions can be made from the above data. First of all rather large secondary isotope effects were found amounting to 20% in the case of cyclopentyl phenyl ketone and 40% in cyclohexyl phenyl ketone under acid-catalyzed conditions. Thus, if we assume that the secondary isotope effect is a valid measure of hyperconjugation, it is reasonable to propose that the transition state for enol formation is very close to enol itself and is stabilized to a very appreciable extent by hyperconjugation involving the β-hydrogen atoms. It is also interesting to note that since an enol is a high energy species relative to ketone, Hammond's postulate[6] correlating reactions rates and equilibria suggests that the transition state for enolization would be very close to enol in its geometry. Also recent stereochemical evidence has been presented which confirms this hypothesis.[7] Accordingly, it is not surprising that hyperconjugation is the dominating factor in determining in which direction an unsymmetrical ketone will enolize under acid-catalyzed conditions. The fact that a larger isotope effect is found in the cyclohexyl ketone than with the cyclopentyl ketone may also be rationalized on the basis of Hammond's postulate. Brown[8] has shown that a cyclohexane with an exocyclic double bond has a considerably higher energy con-

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(4) V. J. Shiner, THIS JOURNAL, **76**, 1603 (1954).

(5) E. S. Lewis and G. M. Coppinger, *ibid.*, **76**, 4495 (1954).

(6) G. S. Hammond, *ibid.*, **77**, 334 (1955).

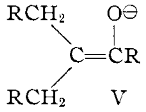
(7) H. E. Zimmerman, *ibid.*, **78**, 1168 (1956).

(8) H. C. Brown, J. H. Brewster and H. Schechter, *ibid.*, **76**, 467 (1954).

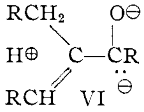
tent (other things being equal) than the corresponding cyclopentyl system. For this reason, the enol from cyclohexyl phenyl ketone will be a higher energy species than that derived from cyclopentyl phenyl ketone. The Hammond postulate[6] suggests, then, that the transition state for formation of the cyclohexyl ketone enol, a higher energy species, will be closer to the enol itself than it will be in the corresponding cyclopentyl system; accordingly, the observation of a larger isotope effect with cyclohexyl phenyl ketone appears quite reasonable. The greater rate of bromination for cyclopentyl phenyl ketone in comparison with cyclohexyl phenyl ketone is also in accord with this analysis. The above discussion assumes that the steric requirements for hyperconjugation are not a major factor in these two ring systems and, while this may be incorrect, so little is known about this question that we cannot consider it at present.

Perhaps the most striking fact which may be derived from Table II is that the base-catalyzed enolization of cyclopentyl phenyl ketone showed a secondary isotope effect of around 20%. This is far beyond experimental error and suggests that the Hughes–Ingold postulate of an enolate anion as an intermediate in this reaction is incorrect and that Swain's termolecular mechanism of ketone enolization more accurately represents the facts, at least under the experimental conditions employed here.

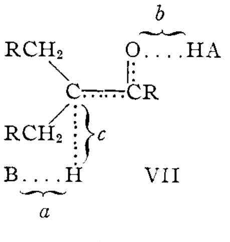
It is highly improbable for an enolate anion such as V or for the transition state leading to its formation to derive significant stabilization from hyperconjugation considered in the normal sense. Indeed this would be tantamount to saying that canonical forms such as VI contribute to the structure of the enolate. This is obviously unlikely since VI violates the adjacent charge rule and would be an extremely high energy structure. Accordingly the existence of this secondary isotope effect in the base-catalyzed enolization appears to be incompatible with an enolate intermediate.[9] This effect readily may be explained, however, using Swain's termolecular mechanism. On this basis the transition state for both acid and base-catalyzed enolization may be broadly represented as VII where B is a general base and HA a general acid. Under these conditions in either the acid or base-catalyzed reactions the transition state will be very close to enol and hence will be stabilized by hyperconjugation. It should be pointed out, however, that while the same model of the transition state will serve for either the acid- or base-catalyzed enolization, the bond distances *a* and *b* will vary considerably. Thus in the acid-catalyzed reaction bond *b* will be relatively tight and bond *a* relatively loose. Hence in the acid-catalyzed enolization steric strain around bond *a* is not observed in most cases and hyperconjugation is, as has been pointed out previously, a dominating factor in the enolization of the ketone. However, in the base-catalyzed reaction bond *a* will be relatively tight and bond *b* relatively loose. Under these conditions a steric factor becomes important and is in fact the probable reason why alkyl groups depress base-catalyzed enolization rates and why differences in preparative halogenations are observed in acid- and base-catalyzed reactions. Indeed the fact that cyclohexyl phenyl ketone could not be brominated at a measurable rate with acetate in acetic acid is inferential evidence for this steric factor. The enolizable hydrogen in cyclohexyl phenyl ketone is almost certainly axial and with a fairly large base such as acetate ion there appears to be sufficient strain in the transition state so that the enolization is extremely slow. Finally it is probably worth mentioning that the secondary isotope effects reported here are at least in part a function of the structure of the ketones under examination. Thus phenyl alkyl ketones are particularly favorable examples for observation of hyperconjugation in the enol since under these conditions the delocalization of the carbon–hydrogen bonding electrons on the β-carbon is maximized by conjugation with the aromatic system.



V



VI



VII

The primary isotope effects summarized in Table II also are worthy of comment and in general fit the picture described above. The isotope effect of 6.17 in the base-catalyzed bromination of cyclopentyl phenyl ketone indicates that bond *c* is quite loose in the transition state. In the acid-catalyzed case the k_H/k_D ratio is somewhat less (a value of 3.96) which again substantiates the hypothesis that in this case bond *b* is relatively tight and bond *a* rather loose. The corollary of this situation is, of course, that bond *c* is fairly tight in the transition state and this results in a lower isotope effect in the acid-catalyzed reaction than in that of base catalysis. The value of 6.72 for the primary isotope effect of acid enolization of cyclohexyl phenyl ketone is also of some interest. Our analysis has already indicated that the transition state for this enolization is very close to enol itself and hence bond *c* is extremely loose in this situation. Accordingly the observation of a larger isotope effect here than in the acid-catalyzed enolization of the cyclopentyl ketone is to be expected and fits the over-all picture of ketone enolization presented above. It should be pointed out, however, that the magnitude of a primary deuterium isotope effect will not always necessarily reflect the amount of bond breaking in the transition state. Indeed, as the transition state gets very close to the products

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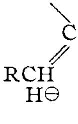
[9] This argument rests on the assumption that hyperconjugation in the enolate anion involving canonical structures such as Va would not contribute enough stabilization to the anion to explain a 20% difference in enolization rate of the hydrogen and deuterium compounds.



Va

of a reaction, there is almost as large a difference in zero point energy in the transition states of the hydrogen and deuterium compounds as there is in the reactants. Under these conditions, then, the isotope effect could be relatively small even though the carbon–hydrogen bond is practically broken. It does not, however, appear that this consideration is of importance in the isotope effects reported here.

Finally it is probably worth pointing out that in terms of the termolecular mechanism the acid-catalyzed rates reported here probably represent the kinetic term with hydronium ion as acid and water as the base. The secondary isotope effect for cyclohexyl phenyl ketone was identical at two acid concentrations suggesting that the same acid and base were involved at both concentrations. Under basic conditions acetate ion was almost certainly the base and acetic acid the acid. Primary isotope effects have also been previously reported for the enolization of several ketones including hexadeuteroacetone.[10] In this case, the values obtained are the result of a combined primary and secondary effect and hence are larger than they should otherwise be.

Experimental

Cyclohexyl phenyl ketone and cyclopentyl phenyl ketone were prepared by standard methods. Cyclohexyl phenyl ketone was purified by a low temperature recrystallization from petroleum ether (−70°) and was sublimed just before use, m.p. 57–58° (lit.[11] m.p. 53–54°). Cyclopentyl phenyl ketone was distilled just before use, n^{20}_{D} 1.5441 (lit.[12] n^{25}_{D} 1.5404).

Cyclopentyl-1-d_1 Phenyl Ketone.—To a solution of 17.4 g. (0.1 mole) of cyclopentyl phenyl ketone in 30 ml. of dry dioxane was added 8.2 ml. of 99% deuterium oxide and 0.1 g. of anhydrous potassium carbonate. The resulting mixture was refluxed under nitrogen for two days and the volatile solvent was then distilled *in vacuo*. The residual ketone was exchanged with deuterium oxide twice more and then purified by distillation. The distillate was exchanged once more under the usual conditions and again purified by distillation. The bromination rates of the ketone after the third and fourth exchanges were identical, indicating that complete exchange had been effected and that pure α-deuterocyclopentyl phenyl ketone was obtained, b.p. 96–98° (0.5 mm.), n^{20}_{D} 1.5455.

Cyclohexyl-1-d_1 Phenyl Ketone.—To a solution prepared from 21 ml. of freshly distilled acetyl chloride and 90 ml. of acetic anhydride was added dropwise with cooling 28 ml. of deuterium oxide. To 42 ml. of this solution was added 17.4 g. of cyclohexyl phenyl ketone, and the resulting mixture was heated under reflux in a nitrogen atmosphere for two days. The volatile solvents were then distilled *in vacuo* and the exchange was repeated. The product was purified by distillation and a small sample was sublimed. The major portion of the ketone was again exchanged, purified by distillation and sublimed at 50° (1.0 mm.). The bromination rates after two and three exchanges were identical indicating that pure α-deuterocyclohexyl phenyl ketone had been obtained, m.p. 58–59°.

Cyclohexyl-2,2,6,6-d_4 Phenyl Ketone.—Three 18.6-g. (0.2 mole) portions of freshly distilled cyclohexanone were exchanged with deuterium oxide using potassium carbonate as catalyst by heating the mixtures under reflux for 24 hr. Successive exchanges were carried out until the exchange was 95% complete. (This was calculated assuming in each case that equilibrium conditions were attained.) The three portions of deuterated cyclohexanone were then combined and converted to cyclohexyl phenyl ketone by standard synthetic methods. The ketone was reduced to cyclohexanol with lithium aluminum hydride which was in turn converted to cyclohexyl chloride. The Grignard reagent was then prepared from the chloride and carbonated. In the final steps of the synthesis cyclohexyl carboxyl chloride was synthesized using thionyl chloride, and a Friedel–Crafts reaction of this reagent with benzene gave the desired product. The deuterated ketone was distilled at 85–90° (0.2 mm.) and then recrystallized from petroleum ether at −70°. There was obtained an over-all yield of 26.2 g. (23%) of ketone which after a final sublimation melted at 58–59°. The infrared spectrum of this ketone showed fairly strong carbon–deuterium stretching bands at 4.65 and 4.75 μ. The deuterium content of this ketone was determined by combustion of a sample and conversion of the water so obtained to hydrogen. The analysis of this gas by a mass spectrometer indicated that the ketone had 3.3 atoms of deuterium per mole of ketone.

Cyclopentyl-2,2,5,5-d_4 Phenyl Ketone.—This ketone was prepared by synthetic methods identical to those outlined above. However, inasmuch as cyclopentanone was destroyed by heating with aqueous base, presumably by aldol condensations, it was necessary to use acid-catalyzed exchange of the ketone with deuterium oxide. Deuterated trifluoroacetic acid was employed as the catalyst and from three 16.8-g. (0.2 mole) portions of cyclopentanone there was obtained 10.7 g. (10%) of the phenyl ketone, b.p. 95–97° (0.5 mm.), n^{20}_{D} 1.5438. The infrared spectrum of this ketone showed carbon–deuterium stretching bands at 4.55 and 4.75 μ. Analysis of the ketone indicated that it had 3.1 atoms of deuterium per mole of ketone.

Rate Measurements.—The stock solution for the base-catalyzed runs was prepared from 150 g. of anhydrous sodium acetate and 85 ml. of water diluted to one liter with glacial acetic acid. The stock solution for the acid-catalyzed runs consisted of 3 ml. of concentrated hyrochloric acid and 50 ml. of water diluted to 500 ml. with glacial acetic acid. A stock solution containing more acid (30 ml. of concentrated hydrochloric acid and 30 ml. of water diluted to 500 ml. with glacial acetic acid) was also used for solvent in the bromination of cyclohexyl phenyl ketone. All measurements were made in a Beckman DU spectrophotometer equipped with thermospacers. Water from a bath maintained at 26.70 ± 0.02° was pumped through the thermospacers. Stoppered matched silica cells (1.0 cm. light path) were used for the determinations and were kept in the cell compartment during the entire run. Weighed samples of each ketone were diluted to volume with the appropriate stock solution, and 3 ml. of this solution was introduced into each cell. At this point 10–25 λ of bromine stock solution (300 λ of bromine per 5 ml. of stock solution) was added. The cells were then placed into the cell compartment, and the reaction was allowed to proceed until the optical density reached values which could be measured accurately (0.1 to 0.7). The reactions were all run under zero-order conditions in the presence of large excesses of ketone. Under these conditions the plot of optical density *vs.* time was of course linear. Measurements were all made at 390 mμ with a slit opening of 1.05 mm. The extinction coefficients of bromine in the acetate solution was 278, in the dilute acid solution 218, and in the concentrated acid solution 243. Blanks were determined and in the absence of ketone the consumption of bromine was negligible in all cases.

In the determination of the acid-catalyzed rates the early portions of the runs were characterized by some curvature of the optical density *vs.* time plots. This is believed to result from traces of peroxides in the ketone which in the presence of acid are capable of oxidizing bromide ion back to bromine. However, the curves all became linear in time so no difficulty was experienced in obtaining accurate zero-order rate constants. It was also found, however, that in order to obtain satisfactory temperature control during the runs, it was necessary to maintain room temperature within two degrees of bath temperature, since otherwise the temperature in the Beckman cell compartment was not reproducible. Also when the small secondary isotope effects were under observation, it was common practice to run the hydrogen and deuterium compounds simultaneously in order to minimize the effects of temperature variation. The accuracy of the rate constants obtained by this method is largely a function of temperature control and is of the magnitude of ±5%.

HUNTSVILLE, ALABAMA

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(10) K. B. Wiberg, *Chem. Revs.*, **55**, 713 (1955).

(11) S. L. Friess and N. Farnham, THIS JOURNAL, **72**, 5518 (1950).

(12) D. H. Hey and O. C. Musgrave, *J. Chem. Soc.*, 1949, 3156.