[Contribution from the Department of Chemistry, Vanderbilt University]

THE QUESTION OF HYPERCONJUGATION OR OF BULK EFFECT IN THE BECKMANN REARRANGEMENT

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The rates of rearrangement of some substituted acetophenone oximes in sulfuric acid were reported in two previous communications (1, 2). It was shown that a plot of log rate of rearrangement *versus* the Hammett sigma constants gives essentially a straight line of negative slope. In this plot, points representing the *p*-chloro and *p*-methoxy substituents fell above the line thus indicating faster rates than predicted. This behavior was attributed to the electromeric properties of the chloro and methoxy groups participating in a reaction of an electrophilic nature. New sigma$_e$ constants were suggested for these groups which seemed applicable in predicting rates of other electrophilic reactions. On the other hand, a point representing the *p-tert*-butyl group fell below the line indicating a slower rate than predicted. This behavior could be explained on the basis of hyperconjugation which has served to explain similar rate sequences in other electrophilic reactions, *i.e.*, the reaction rate of the *p*-methyl derivative is faster than predicted because of conjugative electron release properties of the methyl group which are not inherent in the *p-tert*-butyl substituent. An alternative interpretation of this behavior, however, was that the *p-tert*-butyl group exerted a bulk effect (3), an interpretation which is particularly appealing if *p*-quinoid structures are considered to be involved in the transition complex. The *p*-methyl derivative would then be normal in its rate of rearrangement and the *p-tert*-butyl derivative slower than predicted.

The purpose of the presently reported work was to secure evidence which would serve to indicate which of these alternative explanations, hyperconjugation or bulk effect, is correct. The problem of this distinction was approached in two ways. First, substituents were selected of such a nature that electron release contribution by electromerism would be quite small, such, for example, as to be found in the *m*- and *p*-nitro groups and the *m*-methyl and 3,5-dimethyl groups. The nitro groups, because of their strong electron-withdrawing powers, would resist tendencies toward electron-release under any circumstances (4), and the methyl groups in the *meta* position would not be conjugative with the reaction center nor expected to exert significant bulk effect in *p*-quinoid structures. Accordingly, the rates of rearrangement of acetophenone oximes with these substituents were determined, that of the *p*-nitro compound having been determined previously. Relative to the rates of these compounds, the rate of rearrangement of *p*-methylacetophenone oxime should be more rapid than predicted from Hammett sigma constants if hyperconjugation is an important contributing factor. Second, if the relative slowness of the *p-tert*-butyl derivative

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[1] From the Ph.D. Thesis of J. D. Bruton, Vanderbilt University, 1953; University Microfilms, Ann Arbor, Michigan.

TABLE I

Rate Characteristics of the Rearrangement of Acetophenone Oximes in Sulfuric Acid

OXIME[a]	t°, C.	$k^b \times 10^3$	$t^c_{\frac{1}{2}}$	E^d_A	ΔS^e	SIGMA
m-Nitro	40.9	0.0105 ± 0.0005	66,000	29.5	2.4	+0.71
	50.9	0.0458 ± 0.0001	15,240			
m-Methyl	40.9	0.489 ± 0.0085	1,418	26.0	−1.3	−0.10
	50.9	1.763 ± 0.024	392			
3,5-Dimethyl	40.9	0.671 ± 0.008	1,003	25.6	−1.9	−0.20
	50.9	2.377 ± 0.029	291			
3,4,5-Trimethyl	40.9	1.056 ± 0.056	656	25.2	−1.2	−0.37
	50.9	3.729 ± 0.066	186			

[a] Concentration: 0.001 mole in 10.0 ml. of 94.5% sulfuric acid (Merck). [b]first order rates in reciprocal minutes; standard deviation. [c]minutes. [d]kilocalories. [e]entropy units.

was a result of bulk effect, a similar but perhaps smaller retarding effect might be simulated by flanking the *para* position with alkyl groups in the 3,5-positions. Such compounds as 3,4,5-trimethyl- and 3,5-dimethyl-4-*tert*-butyl-acetophenone oximes should serve this purpose. The latter compound could not be made, a result which was anticipated by Brown (5), but the former was obtained by the unique method of Baddeley (6); by fixing the carbonyl group of acetomesitylene with excess aluminum chloride, to prevent condensation and hydrolytic cleavage (7) as well as to promote rearrangement, and by heating at 170° for several hours, Baddeley isolated 3,4,5-trimethylacetophenone in satisfactory yields. The procedure was duplicated in this laboratory, and the rate of rearrangement of this oxime was included in these studies.

The rates of rearrangement in concentrated sulfuric acid were followed by the gravimetric determination of the 2,4-dinitrophenylhydrazones obtained from the unchanged oximes as previously described (1, 2). The results are shown in Table I and the log rates at 50.9° are plotted *versus* Hammett sigma constants in Figure 1. The sigma constant for the *p*-methyl group has been changed from −0.138, as recorded in a previous communication (2, 8), to −0.17, as originally proposed by Hammett and substantiated by Price and Lincoln (3). Berliner, *et al.* (9) have submitted data in support of an intermediate value and also have pointed out that these values are somewhat variable depending on the medium. The slope of the line of Figure 1 is −1.94 which does not differ significantly from the slope (−1.95) previously calculated (2).

In view of the above uncertainties as well as those of ordinary rate determinations, limitation must be put on interpretation of the results. Accordingly, the Hammett values and slope of the line in Figure 1 were selected to show the least prejudice, and interpretations concern only deviations which seem outside the cumulative limits of error. The results, in the opinion of the authors, are best interpreted in terms of the bulk theory rather than the hyperconjugation theory. The *p*-methyl derivative does not show hyperconjugation with respect to any group other than the *p*-*tert*-butyl group, *i.e.*, the line drawn from the

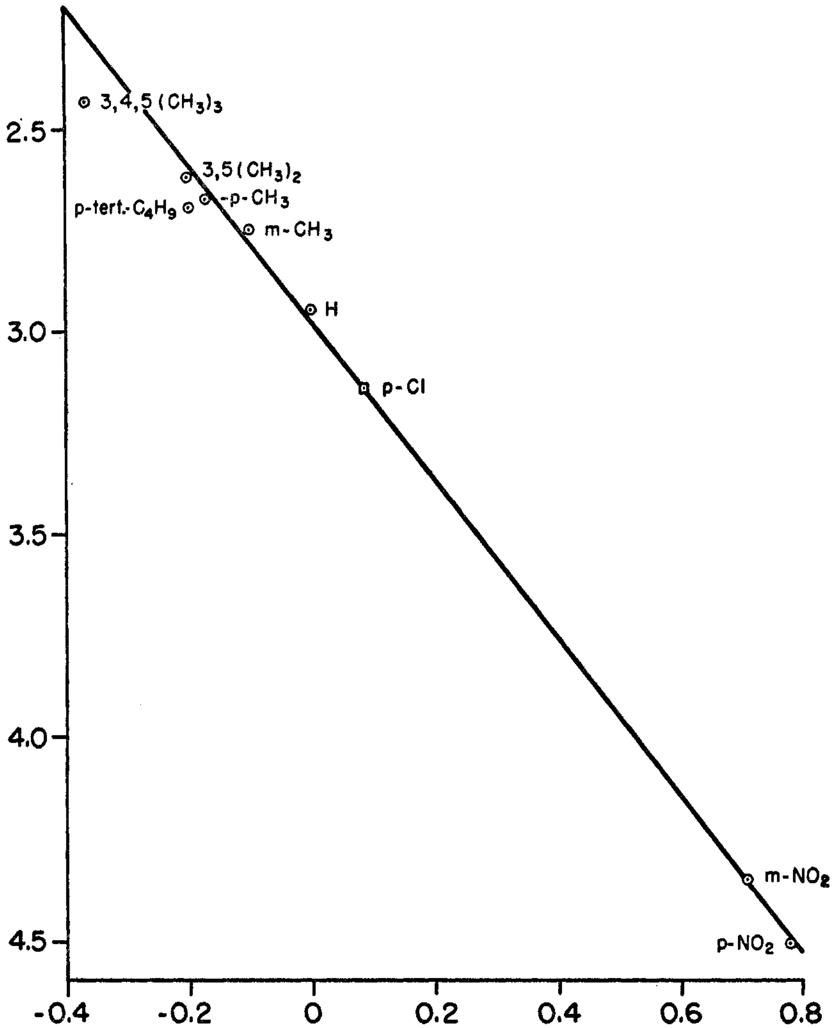

FIG. 1. LOG RATE OF REARRANGEMENT OF SUBSTITUTED ACETOPHENONE OXIMES *versus* SIGMA. Concentration of oxime: 0.001 mole in 10.0 ml. of 94.5% sulfuric acid. Temperature: 50.9°. Rho, the slope: −1.94. First order rates with respect to oxime. Sigma$_e$ used for *p*-chloro point.

p-methyl point to any other single point, *m*-methyl, *m*- or *p*-nitro or others, has a smaller negative slope than −1.94. If the *p*-methyl group did show unusual electron-release powers, the point representing this group would have fallen above the line, as was observed with the *p*-chloro and the *p*-methoxy derivatives. The reaction rates of the *p*-chloro and *p*-methoxy derivatives were, respectively, 1.8 and 3.8 times faster than predicted.[2] In comparison with the electromeric

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[2] The sigma$_e$ constants have been changed slightly from the previous tentative values (2); *p*-chloro sigma$_e$ = +0.086; *p*-OCH$_3$ = −0.56.

effects of the *p*-chloro and *p*-methoxy groups which lead to abnormally fast rates of rearrangement, the hyperconjugative effect of the *p*-methyl group is negligible. It therefore seems more reasonable to assume that the influence of the *p*-methyl group is fairly constant in both nucleophilic and electrophilic reactions and that the electron release ability of the *p*-*tert*-butyl group is smaller in certain electrophilic reactions (probably those involving *p*-quinoid structures) because of a bulk effect previously proposed (2). The behavior of the 3,4,5-trimethylacetophenone oxime in rearrangement may also lend support to the bulk theory, but confirmation of this possibility must await further evidence. Based on the assumption that multiple substituents have additive sigma values [for which there is some but not completely adequate experimental support (10)], the rate of rearrangement of 3,5-dimethylacetophenone oxime was found to be predictable by doubling the sigma constant of the *m*-methyl group (see Fig. 1). On the other hand, the rate of 3,4,5-trimethylacetophenone oxime was found to be markedly slower than would be predicted from the additive sigma constants ($-0.2 + -0.17 = -0.37$). This response was predicted by the bulk theory but may also be accounted for by the hyperconjugation theory in the following way: the crowding of the 3,5-dimethyl groups may force the 4-methyl group partly out of the plane of the ring thus reducing electron-release properties whether they arise from inductive or hyperconjugative causes. If this is true, however, such an effect should also be manifested in nucleophilic reactions such as the saponification rate of ethyl 3,4,5-trimethylbenzoate. Until such direct comparisons are made, the retarded rate of rearrangement of 3,4,5-trimethylacetophenone oxime must not be considered as evidence in favor of the bulk theory.

In summary, one convincing argument in favor of the bulk theory has been found in studying rates of rearrangement of substituted acetophenone oximes, namely, that the *p*-methyl group shows no hyperconjugative properties with respect to any group other than the *p*-*tert*-butyl group. Further available evidence may eventually support the bulk theory, namely, that the 3,4,5-trimethyl grouping shows retarding influences in the Beckmann rearrangement (and probably in other electrophilic reactions); the validity of this evidence must depend upon demonstration, not yet made, that no such retarding influence occurs in nucleophilic reactions.

EXPERIMENTAL[3]

m-Nitroacetophenone and derivatives. The Organic Syntheses' method (11) was followed except that, during the addition of nitric acid, the solution of acetophenone in sulfuric acid was held below −25° by means of a Dry Ice bath. The yield was 75%, reported (11) 55%; m.p. 76–78°.

The oxime of this ketone and of all other ketones was made as follows: a cold, aqueous solution of sodium hydroxide (6.0 g., 0.15 mole in 18 ml. of water) was added slowly to an aqueous solution of hydroxylamine hydrochloride (13.9 g., 0.2 mole in 30 ml. of water), the resultant mixture being neutral to litmus paper. The ketone (0.1 mole) was then added and

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[3] All melting points are corrected and boiling points are uncorrected. Analyses are by Clark Microanalytical Laboratory, Urbana, Ill.

the mixture was heated while sufficient ethanol was added to produce a homogeneous solution at the boiling point. After being heated for one hour, the solution was cooled and the crystals were removed by filtration and washed with cold, aqueous ethanol. The crystals were air-dried and then recrystallized to constant melting point from the appropriate solvent. If the oxime separated as an oil during its preparation, it was extracted with ether after the alcohol was removed by distillation. The yields were nearly quantitative in every case although it was occasionally necessary to obtain a second crop. The melting point of *m*-nitroacetophenone oxime, recrystallized from benzene, was 131.5–132°, reported 131–132°. The 2,4-dinitrophenylhydrazone melted at 231.5–233° (dec.), reported 228°.

m-Methylacetophenone and derivatives. *m*-Tolualdehyde was oximated and the oxime was dehydrated by the Organic Syntheses' method (12) to *m*-tolunitrile, b.p. 106–108° (35 mm.); n_D^{25} 1.5230–1.5232. *m*-Tolunitrile was added to methylmagnesium iodide in a manner previously recorded (13) yielding *m*-methylacetophenone, 70%, b.p. 60–60.5° (2 mm.), n_D^{25} 1.5295; reported b.p. 109° (12 mm.), n_D^{20} 1.5306. The oxime, which oiled out in its preparation and which was therefore distilled (b.p. 106–108° at 2 mm.), was recrystallized from petroleum ether (b.p. 69–70°), colorless needles, m.p. 55–56.5°; reported m.p. 54–56° and 57°. The melting point of the 2,4-dinitrophenylhydrazone was 207–208.5° reported (14) 207°.

3,4,5-Trimethylacetophenone and derivatives. This ketone was made by the Baddeley rearrangement of acetomesitylene (6). One equivalent of acetomesitylene and two equivalents of anhydrous aluminum chloride, protected from moisture, were held at 170–175° for 1.5 hours. After being cooled, the dark red oil was carefully poured onto ice and extracted with ether. The ether extract was washed with a saturated sodium bicarbonate solution, dried with sodium sulfate, and distilled. The yield of crude ketone was 80%, b.p. 90–100° (3 mm.). The crude ketone was then fractionated in a carborundum-packed column yielding 66% of colorless oil, b.p. 101.5° at 3 mm., n_D^{25} 1.5420, d_4^{25} 1.0037. Though the ketone was now of constant refractive index, it was further purified by fractional freezing, the freezing point being raised from 3.7° to 4.7°.

The *oxime*, recrystallized from petroleum ether (b.p. 69–70°), was obtained as large, thick rods, m.p. 148.5–150°, previous softening at 144°.

Anal. Calc'd for $C_{11}H_{15}NO$: C, 74.52; H, 8.53.
Found: C, 74.57; H, 8.53.

The early softening indicated impurity. The ketone was therefore converted to the azine by a procedure previously recorded (15); the azine was recrystallized from benzene to a constant melting point (185–185.5°) and hydrolyzed with acid to the ketone. The purified ketone gave an oxime with melting characteristics identical to those recorded above, indicating that the softening previous to melting is inherent.

The *2,4-dinitrophenylhydrazone*, recrystallized from butyl acetate, was obtained as small, dark-red crystals, m.p. 258–259.5° (gas).

Anal. Calc'd for $C_{17}H_{18}N_4O_4$: N, 16.37. Found: N, 16.38.

3,4,5-Trimethylbenzoic acid was made from the ketone by hypobromite oxidation (16); large rods from 2-propanol, m.p. 220.5–221.5°; reported m.p. 215–216°.

3,4,5-Trimethylacetanilide was made by Beckmann rearrangement of the oxime using concentrated sulfuric acid; needles from methanol, m.p. 167–168°; reported (17) m.p. 171.5–172°.

3,5-Dimethylacetophenone and derivatives. The ketone was made by the Baddeley rearrangement (6) of 2,5-dimethylacetophenone. The crude product (80%, b.p. 88–92° at 3 mm.) was contaminated with 3,4-dimethylacetophenone which was partially removed by two consecutive fractional distillations. 3,5-Dimethylacetophenone (b.p. 82–83° at 3 mm., n_D^{25} 1.5292–1.5295) accumulated in the head fraction while 3,4-dimethylacetophenone (approximate b.p. 88–89° at 3 mm. and approximate n_D^{25} 1.5348) concentrated in the higher-boiling fractions. Five recrystallizations of the oxime of 3,5-dimethylacetophenone from petroleum ether completed the separation, m.p. 115.5–116.5°, reported (18) m.p. 114–114.5°. The oxime from the first recrystallization melted at 109–116° and was evidently contaminated with the oxime of 3,4-dimethylacetophenone, m.p. 85°.

The *2,4-dinitrophenylhydrazone* of 3,5-dimethylacetophenone, obtained from rate studies and recrystallized once from butyl acetate, formed burnt-orange colored needles, m.p. 221–222°.

Attempted Baddeley rearrangement of 2,6-dimethyl-4-tert-butylacetophenone (I, 19). It was thought worthwhile to compare the rates of rearrangement of the oxime of 3,5-dimethyl-4-*tert*-butylacetophenone (II) and of 3,4,5-trimethylacetophenone, if the former could be prepared. I (0.3 mole) and aluminum chloride (0.6 mole), held at 160° for 2 hours, yielded resinous material, 43% of a mixture of dimethylacetophenones, b.p. 77–92° (3 mm.), and 15% of 3,4,5-trimethylacetophenone, identified by a mixture melting point of the oxime. At 120° for one hour, a mixture of I and aluminum chloride yielded 60% 2,4-dimethylacetophenone, b.p. 75–77° (3 mm.); oxime m.p. 65.5–67°, reported 63–64°; hypobromite oxidation of the oxime yielded 2,4-dimethylbenzoic acid, m.p. 123–124°, reported 125°. A small amount of this ketone was also obtained in the preparation of I (19). The above experiments indicated that the *tert*-butyl group was preferentially removed and that II could not be obtained. Brown (5) had anticipated such difficulty in flanking a *tert*-butyl group with two methyl groups.

Analysis of oximes. The oximes were analyzed by gravimetric determination of the 2,4-dinitrophenylhydrazones of the ketones obtained by hydrolysis (2). Six samples of each oxime, varying from 0.0010–0.0005 mole, were accurately weighed and transferred to 50-ml. Erlenmeyer flasks. Each sample was carefully dissolved in 10 ml. of concentrated sulfuric acid which was cooled to prevent rearrangement. About 0.002 mole of 2,4-dinitrophenylhydrazine, weighed to the nearest centigram, was added and the mixture cautiously was diluted with 15–20 ml. of water while being cooled. The precipitated hydrazone was digested for at least two hours by placing the flask in a hot water-bath. The aqueous suspension of hydrazone was then transferred to a 600-ml. beaker, diluted to approximately 400 ml. with water, and allowed to stand for one to two hours. The above digestion and dilution facilitated the filtration of the hydrazone. After filtration in No. 2001 Selas porous crucibles, the hydrazone was washed with 100 ml. of 2 *N* hydrochloric acid and then with 200 ml. of hot water or until the filtrate washings were colorless. The hydrazone was dried at 110° to constant weight. The precision of these determinations was as follows: *m*-nitroacetophenone oxime 99.53 ± 0.34% (correction factor 1.0047); *m*-methylacetophenone oxime 99.95 ± 0.26% (correction factor 1.0005); 3,4,5-trimethylacetophenone oxime 97.73 ± 0.53% (correction factor 1.0232); 3,5-dimethylacetophenone oxime 99.05 ± 0.33% (correction factor 1.0097). The correction factors were used to correct the weights of the 2,4-dinitrophenylhydrazones obtained in the actual rearrangements. The relative effect of the correction factor on the rate constants is illustrated for 3,4,5-trimethylacetophenone oxime: the rate constant at 50.9°, using the correction factor, is 3.729×10^{-3} reciprocal minutes; without correction factor, the rate constant is 3.79×10^{-3} reciprocal minutes. The effect of the correction factor is therefore quite small and does not significantly change the position of the point representing this oxime in Figure 1.

The rate determination. The series sampling technique, previously developed (2), was used except that the original oxime concentrations were reduced. Exactly 0.0010 mole of oxime was weighed and transferred to a 50-ml., standard-tapered Erlenmeyer flask. Ten ml. of conc'd sulfuric acid (Merck, 94.5%) was added cautiously and was cooled before it came in contact with the bulk of the oxime. The well-stoppered flask was swirled to obtain solution and was immersed in a constant temperature bath. At regular intervals one of several such flasks was removed and its entire contents were analyzed by the method just described. Six samples were analyzed for each run and a lesser number for a duplicate run. The first order rate constants were obtained by applying the Least Squares Principle to the data for the plot of log concentration of the oxime *versus* time in minutes. The results are recorded in Table I and are illustrated in Figure 1. A plot of log rate of rearrangement of each oxime *versus* reciprocal absolute temperature[1] gave lines which closely paralleled each other, indicating the validity of comparison of rates at any temperature. Since different concentrations of oximes were used than in previous rate studies (1, 2), the rate constant of *p*-

methylacetophenone oxime was redetermined. The rate, k, at 50.9° = 2.099×10^{-3}, compared favorably with the previously determined rate, k, at 50.9° = 2.101×10^{-3}.

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