Electron Transfer in Reactions of Ketones with Organolithium Reagents. A Carbon-14 Kinetic Isotope Effect Probe

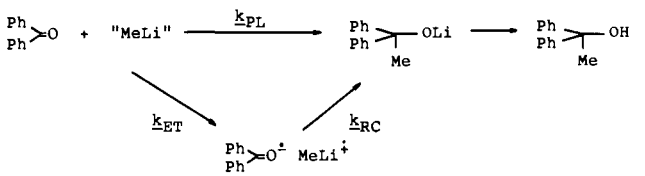
Hiroshi Yamataka,* Naoya Fujimura, Yukie Kawafuji, and Terukiyo Hanafusa

Contribution from The Institute of Scientific and Industrial Research, Osaka University, Ibaraki, Osaka 567, Japan. *Received July 11, 1986*

Abstract: Kinetic isotope effects have been determined for reactions of ketones labeled with carbon-14 at the carbonyl carbon with MeLi and Me_2CuLi in diethyl ether at 0 °C. Observed isotope effects were as follows: $(C_6H_5)_2C{=}O$ + MeLi, $^{12}k/^{14}k$ = 1.000 ± 0.002; $(C_6H_5)_2C{=}O$ + Me_2CuLi, 1.029 ± 0.005; 2,4,6-$Me_3C_6H_2COC_6H_5$ + MeLi, 1.023 ± 0.004. The relative reactivities of ortho-, meta-, and para-substituted benzophenones with these reagents were also determined by the competition experiments. These results are consistent with an electron-transfer step which is followed by a carbon–carbon bond-forming step that is or is not rate determining depending on the structure of ketones and reagents. The reaction of benzophenone with MeLi proceeds via rate-determining electron transfer; the change in nucleophile from MeLi to Me_2CuLi shifts the rate-determining step from electron transfer to recombination; the change in ketone from benzophenone to 2,4,6-trimethylbenzophenone also shifts the rate-determining step from electron transfer to recombination because the latter step becomes slower for the more hindered ketone. The extent of the geometrical change of the substrate at the electron-transfer transition state of the reaction of benzophenone with MeLi was estimated to be small on the basis of the magnitude of the KIE and the ρ value of the Hammett correlation.

The importance of electron transfer (single electron transfer, SET) in the reactions of organic substrates with nucleophilic reagents has been a subject of recent interest.[1-6] A number of reactions of ketones or alkyl halides with RMgX,[2,3] R_2CuLi,[2,4] metal hydrides,[5] and other organometallic reagents[6] have been claimed to involve a SET pathway under certain reaction conditions. However, methods usually employed to study the possibility of a SET process, e.g., spectroscopic detection of radical species or identification of products indicative of radical intermediates, have their inherent limitations. Spectroscopic observation of a radical intermediate does not necessarily mean that SET is involved in the real reaction pathway leading to the product; the formation of the intermediate could simply be a blind step.[6c,7] Product analysis methods are applicable only to a substrate whose radical anion has certain structural features and is stable enough to undergo reactions characteristic of radical species.[2,4a] On the other hand, carbon kinetic isotope effects (KIEs) can be a useful probe to detect SET. This KIE technique has two advantages; first, the results provide information on the real reaction pathway, and second, they bring about a better understanding of the rate-determining step of the reaction. The basic idea in utilizing carbon KIE is that the magnitude of a primary carbon KIE depends not only on the extent of the bonding change of the isotopically labeled carbon atom but also on the dynamic nature of the reaction, and therefore the KIE can be different for a different mechanism. Thus, a considerable KIE is expected at the carbonyl carbon if the reaction proceeds via the polar mechanism (k_{PL}, Scheme I) or via initial fast ET followed by slow recombination of the radical ion pair (k_{RC}, rate determining), whereas the magnitude of the KIE is expected to be different for

Scheme I



the SET mechanism in which the ET step (k_{ET}) is rate determining.

Another possible probe for the SET process is the steric effect on the overall rates of the reactions; the electron-transfer process is expected to suffer less steric rate retardation compared to the polar nucleophilic process. In the present investigation, we chose the reactions of benzophenones with Me_2CuLi and MeLi as the first reaction system to apply the KIE method and determined the carbonyl carbon KIEs as well as the substituent effects. The results are discussed in terms of the possible involvement of an ET process in these reactions.

Experimental Section

Materials. Diethyl ether was dried over $LiAlH_4$ and distilled before use. Commercial ethereal solutions of MeLi (Merck) were standardized by using 2,5-dimethylbenzyl alcohol as described in the literature.[8] Lithium dimethylcuprate was prepared from a 1:2 molar ratio of Me_2SCuBr and MeLi in diethyl ether at 0 °C.[4b] Substituted benzophenones were synthesized by either the Friedel-Crafts reactions of substituted benzoyl chlorides with benzene (*m*-Cl and *o*-CH_3) or the Grignard reaction of arylmagnesium bromide with benzaldehyde followed by the oxidation of the resulting benzhydrol with $KMnO_4$ (*m*-CF_3). In the case of *m*-methoxy derivative, the Friedel-Crafts reaction gave *m*-hydroxybenzophenone, which was then methylated with CH_3I. Other substituted benzophenones were commercially available and used after appropriate purification procedures. Benzophenone labeled with ^{14}C at the carbonyl carbon was prepared by the Friedel-Crafts benzoylation of benzene with benzoyl-^{14}C chloride, which was obtained by chlorination of benzoic-7-^{14}C acid (NEN) with thionyl chloride. 2,4,6-Trimethylbenzophenone labeled with ^{14}C at the carbonyl carbon was synthesized as above except that 1,3,5-trimethylbenzene was used instead of benzene.

Competition Experiments. A pair of ketones (normally the parent and substituted benzophenones, 0.2 mmol each) and an appropriate internal standard (1,2-diphenoxyethane or dibenzyl ether, 0.25 mmol) were placed in a flame-dried, serum-capped test tube and dissolved in 2.0 mL of dry ether. Half of the solution was withdrawn and used for calibration in the GLC analysis. To the rest of the solution, 0.1 mmol of MeLi or

(1) Bordwell, F. G.; Clemens, A. H. *J. Org. Chem.* **1981**, *46*, 1035-1037.
(2) Ashby, E. C.; Wiesemann, T. L. *J. Am. Chem. Soc.* **1978**, *100*, 3101-3110.
(3) (a) Holm, T. *Acta Chem. Scand. B* **1983**, *37*, 567-584. (b) Ashby, E. C. *Pure Appl. Chem.* **1980**, *32*, 545-569 and references cited therein.
(4) (a) House, H. O. *Acc. Chem. Res.* **1976**, *9*, 59-67. (b) House, H. O.; Chu, C.-Y. *J. Org. Chem.* **1976**, *41*, 3067-3076, 3076-3083, 3083-3091. (c) Ashby, E. C.; DePriest, R. N.; Tuncay, A.; Srivastava, S. *Tetrahedron Lett.* **1982**, *23*, 5251-5254.
(5) (a) Ashby, E. C.; Goel, A. B.; DePriest, R. N. *J. Am. Chem. Soc.* **1980**, *102*, 7779-7780. (b) Ashby, E. C.; DePriest, R. N.; Goel, A. B.; Wenderoth, B.; Pham, T. N. *J. Org. Chem.* **1984**, *49*, 3545-3556.
(6) (a) Alnajjar, M. S.; Kuivila, H. G. *J. Am. Chem. Soc.* **1985**, *107*, 416-423. (b) Ashby, E. C.; DePriest, R. N.; Su, W.-Y., *Organometallics* **1984**, *3*, 1718-1727. (c) Ashby, E. C.; Argyropoulos, J. N. *J. Org. Chem.* **1986**, *51*, 472-476.
(7) Newcomb, M.; Burchill, M. *J. Am. Chem. Soc.* **1984**, *106*, 8276-8282.
(8) Winkle, M. R.; Lansinger, J. M.; Ronald, R. C. *J. Chem. Soc., Chem. Commun.* **1980**, 87-88.

0002-7863/87/1509-4305$01.50/0

Table I. Kinetic Isotope Effects in Reactions of Ketones with Organolithium Reagents[a]

substrate	reagent	R_0, R_r, R_p	f, R_0, R_r	f, R_0, R_p	f, R_r, R_p	$^{12}k/^{14}k$ (av)
$(C_6H_5)_2CO$	MeLi	1.000 ± 0.005	1.000 ± 0.003	1.002 ± 0.004	1.000 ± 0.001	1.000 ± 0.002
	MeLi[b]	0.999 ± 0.002	1.002 ± 0.002	0.995 ± 0.006	0.999 ± 0.001	0.999 ± 0.002
$(C_6H_5)_2CO$	Me_2CuLi	1.026 ± 0.008	1.025 ± 0.005	1.026 ± 0.013	1.026 ± 0.006	1.026 ± 0.008
	Me_2CuLi[b]	1.031 ± 0.006	1.035 ± 0.004	1.030 ± 0.008	1.025 ± 0.006	1.030 ± 0.005
$2,4,6\text{-}Me_3C_6H_2COC_6H_5$	MeLi		1.023 ± 0.004[c]			1.023 ± 0.004

[a] Reactions were carried out in diethyl ether at 0.0 ± 0.1 °C. Reaction solution of Me_2CuLi contains dimethyl sulfide. The KIEs are the average of 4–7 runs with fractions of reaction in the range of 30–70%. Error limits are the standard deviations. For definition of R_0, R_r, R_p, f, see text. [b] The isotope effect determination was repeated with a different batch of reagent. [c] Average of 9 runs with fractions of reaction in the range of 20–70%.

Table II. Reactivity of Substituted Benzophenones[a]

substituent	k_X/k_H MeLi	k_X/k_H Me_2CuLi
2,4,6-Me_3	0.084 ± 0.028	0.009
p-MeO	0.900 ± 0.043	0.245 ± 0.040
m-MeO	0.862 ± 0.115	1.051 ± 0.049
p-Me	0.833 ± 0.175	0.479 ± 0.003
m-Me	0.925 ± 0.149	0.724 ± 0.007
o-Me	0.477 ± 0.035	0.117 ± 0.006
p-F	1.054 ± 0.242	0.945 ± 0.211
p-Cl	1.320 ± 0.077	2.504 ± 0.097
m-Cl	1.134 ± 0.128	4.655 ± 0.807
o-Cl	0.642 ± 0.104	*b*
m-CF_3	1.229 ± 0.001	7.403 ± 0.264

[a] Reactions were carried out in diethyl ether at 0.0 ± 0.1 °C. Listed values are the average of 2–6 determinations. Error limits are the standard deviations. [b] Not determined due to the side reactions; see text.

Me_2CuLi was added by means of a hypodermic syringe at 0.0 °C, and the solution was worked up in the usual manner and subjected to GLC analysis (1-m glass column packed with 3% PEG-HT). The relative intensity of the ketones to the internal standard was used to determine the fraction of reaction, f, and the rate ratio was calculated according to the equation

$$k_A/k_B = \log (1 - f_A)/\log (1 - f_B)$$

All ketones were found to give the corresponding tertiary alcohol except for one case; the reaction of *o*-chlorobenzophenone with Me_2CuLi gave dechlorinated products, benzophenone and 1,1-diphenylethanol, in addition to the normal addition product.

Determination of Carbon-14 Kinetic Isotope Effects. Carbon-14 KIEs were determined as described previously.[9] Four equations of Tong and Yankwich[10] were used; these equations allow KIE calculations in four ways by using any three of the following measured parameters: fraction of reaction (f), radioactivity of the starting ketone (R_0), activity of the recovered ketone (R_r), and activity of the product alcohol (R_p). Agreement among the KIEs calculated by the four different equations was excellent in all cases and the isotope effects thus obtained showed no trend with the fraction of reaction. In the case of 2,4,6-trimethylbenzophenone, however, the KIE was calculated only from the variation in radioactivity of the ketone because the product alcohol was so unstable that accurate radioactivity measurements could not be made.

Results and Discussion

Table I lists the observed carbon-14 KIEs. Normal KIEs were observed in the following two reactions: $(C_6H_5)_2C{=}O + Me_2CuLi$ and $2,4,6\text{-}Me_3C_6H_2COC_6H_5 + MeLi$. Although these observed ^{14}C KIEs are smaller in comparison with those reported for typical nucleophilic additions to ketones (e.g., $^{12}k/^{14}k = 1.066$ for $(C_6H_5)_2C{=}O + NaBH_4$[9b] and 1.054 for $C_6H_5COCH_3 + 2,4\text{-}(NO_2)_2C_6H_3NHNH_2$[11]), they are still significantly large; the bonding of the carbonyl carbon clearly changes in the transition state of these two reactions. In contrast, no KIE was detected in the reaction of benzophenone with MeLi, which indicates that there is no bonding change at the carbonyl carbon in the transition state. Thus the reaction mechanism appears to be different in these two cases.

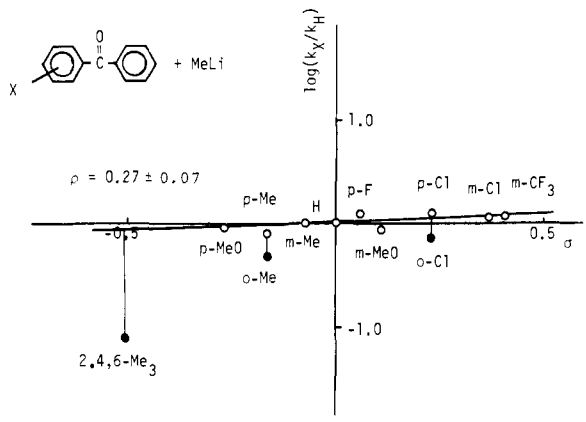


Figure 1. Variations of reactivity with σ values for the reactions of substituted benzophenones with MeLi.

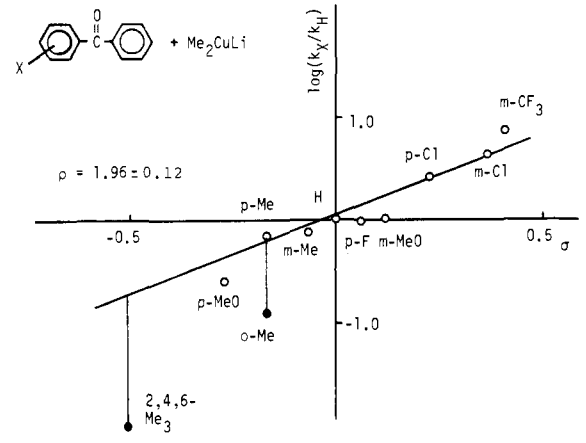


Figure 2. Variations of reactivity with σ values for the reactions of substituted benzophenones with Me_2CuLi.

Table II summarizes the results of the competition experiments. Figures 1 and 2 show the relationship betwen log (k_X/k_H) and substituent constant, σ, for the reactions with MeLi and Me_2CuLi, respectively. Since the σ constants of the ortho substituents were not available, the log (k_X/k_H) values for the ortho derivatives were plotted against the corresponding para-substituent constants and are indicated by closed circles. The downward deviations observed for *p*- and *m*-MeO derivatives in Figure 2 may be attributed to the inadequacy of applying the standard σ constants of the hydrogen bond accepting substituents for the reaction carried out in the nonpolar solvent and/or the additional demand of the σ^+-type resonance in the transition state of this reaction. Other substituents gave reasonably good straight lines in both reactions, from which the ρ values were calculated. It is apparent in Figures 1 and 2 that the substituent effects are different in these two reactions. In the reaction with Me_2CuLi, the ρ value is large and the rate retardations for the ortho-substituted derivatives are substantial. In the case of MeLi, on the other hand, the ρ value is very small and only 2,4,6-trimethylbenzophenone deviates from the correlation line substantially; the rate retardations for the *o*-Me and *o*-Cl derivatives are not large compared with that observed

(9) (a) Yamataka, H.; Tamura, S.; Hanafusa, T.; Ando, T. *J. Am. Chem. Soc.* **1985**, *107*, 5429–5434. (b) Yamataka, H.; Hanafusa, T. *J. Am. Chem. Soc.* **1986**, *108*, 6643–6646.

(10) Tong, J. Y.; Yankwich, P. E. *J. Phys. Chem.* **1957**, *61*, 540–543.

(11) Raeen, V. F.; Dunham, T. K.; Thompson, D.; Collins, C. J. *J. Am. Chem. Soc.* **1963**, *85*, 3497–3499.

for the *o*-Me derivative in the reaction with Me_2CuLi.

House and co-workers have carried out extensive investigations on reactions of various ketones with Me_2CuLi and MeLi.[4a,b] Observation of benzophenone ketyl during the reaction of benzophenone with Me_2CuLi suggested that the reaction proceeds via an initial electron transfer. On the other hand, no ketyl formation (even coloration) was detected in the reaction of benzophenone with MeLi. House et al. also noted that the two reagents showed different behavior when mixed with the sterically crowded 2,4,6-trimethylbenzophenone. At above −10 °C the MeLi solution exhibited a yellow-brown color and subsequent quenching yielded the tertiary alcohol while the Me_2CuLi solution gave unreacted ketone on quenching.

The present results for the Me_2CuLi reagent are consistent with the reaction mechanism in which the rate-determining step is, at least partly, the recombination of the radical ion pair formed in a fast initial ET step; the normal carbon-14 KIE, the large ρ value, and the large para vs. ortho reactivity difference indicate the involvement of the carbon–carbon bond formation in the rate-determining transition state; the fact that the dechlorinated products, benzophenone and 1,1-diphenylethanol, were observed during the reaction of *o*-chlorobenzophenone with Me_2CuLi suggested the presence of a ketyl radical of significant lifetime.

The reaction with MeLi, on the other hand, showed no KIE and a very small substituent effect on reactivity; only for 2,4,6-trimethylbenzophenone was a large rate retardation observed. Apparently little bonding change occurs at the carbonyl carbon in the transition state, at least for the parent and the meta- or para-substituted compounds. One interpretation of these results is that the rate-determining step of the reaction is electron transfer in which the geometrical change of the ketone is little advanced in the transition state. Since the transfer of electron occurs much faster than nuclear motions and brings about a sudden change in substrate polarity, the estimation of the transition-state structure of the electron-transfer step in solution requires consideration of the conditions under which an electron can transfer. This will be discussed in detail below. An alternative interpretation is that the reaction proceeds via the polar mechanism with a reactant-like transition state, in which the interaction between MeLi and the carbonyl carbon of the ketone is small. Recently, Schleyer and Houk et al. obtained an early transition state by the ab initio MO calculations for the reaction of $H_2C{=}O$ with MeLi,[12] although the mechanism can be different in the absence of solvent.

Although a single KIE measurement does not allow one to determine which mechanism is more probable, comparison of the results for the two substrates provides a clue to the problem. If the second alternative is operative, benzophenone and 2,4,6-trimethylbenzophenone are likely to react in a similar manner because the steric bulkiness has little influence in the early transition state. On the other hand, if the reaction proceeds via the ET–RC sequence in Scheme I, it is possible for the two *o*-methyl groups of 2,4,6-trimethylbenzophenone to retard the recombination rate substantially, causing the shift of the rate-determining step from ET to RC. The normal KIE and the rate retardation observed for 2,4,6-trimethylbenzophenone are consistent with this ET mechanism. Coloration reported by House during the reaction of MeLi with 2,4,6-trimethylbenzophenone, and not with benzophenone, is also consistent with this reaction mechanism.[13]

The question which should be answered, then, is why the geometrical change of the ketone is negligibly small in the rate-determining transition state of the ET process. Rationalization may be given as follows by using eq 1, the schematic representation

$$A + D \underset{}{\overset{k_a}{\rightleftharpoons}} \underset{R}{A\cdots D} \overset{k_b}{\rightleftharpoons} [\underset{TS1}{A\cdots D} \leftrightarrow \underset{TS2}{A^{\bullet-}\cdots D^{\bullet+}}]^{\neq} \overset{k_c}{\rightleftharpoons} \underset{P}{A^{\bullet-}\cdots D^{\bullet+}} \overset{k_d}{\rightleftharpoons} A^- + D^+ \quad (1)$$

of the ET process.[14] The first step (k_a) represents the encounter between the two reacting species. The formation of the encounter complex increases the electron-accpeting ability of A and the electron-donating ability of D. Ab initio calculations by Schleyer and Houk[12] showed that there is indeed a complex formation between $H_2C{=}O$ and MeLi in the gas-phase reaction. However the complex formation exerted a very small geometrical change in $H_2C{=}O$ (the C—O bond was lengthened by 0.007 Å), and therefore the geometrical change in solution should be small in this step. The next two steps (k_b and k_c) constitute the actual ET process, which includes two forms of the transition state, TS1 and TS2, both with exactly the same nuclear structure.

The question here is to what extent the geometrical change in the reacting species occurs in TS1. In the absence of solvent, the structure of TS1 should simply be governed by the endothermicity of the reaction as expected from the Leffler–Hammond principle.[15] In solution, on the other hand, the situation is very complex due to a large solvation effect. It is well recognized that the solvent reorganization is the dominant factor in ET reactions in solution,[14] although this is true in terms of energy and does not necessarily mean that the extent of the geometrical change is negligibly small in TS1.

An important point is the sudden polarity change which happens upon electron transfer; this means that the solvent reorganization cannot be synchronized with the geometrical change in the substrates throughout the reaction path. Kurz[16] and Bernasconi[17] proposed that the two events occur nonsynchronously even in conventional polar reactions. In the present reaction in which ET gives rise to sudden increase in polarity (from less polar R to polar P), we can expect that the solvent molecules have an orientation which stabilizes more polar TS2 than less polar TS1 in the transition state in order to reduce the total activation energy of the ET process. Thus, the solvent orientation in the transition state is similar to that in P. If we look at the reverse reaction from P to R, the lowest energy path may be such that the geometrical change first occurs as a main process to reach TS2. Since the change in polarity of the reacting species is small in this process, the energy loss in solvation is minimal. Then, the fast ET occurs to give TS1. The final process is mainly the sovlent relaxation to yield R. According to the principle of the microscopic reversibility, the forward reaction first involves the solvent reorganization as the main activation process. As a result, the geometrical change of the reacting species is small in the transition state as assumed above. Of course, the two events, the geometrical change and the solvent reorganization, are not perfectly separated, and some geometrical change should occur on going to TS1. The small positive ρ value in the reaction of benzophenone with MeLi may reflect this change.

It should also be noted that primary carbon KIEs are known to be large when the isotopically labeled carbon atom is dynamically involved in the reaction coordinate vibrational motion at the transition state;[9,18] thus, carbon KIEs are much larger in general than the effects expected for any related equilibrium

(12) Kaufmann, E.; Schleyer, P. v. R.; Houk, K. N.; Wu, Y.-D. *J. Am. Chem. Soc.* **1985**, *107*, 5560–5562.

(13) There is another interpretation in which complex formation between benzophenone and MeLi is rate determining and the C–C bond formation occurs after the rate-determining step via either the polar or the radical pathway. This possibility cannot completely be eliminated on the basis of the present results. However, we feel it less probable because the shift of the rate-determining step from the complex formation (in the case of benzophenone) to the C–C bond formation (in the case of 2,4,6-trimethylbenzophenone) seems less likely. Furthermore, the substituent effect is expected to yield a negative ρ value if the complex formation is rate determining, which is incompatible with the observed small positive ρ value, although the magnitude is small and less conclusive.

(14) Eberson, L. In *Advances in Physical Organic Chemistry*; Gold, V., Bethell, B., Eds.; Academic Press: London, 1982; Vol. 8.

(15) (a) Leffler, J. E. *Science (Washington, D.C.)* **1953**, *117*, 340–341. (b) Hammond, G. S. *J. Am. Chem. Soc.* **1955**, *77*, 334–338.

(16) Kurz, J. L.; Lee, J.; Love, M. E.; Rhodes, S. *J. Am. Chem. Soc.* **1986**, *108*, 2960–2968.

(17) Bernasconi, C. F. *Tetrahedron* **1985**, *41*, 3219–3234. See also: Richard, J. P.; Jencks, W. P. *J. Am. Chem. Soc.* **1984**, *106*, 1373–1383.

(18) (a) Buddenbaum, W. E.; Shiner, V. J., Jr. In *Isotope Effects on Enzyme-Catalyzed Reactions*; Cleland, W. W., O'Leary, M. H. Northrop, D. B., Eds.; University Park Press: Baltimore, 1977; Chapter 1. (b) Yamataka, H.; Ando, T. *J. Phys. Chem.* **1981**, *85*, 2281–2286.

process.[18a] This type of kinetic effect cannot be expected for the KIE in the ET process because the heavy atom reorganization occurs as a separate process from the transfer of electron; the KIE in the ET process is an equilibrium IE in this sense. A small IE would therefore be expected for an ET process even if a significant geometrical change is involved in the transition state.

In summary, the present study shows that carbon KIE, together with other mechanistic evidence, can be a useful means to distinguish an ET process from bond-forming processes. It was concluded that the reactions of ketones with organolithium reagents proceed via an initial ET and that the rate-determining step varies depending on the structure of ketones and the lithium reagents. The kinetic isotope effect study on ET has some precedent in deuterium IEs,[19] but we believe that carbon KIE is more useful and has wider applicability.

Acknowledgment. The present work was supported in part by a Grant-in-Aid for Science Research (No. 59540315) from the Ministry of Education, Science and Culture, Japan.

(19) (a) Pryor, W. A.; Hendrickson, W. H., Jr. *J. Am. Chem. Soc.* **1983**, *105*, 7114-7122. (b) Baciocchi, E.; Rol, C.; Mandolini, L. *J. Am. Chem. Soc.* **1980**, *102*, 7598-7600. (c) Muller, P.; Joly, D. *Tetrahedron Lett.* **1980**, *21*, 3033-3036.

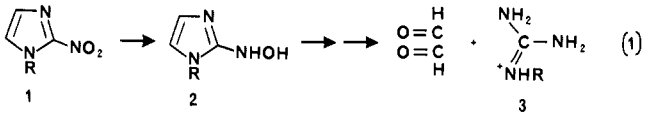
Products of the Reductions of 2-Nitroimidazoles

Robert A. McClelland,*[†] Rick Panicucci,[†] and A. Michael Rauth[‡]

Contribution from the Department of Chemistry, University of Toronto, Toronto, Ontario M5S 1A1, Canada, and the Physics Division, Ontario Cancer Institute, Toronto, Ontario M4X 1K9, Canada. *Received October 29, 1986*

Abstract: Reductions under neutral conditions of misonidazole (1-(2′-hydroxy-3′-methoxypropyl)-2-nitroimidazole) and 1-methyl-2-nitroimidazole have been studied with radiation chemical, electrochemical, and chemical (zinc/ammonium chloride) techniques. Major products accounting for 70–85% of the reduction mixture have been identified as the cis:trans isomers of **4** (1-substituted 2-amino-4,5-dihydro-4,5-dihydroxyimidazolium ions). These have been independently synthesized by the reaction of glyoxal and the appropriate guanidinium ion. Their presence after nitroreduction has been established by ^{1}H NMR and by a spectroscopic analysis in which **4** is converted into glyoxal bis-oxime. The ability of misonidazole reduction mixtures to form glyoxal derivatives has been noted previously, even in vivo; the presence of the cyclic **4** accounts for this. The four-electron-reduced product, a 2-(hydroxylamino)imidazole, is the precursor of **4**. The hydroxylamine is unstable at pH 7, but it can be observed in acid where decomposition also gives **4** but in a much slower reaction. Nitroreduction or hydroxylamine decomposition in pH 7 phosphate gives two additional products which have been identified on the basis of their ^{1}H NMR spectra as cis:trans isomers of monophosphate esters of **4**. The reaction leading to these may model the DNA binding which is observed with reduced misonidazole. Azomycin (2-nitroimidazole) has been investigated by the radiation chemical technique. At pH 7 the isomers of **4** are formed, but they are minor products. The major product (70%) is 2-aminoimidazole.

Extensive biological and biochemical examinations of the radiation sensitizer misonidazole (**1a**) have shown a number of effects correlating with reductive metabolism.[1] These include a preferential toxicity toward hypoxic cells as compared to aerobic cells,[2] mutagenicity,[3] chemosensitization (the potentiation of the effect of other chemotherapeutic agents),[4] DNA binding,[5] and depletion of cellular thiols.[6] The implication that reduction is involved has led to an interest in the reduction chemistry. The six-electron product, a 2-aminoimidazole, is formed upon catalytic hydrogenation.[7] Other methods however have shown a four-electron stoichiometry,[8-15] implicating the (hydroxylamino)imidazole **2a**. Although there are indications of such a product after zinc reduction,[16] we have found that it is unstable, particularly at neutral pH.[11]



a, R = $CH_2CHOHCH_2OCH_3$
b, R = CH_3
c, R = H

The subject of this paper is the nature of the decomposition products. Two groups have established that derivatives of glyoxal can be formed after misonidazole reduction.[17-19] This two-carbon dialdehyde presumably arises from C4,C5 of the imidazole ring, and a candidate for the other fragment, the guanidinium ion **3a**, has also been detected.[20] There is some question as to whether

[†] Department of Chemistry, University of Toronto.
[‡] Ontario Cancer Institute.

(1) Rauth, A. M. *Int. J. Radiat. Oncol. Biol. Phys.* **1984**, *10*, 1293-1300.
(2) Brown, J. M. *Int. J. Radiat. Oncol. Biol. Phys.* **1982**, *8*, 1491-1497.
(3) Chin, J. B.; Sheinin, D. M. K.; Rauth, A. M. *Mutat. Res.* **1978**, *58*, 1-10; Kacinski, B. M.; Mroczkowski, Z.; Rupp, W. D. *Cancer Clin. Trials* **1980**, *3*, 69-71.
(4) McNally, N. J. *Int. J. Radiat. Oncol. Biol. Phys.* **1982**, *8*, 593-598.
(5) (a) Varghese, A. J.; Gulyas, S.; Mohindra, J. K. *Cancer Res.* **1976**, *36*, 3761-3765. (b) Varghese, A. J.; Whitmore, G. F. *Ibid.* **1980**, *40*, 2165-2169. (c) Silver, A. R. J.; O'Neill, P.; Jenkins, T. C. *Biochem. Pharmacol.* **1985**, *19*, 3537-3542.
(6) Bump, E. A.; Taylor, Y. C.; Brown, J. M. *Cancer Res.* **1983**, *43*, 997-1002.
(7) Flockhart, I. R.; Large, P.; Troup, D.; Malcolm, S. L.; Marten, T. R. *Xenobiotica*, **1978**, *8*, 97-105.
(8) Whillans, D. W.; Whitmore, G. F. *Radiat. Res.* **1981**, *86*, 311-324.
(9) Wardman, P.; Anderson, R. F.; Clarke, E. D.; Jones, N. R.; Minchinton, A. I.; Patel, K. B.; Stratford, M. R. L.; Watts, M. E. *Int. J. Radiat. Oncol. Biol. Phys.* **1982**, *8*, 777-780.
(10) Kagiya T.; Ide, H.; Nishimoto, S.; Wada, T. *Int. J. Radiat. Biol.* **1983**, *44*, 505-517.
(11) McClelland, R. A.; Fuller, J. R.; Seaman, N. E.; Rauth, A. M.; Battistella, R. *Biochem. Pharmacol.* **1984**, *33*, 303-309.
(12) Middlestadt, M. V.; Rauth, A. M. *Int. J. Radiat. Oncol. Biol. Phys.* **1982**, *8*, 709-712.
(13) Knox, R. J.; Knight, R. C.; Edwards, D. I. *Biochem. Pharmacol.* **1983**, *32*, 2149-2156.
(14) Clarke, E. D.; Wardman, P.; Goulding, K. H. *Biochem. Pharmacol.* **1980**, *29*, 2684-2687.
(15) Josephy, P. D.; Palcic, B.; Skarsgard, L. D. *Biochem. Pharmacol.* **1981**, *30*, 849-853.
(16) Varghese, A. J.; Whitmore, G. F. *Chem. Biol. Interact.* **1981**, *36*, 141-151.
(17) Varghese, A. J.; Whitmore, G. F. *Cancer Res.* **1982**, *43*, 78-82.
(18) Raleigh, J. A.; Liu, S. F. *Biochem. Pharmacol.* **1983**, *32*, 1444-1446.

0002-7863/87/1509-4308$01.50/0