[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF HAWAII]

Free Radical Intermediates in the Oxidation of Benzoin

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The oxidation of benzoin to benzil in alkaline alcoholic solution gives rise to a purple colored intermediate. This has previously been interpreted as a bimolecular compound akin to a quinhydrone and later as a semiquinone free radical. The magnetic susceptibility of the oxidizing benzoin system has been investigated and the intermediate identified as a relatively stable free radical, an aliphatic analog of the semiquinones. In the course of this work a "slow oxidation" technique has been developed. Purely chemical tests indicate the presence of more labile radicals, either hydroxyl or perhydroxyl or both. The available evidence indicates that a non-chain free radical mechanism is operative in the benzoin oxidation.

Oxidation of benzoin and other α-ketols in alkaline alcoholic solution gives rise to an intensely purple-colored intermediate whose nature has been a subject of controversy.[2-5] Michaelis and Fetcher refuted the dimeric structure originally postulated by Weissberger and proposed instead a stable semiquinone free radical. This has subsequently been accepted by Weissberger.[6,7] The experimental evidence for the stable radical has remained equivocal. Kawai[8] on theoretical grounds has predicted too short a lifetime for facile experimental determination of the radical, a statement at variance with Michaelis' conclusion based on a colorimetric dilution test.

Thus it seemed desirable to investigate the magnetic susceptibilities of oxidizing benzoin solutions for possible paramagnetic increments which would provide definite evidence for a stable semiquinone. Semiquinone oxidation theory requires also the presence of more labile radical species which cannot be detected magnetically. It was deemed advisable to apply also the phenol tests of Stein and Weiss[9] which are diagnostic for hydroxyl or perhydroxyl radicals.

Further interest was provided by the fact that all "stable" semiquinones reported have been aromatic in nature whereas the one postulated by Michaelis is essentially aliphatic.

Experimental

All chemicals used were the best commercial grades available, purified by standard methods. The Folin–Denis reagent for phenols was prepared according to Snell and Snell.[10]

The magnetic measurements were made with a Gouy-type balance utilizing a permanent magnet. The details of this equipment may be found elsewhere.[11]

The simplest type of measurement made was of the susceptibility of intensely colored purple solutions relative to the same solutions decolorized. In a typical run a solution of benzoin in alcohol was placed in the sample tube and aqueous sodium hydroxide added. Sufficient air to cause an intense purple color was then bubbled through. After the measurement the purple color was destroyed by bubbling air through the sample until the color disappeared and did not reappear upon standing. The value for the decolorized solution was then determined. Several hours standing was usually necessary before a steady value could be obtained.

The change in the force exerted upon the sample tube by the magnetic field was due not only to susceptibility differences but also to solvent evaporation and to the different amounts of air dissolved in the purple and the decolorized solutions. Two types of blank runs were made to correct for these effects. Details may be found in the thesis.[1]

Experiments were made using the slow reduction method of Michaelis[12] with glucose as the reductant and nitrogen gas to purge the solutions of air. In a similar manner runs were made using oxidizing agents instead of the glucose and benzoin in place of benzil. This method of "slow oxidation" seems not to have been reported heretofore but should be of general applicability. Nitrobenzene and benzoyl peroxides were the oxidants investigated; only with the latter were significant magnetic changes observed at the high *p*H's of our experiments.

Further runs in which both benzoin and benzil plus oxidant (benzoyl peroxide or air) were present were performed. In these the relative proportions of benzoin and benzil were changed while the total number of moles of organic solute was held constant as was the base strength. Finally, susceptibility change curves were run at two different base concentrations to determine the influence of base concentration upon the stability of the intermediate.

Chemical tests for the presence of phenolic products were carried out by adding benzene to alkaline alcoholic solutions of benzoin. Under these conditions it has been found[9] that labile radicals like ·OH attack the added benzene, eventually producing mono- or polyhydric phenols. Oxygen gas was bubbled through the solution for several hours to oxidize the organic solute. All but about 50 ml. of the solvent was then removed by evaporation under reduced pressure. The remaining solution was acidified with concentrated hydrochloric acid and extracted with ether. The ether layer was extracted with 10% sodium bicarbonate solution and then with 10% sodium carbonate solution. The remaining ether layer was then extracted with 10% sodium hydroxide solution, and the sodium hydroxide layer was acidified with concentrated hydrochloric acid. This solution was then extracted with ether, and the ether layer was evaporated. Less than 0.5 ml. of liquid remained. Concentrate obtained in this way was used in the ferric chloride, Folin–Denis and bromine water tests for phenols.

Results

Magnetic Experiments. (1).—The method of slow reduction employing glucose and benzil did not yield any appreciable magnetic changes corresponding to the color change which progressed from pale yellow to dark amber. It seems probable that at the high concentration of sodium hydroxide (about 0.1 *M*) polymerization competes too effectively with the simpler reduction reaction. Michaelis[12] gives an upper limit of *p*H 12 for the method.

The analogous slow oxidation, though, gave rise

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(1) From the M.S. thesis of Robert G. Caldwell, University of Hawaii, 1955.

(2) R. Scholl, *Ber.*, **32**, 1809 (1899).

(3) A. Hantzsch and W. A. Glower, *ibid.*, **40**, 1519 (1907).

(4) A. Weissberger, H. Mainz and E. Strasser, *ibid.*, **62B**, 1942 (1929).

(5) L. Michaelis and E. S. Fetcher, THIS JOURNAL, **59**, 1246 (1937).

(6) J. E. LuValle and A. Weissberger, *ibid.*, **69**, 1567 (1947).

(7) A. Weissberger, *Biol. Antioxidants*, Trans. 3rd Conf., 33 (1948).

(8) W. Kawai, *Kagaku*, **23**, 363 (1953).

(9) G. Stein and J. Weiss, *J. Chem. Soc.*, 3245 (1949).

(10) F. D. Snell and C. T. Snell, "Colorimetric Methods of Analysis," Vol. II, D. Van Nostrand Co., Inc., New York, N. Y., 1937, p. 348.

(11) J. L. Ihrig and R. G. Caldwell, *J. Chem. Educ.*, **32**, 320 (1955).

(12) L. Michaelis, in A. Weissberger, ed., "Physical Methods of Organic Chemistry," 2nd Ed., Interscience Publishers, New York, N. Y., 1949, pp. 1912–14.

to a decided paramagnetic increment with approximately equimolar solutions of benzoin and benzoyl peroxide. When the solutions were first mixed they took on a purple color which soon faded and then changed to a dark brownish hue and finally to amber. The magnetic changes roughly paralleled these color changes. The initial fading of the purple color was accompanied by a sharp drop in the paramagnetism of the solution. As the solution again darkened, its susceptibility was found to rise. Finally as the color faded to a lighter amber, the paramagnetic increment again became lower.

The magnetic changes for two representative runs are illustrated in Fig. 1. Here the changes in weight difference of the sample suspension in and out of the field are plotted against time. Quantitative agreement cannot be expected since the solute concentrations were not exactly the same and also because of the small (10–20 micrograms) differences in Δw values at the maximum and minimum points of the curves. Good qualitative agreement was always obtained, however.

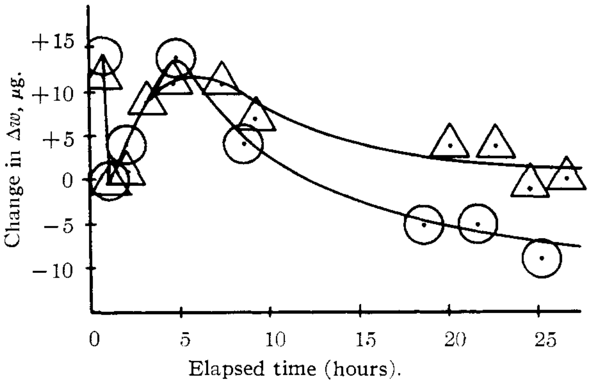

Fig. 1.—Susceptibility runs at 29.0° with solvent 73% ethanol by volume and base concentration 0.462 *M*: ⊙, benzoin 0.0309 *M* and peroxide 0.0308 *M*; ◬, benzoin 0.0305 *M* and peroxide 0.0326 *M*.

(2).—In a run with base concentration the same and benzoyl peroxide concentration very nearly the same as in (1) and with a mixture of 80% benzoin and 20% benzil, the initial susceptibility drop seems to be slightly larger. The subsequent maximum is reached more slowly and is slightly less than in previous runs (Fig. 2).

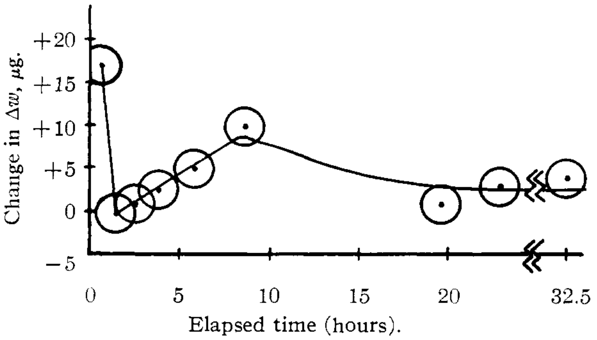

Fig. 2.—Same conditions as Fig. 1 except benzoin replaced by same concentration of 80% benzoin–20% benzil mixture.

(3).—Two runs were made as described above in (1) except that in one the benzoyl peroxide concentration was doubled, *i.e.*, 2 moles of peroxide per mole of benzoin. In the other this ratio was reversed, *i.e.*, one-half mole of peroxide per mole of benzoin. The initial purple color of the solution for the 2:1 case was discharged before a magnetic measurement could be taken. The Δw values obtained were constant to ± 3 micrograms.

The results of the 1:2 case are illustrated in Fig. 3. The initial paramagnetic decrease for this run was much more gradual than in any of the preceding runs. The paramagnetism slowly fell to a constant value. The initial purple color of the solution did not completely fade, as in the previous runs, but slowly changed to a dark solution with a brownish hue.

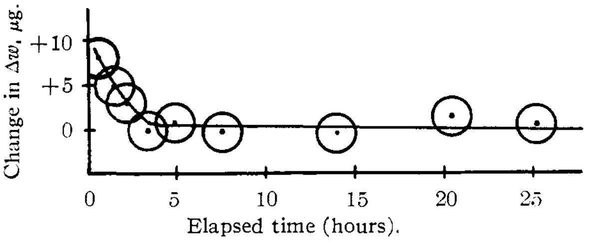

Fig. 3.—Same conditions as Fig. 1 except for peroxide concentration 0.0154 *M*.

(4).—In every simple determination of susceptibility difference between the purple and decolorized solutions, the paramagnetic increment fell off upon decolorization of the solution. The change in Δw values was close to -17 micrograms in a series of refined measurements, and this may be taken as a measure of susceptibility fall. However, in decolorizing the solutions air is passed through and this opens the possibility that there could have been a hidden paramagnetic increment due to dissolved oxygen. It is obvious that such could not have been the case when the solutions were purple, but it is possible that excess oxygen might have been present after decolorization. Blank runs measured first under nitrogen and then saturated with air invariably showed a rise in susceptibility amounting to about $+35$ micrograms. This value also includes the correction of $+6$ micrograms (value determined independently) due to solvent evaporation over the hours. Thus if there were no complicating factors a simple algebraic addition would provide an upper limit of the paramagnetic increment caused by the presence of the semiquinone. The sum would be $+35-(-17)$ or $+52$ micrograms.

However, it seemed almost certain that oxygen was being consumed by further reaction. In the first place, the susceptibility of the decolorized solutions fell rather slowly over a period of several hours to its final value. This indicated that the dissolved oxygen continued to react. Then too, Weissberger[4] found that the end products of the reaction were largely acids rather than the diketone, benzil, and that longer standing increased the yield of these secondary oxidation products. In view of this, we may set as a *lower* limit of the increment the value obtained assuming all dissolved oxygen is ultimately consumed or $\Delta w = 0 + 6-(-17) = +23$ micrograms. To obtain more information on this point a series of composition–susceptibility experiments were made.

(5).—Figure 4 shows the results of runs made at the same solvent composition and base concentration as before, and the organic solute concentration was kept the same but now consisted of varying proportions of benzoin and benzil. As in the runs described in (4), air was also admitted initially. At 20% benzil concentration a maximum paramagnetic increment of ~20 micrograms is obtained. At 100% benzil the susceptibility rises to a high value due to dissolved oxygen. Here the solution was not purple colored nor had it stood long enough for the slow reaction of oxygen and benzil. Such a result tends to confirm the idea that a correction of the final Δw value in the previous runs is not warranted. The maximum increment of 20 obtained here agrees well with our lower limit value of 23 obtained in the slow oxidation experiments.

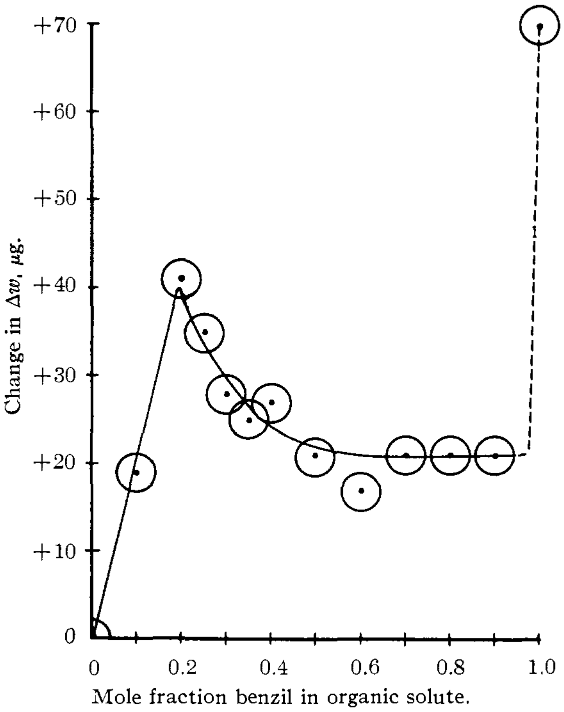

Fig. 4.—Solvent 73% ethanol, base concentration 0.462 *M* varying benzoin–benzil proportions.

(6).—A similar run at lower base strength is shown in Fig. 5. Here the solution was only 0.115 *M* in sodium hydroxide as opposed to 0.462 *M* in the runs of Fig. 4. Not only was the maximum in the curve decreased but there was also a shift toward the 50% composition mark. This behavior will be interpreted subsequently.

Chemical Experiments.—Concentrated extract from the oxidation of benzoin solutions gave strongly positive ferric chloride and Folin–Denis tests for phenols. In addition, when bromine water was added to a portion of extract, the solution turned cloudy. There was not enough precipitate to collect and purify. However, the cloudiness of the solution was taken as an indication of phenolic products.

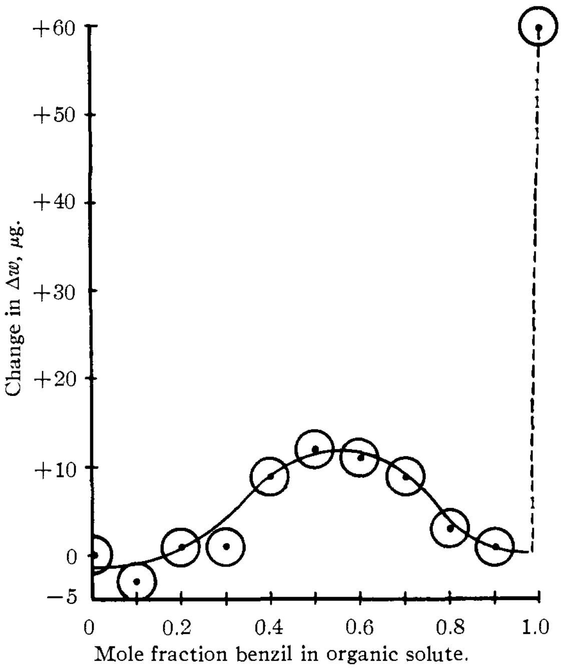

Fig. 5.—Same conditions as Fig. 4 except for base concentration 0.115 *M*.

Discussion

Before discussing the results, it is to be emphasized that not much *quantitative* significance should be ascribed to the curves, due to the small magnitude of the magnetic effect and also to the lack of knowledge of the exact processes taking place in the solution.

The observed magnetic changes in section (1) can be explained as follows, if free semiquinone radicals are assumed to be present as an intermediate. When the solution was first mixed, the oxygen present in dissolved air reacted with benzoin to form some semiquinone radicals whose presence was indicated by the purple color. As the benzoyl peroxide broke down to form radicals, these reacted rapidly with the semiquinone radicals originally present. The lowering of the semiquinone concentration corresponded to the sharp initial drop in the paramagnetism of the solution. Upon the depletion of the semiquinone radicals, the benzoate or phenyl radicals then attacked the benzoin anion. As the number of free radicals being produced from peroxide was diminished, due to less undissociated benzoyl peroxide remaining in solution, the semiquinone concentration was allowed to build up slowly. The semiquinone concentration reached a maximum and then fell off as the semiquinone radicals eventually reacted in various ways. This corresponds to the formation of the maximum in the paramagnetic increment of the solution and its subsequent drop as the fully diamagnetic state was re-established.

With a substrate of benzoin plus benzil, as in section (2), there should be a higher initial concentration of semiquinone radicals due to the interaction of benzoin and benzil. This prediction is borne out by the slightly greater initial susceptibility drop. If the previous explanation is correct, then the observed depression of the subsequent maximum in the curve and the fact that it is not attained so rapidly are results to be expected because of the higher initial semiquinone concentration and lower benzoin concentration.

The results of the runs section (3) with a doubled amount of peroxide also support the explanation offered. If the concentration of benzoyl peroxide is great enough, the increased number of benzoate or phenyl radicals being formed will react with any semiquinone as it is formed. If the benzoin is consumed before the benzoyl peroxide concentration is sufficiently decreased, no semiquinone concentration build-up can be expected and, consequently, no paramagnetic increment would be added to the susceptibility of the solution. This agrees with the experimental observations.

The curve obtained (Fig. 3) when the peroxide was halved [section (3)] is also consistent with the semiquinone explanation. Since the benzoyl peroxide concentration was initially lower, fewer of its radicals were available to react with the semiquinone. The paramagnetism of the solution fell slowly, as the semiquinone reacted with the smaller number of radicals from the peroxide and reached constancy as the solution became essentially depleted of peroxide radicals. The magnitude of the paramagnetic decrease is smaller than in the previous runs, but has the expected behavior at least qualitatively. The final solution may also still have a paramagnetic increment, due to some semiquinone radicals left in solution after the peroxide radicals have disappeared. The combined evidence of the slow oxidation runs supports the contention that semiquinone radicals of reasonable stability are intermediates in the oxidation process.

The simple susceptibility comparisons between purple and decolorized solutions of section (4) further confirm the hypothesis that the purple material must be a "stable" semiquinone. That this susceptibility difference was merely an artifact was a possibility eliminated by the blank runs of section (5). In addition, the combined data of these last two types of experiment permit more exact estimates of the stability of the radical and of its concentration.

Although the general shape of the curve in Fig. 4 was that expected for a semiquinone intermediate, the maximum did not occur at the expected composition of 50% benzil.

The reason for the shift probably lies in the fact that the benzilic acid rearrangement in these strongly basic mixtures may well remove benzil from the solution, displacing the benzoin–benzil equilibrium so as to cause a decrease in semiquinone concentration. This would result in a shift of the maximum to the left in the figure.

An even more likely explanation is that at high base strengths doubly ionized benzoin enol would constitute an important part of the reactive material (considered by Weissberger[13] to be largely singly ionized enol under his conditions). This new form would produce an increased concentration of stabilized *ionized* semiquinone at the expense of the less stable un-ionized semiquinone.

If either or both of these explanations are valid, we should expect that similar experiments at lower base concentration should result not only in a lowering of the amount of semiquinone present but also in a shift of the maximum toward the 50% mark. Figure 5 shows that this prediction is borne out.

The results may be used to obtain a rough estimate of maximum semiquinone radical concentration. Since the molar susceptibility of a monoradical is about $+1230 \times 10^{-6}$ c.g.s. units at 29°, the susceptibility of one ml. (the volume susceptibility) of a solution which has a free radical concentration of one mole per liter is $+1.23 \times 10^{-6}$ c.g.s. units. The maximum paramagnetic increment due to the presence of semiquinone radical was about 20 micrograms. This value multiplied by the cell constant obtained in calibrating the apparatus gives the increment in terms of volume susceptibility. This amounted to $+20 \times 0.62 \times 10^{-10}$ or $+1.24 \times 10^{-9}$ c.g.s. units. Thus the semiquinone concentration must be $1.24 \times 10^{-9}/1.23 \times 10^{-6}$ or about 1.0×10^{-3} *M*. Since the total organic solute concentration was roughly 0.031 *M*, the amount of solute in radical form is seen to be approximately 3.2%.

From this we may approximate the equilibrium constant for the reaction $R + T \rightleftarrows 2S\cdot$ Because of the uncertainty in the concentrations of the various components, we cannot use the results graphed in Fig. 4. At the lower base concentration of the experiments of section (6), we are perhaps justified in attempting a calculation. If an increment of 20 micrograms corresponds to a radical concentration of 1.0×10^{-3} *M*, then the 12 microgram increment in Fig. 5 represents a concentration of 6.0×10^{-4} *M*. The equilibrium constant, K, can be estimated for the reaction in the solutions having a total organic solute concentration of about 0.031 *M* and a base concentration of 0.115 *M* at a temperature of 29.0° as

$$K = \frac{[S\cdot]^2}{[R][T]}$$

At the maximal free radical concentration, $[S\cdot] = 6.0 \times 10^{-4}$ *M*, the concentrations of the reduced and the oxidized forms are equal, *i.e.*, $[R] = [T]$. Then $[R][T] = [T]^2$, and $[T]$ is equal to $^1/_2$ the total organic solute concentration minus the semiquinone concentration.

$$K = \frac{[6.0 \times 10^{-4}]^2}{\left[\frac{0.031 - 0.0006}{2}\right]^2} = \frac{3.6 \times 10^{-7}}{2.2 \times 10^{-4}} = 1.6 \times 10^{-3}$$

The effective dismutation constant of the semiquinone under the given experimental conditions is the reciprocal of the above equilibrium constant or about 6.2×10^2 at a base concentration of 0.115 *M*.[14]

The semiquinone theory of oxidation requires the presence of other free radicals besides the semiquinone. Such species as hydroxyl or perhydroxyl radicals are commonly found in these oxidation re-

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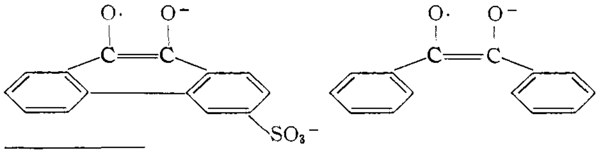
[13] A. Weissberger, E. Strasser, H. Mainz and W. Schwarze, *Ann.*, **478**, 112 (1930).

[14] This equilibrium as formulated implies that the purple radical will be produced in an alkaline alcoholic solution of benzoin and benzil with no other reagent present. This is true and has been observed and reported by Michaelis and Fetcher.

actions. Of course, these cannot be detected magnetically and so recourse was had to the indirect chemical tests described previously. These tests proved positive for either hydroxyl or perhydroxyl radicals or both, but it was not felt possible to decide between them.[15] In any case, there is strong evidence for the presence of labile radical intermediates in addition to the relatively stable semiquinone.

Conclusions

The magnetic and chemical evidence point quite definitely to a free radical mechanism operative in this oxidation. Thus the view of Michaelis and Fetcher that a stable aliphatic semiquinone is formed appears to be confirmed. It is interesting to compare the maximum radical concentration of 3% found here with that of the semiquinone of phenanthrenequinone-3-sulfonate (9,10-dihydro-9,10-dioxo-3-phenanthrenesulfonate)[16] which has an equilibrium radical concentration of 31–44%. Structurally the two semiquinones are not unlike as shown below in their enediolate form



It can be seen that radical stabilization due to resonance structures with the odd electron or the charge, or both, located in the benzene rings must be much greater in the case of the phenanthraquinone semiquinone than with its benzil counterpart. For such structures to play an important role it is necessary that the benzene rings be coplanar with the enediolate portion.[17] This coplanarity is of course, fixed at all times in the phenanthrene semiquinone thus making a much greater stability possible.

Although a complete formulation of the reaction mechanism is probably premature at this stage, one final point may be of interest in this connection.

The data so far obtained in the study of the benzoin oxidation by Weissberger and by us have given no indication that this oxidation is a chain reaction. This may be offered as further support, at least, for the differentiation theory of Merz and Waters.[18] These authors have concluded that a substance having a free radical intermediate in which the electron density at the point of free valency is high will display a chain oxidation. The unpaired electron of the benzil semiquinone is considerably delocalized and thus should not be oxidized by a chain mechanism.

Acknowledgments.—We gratefully acknowledge the financial support of the University of Hawaii Research Committee. We also wish to thank Dr. P. J. Scheuer for many helpful discussions.

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[15] Stein and Weiss have stated that the phenolic tests are specifically diagnostic for hydroxyl radicals. However, we feel that there is no unequivocal evidence to dispute the possibility of benzene dehydrogenation by perhydroxyl radicals as well.

[16] L. Michaelis, G. F. Boeker and R. K. Reber, THIS JOURNAL, **60**, 202 (1938).

[17] G. W. Wheland, "The Theory of Resonance," John Wiley and Sons, Inc., New York, N. Y., 1944, pp. 92–94.

[18] J. H. Merz and W. A. Waters, *J. Chem. Soc.*, 2427 (1949).

HONOLULU 14, HAWAII

[A JOINT CONTRIBUTION FROM OAK RIDGE NATIONAL LABORATORY AND EMORY UNIVERSITY]

The Application of Isotope Dilution Technique in Studies of Reaction Rates and Equilibria: The Effect of Diene Structure on the Rate of the Diels–Alder Reaction

BY ELMER J. DEWITT,[1] CHARLES T. LESTER[2] AND GUS A. ROPP

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By applying a combination of techniques, it has been found possible to make for the first time a rigorous study of the effect of the electronic character of dienes on the rates of Diels–Alder reaction with maleic anhydride. Pairs of *para*-substituted 1-phenyl-1,3-butadienes were permitted to compete for maleic anhydride at low temperatures. The product mixtures were analyzed by making application of isotope dilution technique, and the effects of the *para* substituents on the reaction rate constants were quantitatively evaluated at several temperatures. Results were correlated using the Hammett equation, and the effect of the electronic character of the series of substituents was found to be in accord with accepted ideas of the Diels–Alder reaction mechanism.

I. Method

The use of competitive rate studies is a well-established method of investigating a chemical reaction.[3] If proper precautions regarding changes in concentration and reversibility are taken, it is possible to equate product ratios with reaction rate ratios. Many reaction rates can be studied only in this way.

The practical utility of competitive rate studies has been greatly enhanced in recent years by the development of the isotope dilution technique.[4] By the use of C-14 labeled compounds, followed by radioassay[5] of the carbon dioxide produced by the oxidation of a quantitatively diluted sample one can determine the yield of a particular compound without the tedium of quantitative isolation.

The application of these techniques has been made to the Diels–Alder reaction. This is a reaction for which precise rate studies have been reported in only a few cases. For a number of other

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[1] Research Fellow, Emory University, Emory University, Ga.

[2] Research Participant at Oak Ridge National Laboratory, Summer, 1953.

[3] For a concise discussion of competing reactions, see the section by T. S. Lee in "Techniques of Organic Chemistry, Volume VIII, Rates and Mechanisms of Reactions," A. Weissberger, Interscience Publishers, Inc., New York, N. Y., 1953, p. 100.

[4] For a discussion of such applications to organic chemistry, see G. A. Ropp and O. K. Neville, *Nucleonics*, **9**, 22 (1951).

[5] (a) O. K. Neville, THIS JOURNAL, **70**, 3501 (1948); (b) V. F. Raaen and G. A. Ropp, *Anal. Chem.*, **25**, 174 (1953); (c) C. J. Collins and G. A. Ropp, THIS JOURNAL, **77**, 4160 (1955).