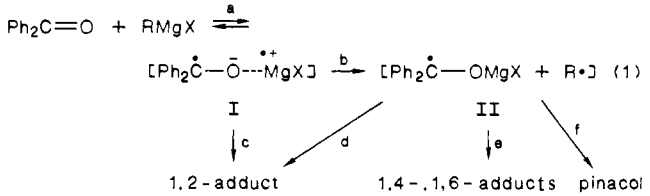
Rate-Determining Step of the Reactions of Benzophenone with Various Grignard Reagents

Hiroshi Yamataka,* Toyoki Matsuyama, and Terukiyo Hanafusa

Contribution from The Institute of Scientific and Industrial Research, Osaka University, Ibaraki, Osaka 567, Japan. *Received October 3, 1988*

Abstract: Carbonyl carbon kinetic isotope effects (KIEs) have been determined for the reaction of benzophenone-7-^{14}C with various Grignard reagents at 0 °C. The observed KIEs are as follows: MeMgI/Et_2O, $^{12}k/^{14}k$ = 1.056 ± 0.002; MeMgBr/Et_2O, 1.050 ± 0.011; MeMgBr/THF, 1.056 ± 0.004; PhMgBr/Et_2O, 1.056 ± 0.004; *o*-$CH_3C_6H_4MgBr/Et_2O$, 1.060 ± 0.014; CH_2=$CHCH_2MgBr/Et_2O$, 0.999 ± 0.003; CH_3CH=$CHCH_2MgBr/Et_2O$, 0.999 ± 0.002; $PhCH_2MgBr/Et_2O$, 1.024 ± 0.007; *t*-BuMgCl/Et_2O, 1.010 ± 0.007, 1.004 ± 0.004; MeMgI + 5 mol % $FeCl_3/Et_2O$, 1.063 ± 0.033 (for 1,2-adduct formation), 0.997 ± 0.019 (for pinacol formation). The relative reactivities of ortho-, meta-, and para-substituted benzophenones with these reagents were also determined by competition experiments. The reactions can be classified into three groups on the basis of these results: the first group gives a large ^{14}C KIE, a medium-sized Hammett ρ value, and a large steric rate retardation due to ortho substituents; the second gives a KIE of unity, a near-zero ρ value, and no steric rate retardation; and the third gives a small ^{14}C KIE, a large ρ value, and no steric rate retardation. It was concluded that the intimate mechanism of these Grignard reactions is different although they all follow the single-electron-transfer (SET) scheme; specifically, the rate-determining step for MeMgX, ArMgBr, and $PhCH_2MgBr$ is C–C bond formation while that for allylic reagents is initial SET. The rate-determining step for *t*-BuMgCl is the isomerization of the radical ion pair intermediate.

The mechanism of the Grignard reaction has extensively been studied for more than 2 decades, and the radical nature of the reaction has been indicated by means of a variety of techniques.[1] It is now widely believed that the reaction proceeds via an initial single-electron transfer (SET) from a Grignard reagent to a ketone.[2-4] Recent attention has been focused on the characterization of intermediates and the identification of the rate-determining step of this multistep reaction. In 1981 Ashby proposed that two intermediates are involved in the Grignard reaction, one to give a 1,2-addition product and the other to give 1,4- and 1,6-adducts and pinacol together with the 1,2-adduct (eq 1).[2a]



Recently, Maruyama presented spectroscopic evidence that suggests that the initial radical ion pair formed by SET dimierizes very quickly before yielding a 1,2-adduct.[3d-f] Here, the dimerization of the initially formed radical ion pair is much faster than the other steps. Thus, there appear to be at least three intermediates involved in the reaction.

Under such circumstances, an important mechanistic problem remaining is the identification of the rate-determining step among a sequence of steps. The first impressive report on this problem was presented by Holm in 1971.[4] He and his co-worker found that the reactions of benzophenones with *t*-BuMgCl give a linear Hammett plot with a ρ value of 3.0 and that ortho-substituted derivatives exhibit the same reactivity as the corresponding para-substituted counterparts. The results together with the findings that the product distribution suffers steric effects of ortho substituents led them to conclude that the rate-determining step and the product-determining step are different in the reactions.[4] The former step was considered SET on the basis of the absence of the steric effects on reactivity. In contrast, the reactions with MeMgBr were noted to suffer large steric rate retardation, and the reactions were concluded to proceed via a polar mechanism. Later the extensive study by Ashby showed that the reactions with MeMgX may go through the SET mechanism rather than the polar one.[2] The reactivity orders for the RMgX series, reported by Holm,[5] i.e., R = *t*-Bu > *i*-Pr > Et > Me for the reactions with benzophenone and R = Me > Et > *i*-Pr > *t*-Bu for acetone, also suggested that the reactions with benzophenone go through the SET mechanism.

We have recently demonstrated that carbon kinetic isotope effects (KIEs) are useful to distinguish an electron-transfer (ET) process from a bond-forming process.[6] The rate-determining step of the reactions of benzophenone with unbranched alkyl Grignard reagents was shown to be C–C bond formation (R-transfer step)

Table I. Kinetic Isotope Effects in Reactions of Benzophenone with Grignard Reagents[a]

entry	reagent/solvent	$^{12}k/^{14}k$	ρ value
1	MeMgI/Et_2O	1.056 ± 0.002	0.54 ± 0.16
2	MeMgBr/Et_2O	1.050 ± 0.011	
3	MeMgBr/THF	1.056 ± 0.004	0.90 ± 0.11
4	PhMgBr/Et_2O	1.056 ± 0.004	0.59 ± 0.10
5	*o*-$CH_3C_6H_4MgBr/Et_2O$	1.060 ± 0.014	
6	$PhCH_2MgBr/Et_2O$	1.024 ± 0.007	
7	CH_2=$CHCH_2MgBr/Et_2O$	0.999 ± 0.003	−0.02 ± 0.09
8	CH_3CH=$CHCH_2MgBr/Et_2O$	0.999 ± 0.002	0.01 ± 0.03
9	*t*-BuMgCl/Et_2O	1.010 ± 0.007	3.0[f]
	t-BuMgCl/Et_2O[b]	1.004 ± 0.004	
10	MeMgI + $FeCl_3/Et_2O$[c]	1.063 ± 0.033[d]	
		0.997 ± 0.019[e]	

[a] The reactions were carried out at 0.0 ± 0.1 °C. Listed KIEs are averages from four to six runs whose fractions of reaction are in the range of 30–70%. Error limits are the standard deviations. [b] Repeated by using different batches of ketone and solvent. [c] 5 mol % $FeCl_3$ was added. [d] For 1,2-adduct formation. [e] For pinacol formation. [f] Taken from ref 4.

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(3) (a) Maruyama, K. *Bull. Chem. Soc. Jpn.* **1964**, *37*, 897. (b) Okubo, M. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 2057. (c) Maruyama, K.; Katagiri, T. *J. Am. Chem. Soc.* **1986**, *108*, 6263. (d) Maruyama, K.; Hayami, J.-i.; Katagiri, T. *Chem. Lett.* **1986**, 601. (e) Maruyama, K.; Katagiri, T. *Chem. Lett.* **1987**, 731. (f) Maruyama, K.; Katagiri, T. *J. Phys. Org. Chem.* **1988**, *1*, 21.
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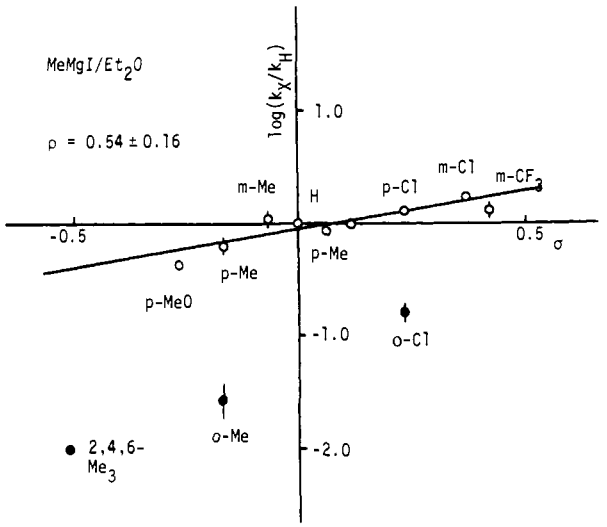

Figure 1. Variations of reactivities with σ values for the reactions of substituted benzophenones with MeMgI in diethyl ether.

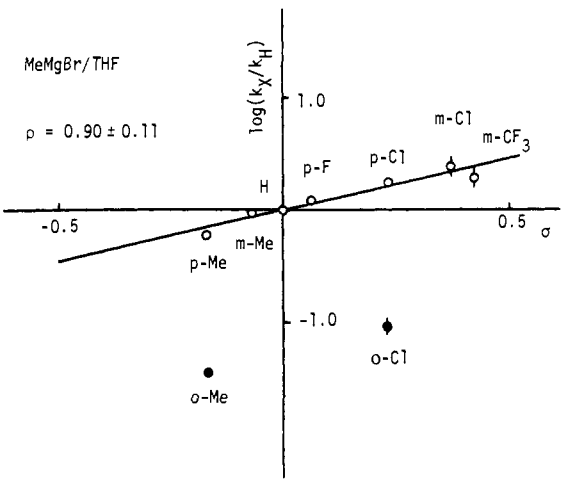

Figure 2. Variations of reactivities with σ values for the reactions of substituted benzophenones with MeMgBr in THF.

by our study by means of KIEs and substituent effects[7] and by the study of Maruyama et al. based on kinetic analyses of the spectroscopic (ESR) data.[8] In the present paper, we describe the full account of the carbonyl carbon KIEs and substituent effects on the reactions of benzophenone with various Grignard reagents. The results are discussed in terms of the identification and the change of the rate-determining step of the reactions.

Results and Discussion

The Grignard reactions of benzophenone with various reagents were carried out in diethyl ether or THF at 0 °C. In all but two cases (MeMgI + $FeCl_3$ and *t*-BuMgCl), the reactions gave the expected normal adducts exclusively. Material balances of the reactions were found to be excellent. The carbonyl carbon-14 KIEs of the reactions were measured as described previously[9] and are listed in Table I. Substituent effects on reactivity were determined by the competition experiments as reported before[6a] and the Hammett plots are shown in Figures 1–5. Here, log (k_X/k_H) values were plotted against the standard σ constants. Since the σ values 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 filled circles. The downward deviations observed for *p*- and *m*-MeO derivatives may be attributed to the inadequacy of applying the standard σ constants of the hydrogen bond accepting substituents for reactions carried out in the aprotic solvent and/or the additional demand of the σ^+ type resonance in the transition state (TS). Other substituents gave reasonably good straight lines, from which the ρ values were calculated.[10] The size of the ρ values observed for MeMgX and PhMgBr is in qualitative agreement with those reported for related reactions.[4,11] Specific radioactivities and relative reactivities are reported in the supplementary material.

Methyl and Aryl Grignard Reagents. Grignard reagents are known to be in a different aggregate state depending on the identity of the halogen atom and solvent.[1a] However, as shown in entries 1–3 in Table I, KIEs for MeMgI/Et_2O, MeMgBr/Et_2O, and MeMgI/THF are similar. Substituent effects on reactivity for MeMgI/Et_2O (Figure 1) and MeMgBr/THF (Figure 2) also show a similar pattern: small ρ values and large rate retardation due to ortho substituents for both reactions. These results suggest that the characteristics of the rate-determining TS are not much different for different halogens and solvents. Note that the magnitudes of the carbonyl-^{14}C KIEs are similar to those reported for other addition reactions to carbonyl compounds (e.g., $^{12}k/^{14}k$ = 1.043 for $(C_6H_5)_2C{=}O$ + $LiBH_4$[9] and 1.054 for $C_6H_5COCH_3$ + 2,4-$(NO_2)_2C_6H_3NHNH_2$[12]). The large KIEs as well as the large steric rate retardation clearly indicate that the C–C bond formation step is rate determining of the reactions. The present results are consistent with the mechanism in which the reaction proceeds via initial fast SET followed by a slow R-transfer step, although they are also compatible with the polar nucleophilic addition mechanism.[13]

The mechanism of the MeMgX reaction can be considered similar to that of Me_2CuLi in a sense that both react via initial fast SET followed by a slow R-transfer step.[6a,14] However, the size of the carbonyl-^{14}C KIEs and the substituent effects is different; the KIE is smaller (1.029), the Hammett ρ value is larger (1.96), and the steric rate retardation due to ortho substituents is smaller for the Me_2CuLi reaction.[6a] It may be assumed that these differences reflect the different extent of C–C bond formation in the TS of these reactions: large for MeMgX and small for Me_2CuLi.

We have previously reported that the extent of C–H bond formation is different in the $LiAlH_4$ and $NaBH_4$ reductions.[9] The C–H bond order at the TS was determined to be about 0.35 for $LiAlH_4$ and 0.75 for $NaBH_4$ on the basis of the theoretical analysis of the observed KIEs. The difference in the ^{14}C KIE, the Hammett ρ value, and the steric rate retardation for the two reductions were all consistent with the difference in the extent of C–H bond formation in the TS; the $LiAlH_4$ reduction gave a smaller KIE (1.024 vs 1.066), a smaller Hammett ρ value (0.46 vs 2.45), and a smaller degree of steric rate retardation than the $NaBH_4$ reduction.[6b]

Although the mechanism of these reductions is polar while that of MeMgX and Me_2CuLi is SET, a similar argument is possible for the latter set of reactions. Thus, the larger ^{14}C KIE and the larger steric rate retardation for MeMgX can be taken as an indication of a larger extent of C–C bond formation for the MeMgX reaction. The smaller ρ value for MeMgX appears to be inconsistent with this conclusion, but it is reasonable if one takes into consideration that the C–C bond formation occurs after the initial SET equilibrium. A larger extent of C–C formation reduces the negative charge on the ketone fragment and hence gives a

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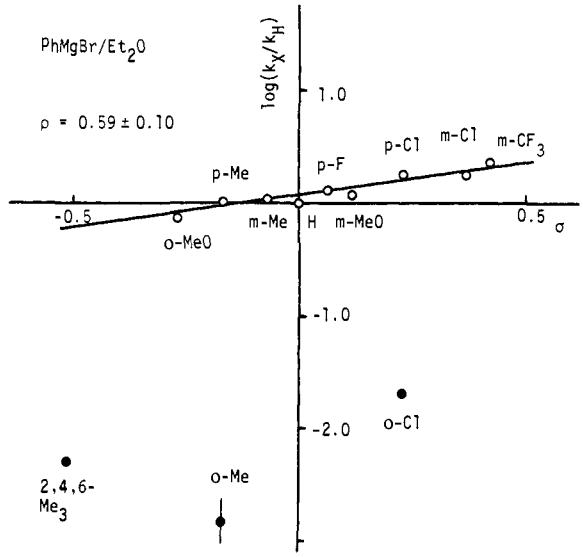

Figure 3. Variations of reactivities with σ values for the reactions of substituted benzophenones with $PhCH_2MgBr$ in diethyl ether.

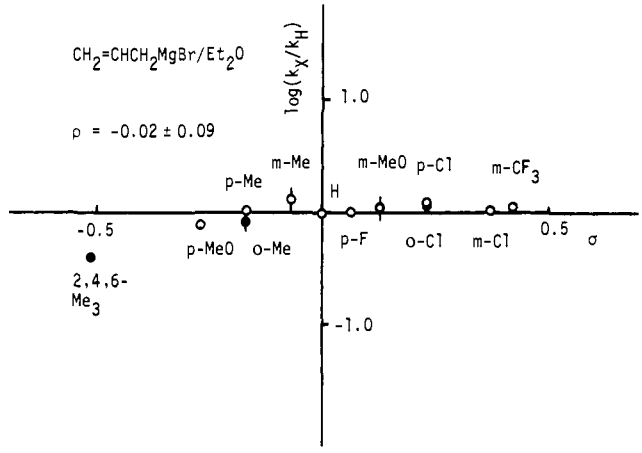

Figure 4. Variations of reactivities with σ values for the reactions of substituted benzophenones with CH_2=$CHCH_2MgBr$ in diethyl ether.

smaller Hammett ρ value. Thus, the three experimentally observable features may be used effectively to determine the relative extent of bond formation in the TS as well as the reaction mechanism (polar vs SET).

The reactions of PhMgBr and o-$CH_3C_6H_4MgBr$ in Et_2O gave similar KIEs of 1.056 and 1.060. These large KIEs are consistent with rate-determining C–C bond formation as in the MeMgX reactions. It was reported that the lifetime of the benzophenone ketyl radical formed in the PhMgBr reaction becomes longer on introducing methyl groups either on benzophenone or on the phenyl Grignard reagent.[3b,15] The present KIE results suggest that the nature of the rate-determining TS is not much changed by the introduction of one o-Me group on the Grignard reagent. The substituent effects in the PhMgBr reaction (Figure 3) are similar to those for MeMgX. The steric rate retardation is larger for PhMgBr, due probably to the difference in size of the incoming group (Ph vs Me). The carbonyl carbon KIE for $PhCH_2MgBr$ is smaller but still of significant magnitude, suggesting that the mechanism for $PhCH_2MgBr$ is also the same as for MeMgX and ArMgBr.

Allylic Grignard Reagents. The reactions of allyl and crotyl Grignard reagents gave quite different KIEs (0.999, entries 6 and 7 in Table I) from those for the methyl and aryl Grignard reagents. The substituent effects also show a different pattern: near-zero ρ values and very little steric rate retardation for the ortho-substituted derivatives (Figures 4 and 5). Apparently the reaction

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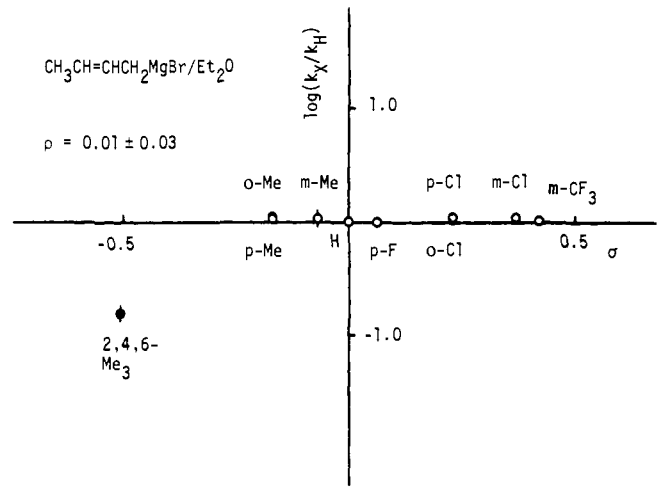
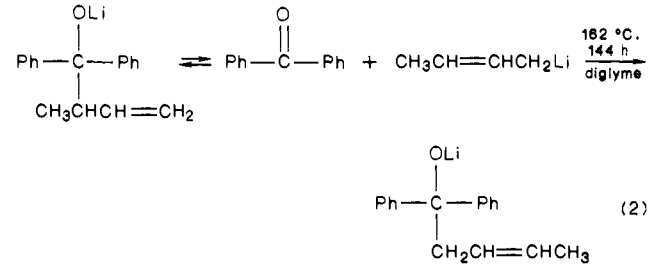


Figure 5. Variations of reactivities with σ values for the reactions of substituted benzophenones with CH_3CH=$CHCH_2MgBr$ in diethyl ether.

mechanism is different from that for MeMgX and PhMgBr.

The reactions of allylic lithium and magnesium reagents with ketones are known to be reversible.[16] In the reaction of benzophenone with crotyllithium, for example, the kinetically controlled methallyl adduct CH_2=$CHCH(CH_3)C(C_6H_5)_2OLi$ was shown to be converted through the equilibrium to the more stable crotyl adduct CH_3CH=$CHCH_2C(C_6H_5)_2OLi$ on standing at 162 °C for 144 h in diglyme (eq 2).[16c] Thus, although the reactions of



allyl- and crotylmagnesium bromide with benzophenone yield exclusively 1,1-diphenyl-3-butenol (**1**) and 1,1-diphenyl-2-methyl-3-butenol (**2**), respectively, the observed negligible KIEs and the ρ values may be deteriorated by such an equilibrium. In order to check whether the observed values are totally of a kinetic nature, the following experiments were carried out. To **1** and **2** MeMgBr was added to produce the magnesium bromoalkoxides. Then ^{14}C-labeled benzophenone was added and allowed to react at 0 °C for 30 min. After appropriate workup, the radioactivity of the recovered benzophenone was measured. The results that the molar radioactivity of the recovered ketone was identical within the experimental errors to that of the added ketone confirmed that the reversal from the bromoalkoxides to benzophenone does not occur under the reaction conditions.

The small KIEs and substituent effects in the allylic reagents show that there is little bonding change occurring at the carbonyl carbon in the rate-determining TS. Similar results have been observed previously in the reaction of benzophenone with MeLi, where the reaction was concluded to proceed via rate-determining SET followed by relatively fast C–C bond formation.[6a] We assume that the reaction mechanism for the allylic Grignard reagents is similar to that for MeLi. It is interesting to note that in both cases 2,4,6-trimethylbenzophenone deviates downward from the Hammett correlation. This deviation can be rationalized by slow C–C bond formation for this substrate due to the steric bulkiness of the mesityl moiety, which results in the shift in the rate-determining step from ET to R transfer. The observed positive ^{14}C

(16) (a) Benkeser, R. A.; Broxtermar, W. E. *J. Am. Chem. Soc.* **1969**, *91*, 5162. (b) Benkeser, R. A.; Siklosi, M. P. *J. Org. Chem.* **1976**, *41*, 3212. (c) Benkeser, R. A.; Siklosi, M. P.; Mozdzen, E. C. *J. Am. Chem. Soc.* **1978**, *100*, 2134.

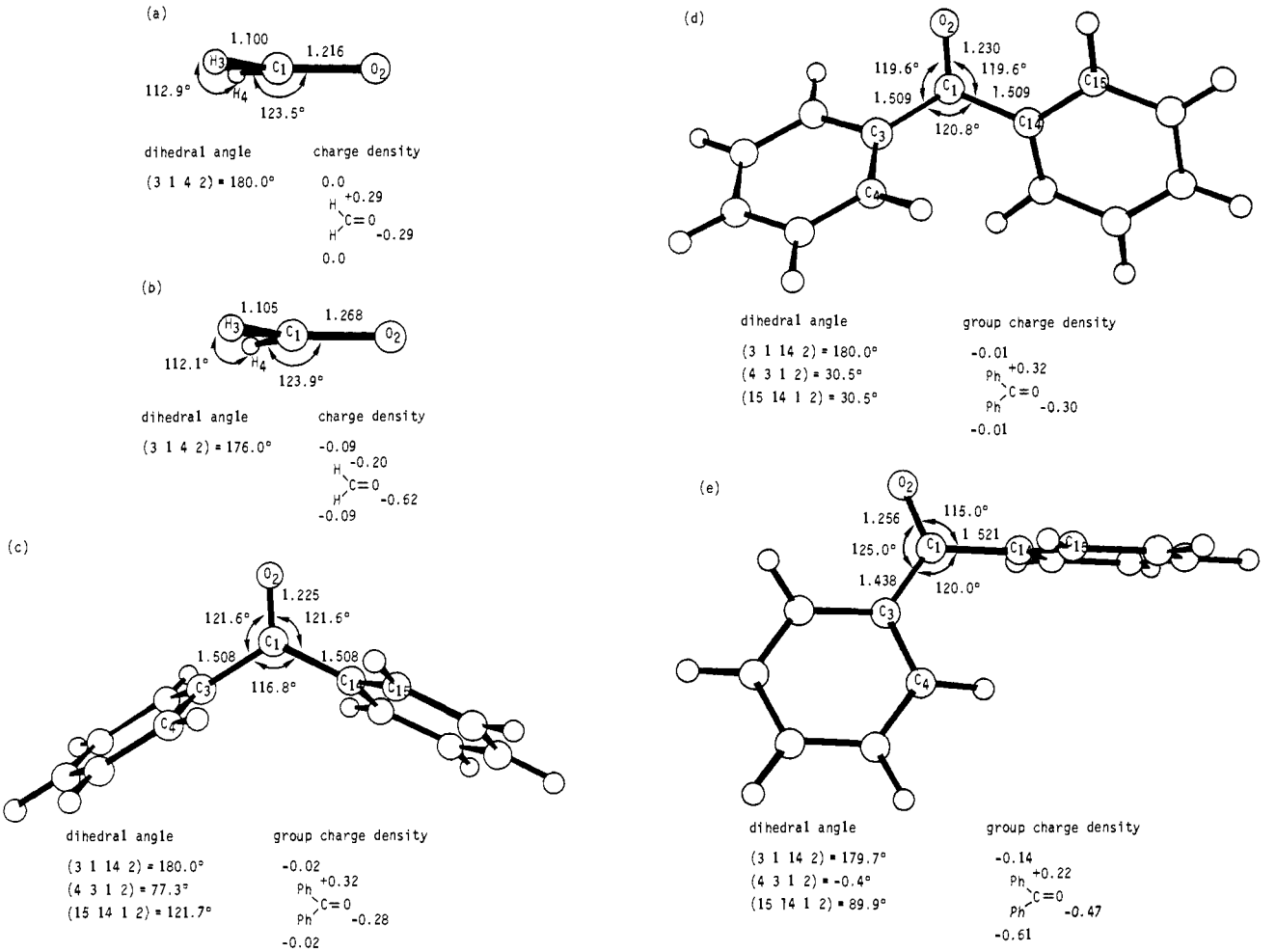


Figure 6. MNDO optimized geometries of (a) $H_2C{=}O$; (b) $H_2C{=}O$ radical anion; (c) $Ph_2C{=}O$; (d) $Ph_2C{=}O$, twist angle fixed at 30.5°; and (e) $Ph_2C{=}O$ radical anion.

KIE for the reaction of 2,4,6-trimethylbenzophenone with MeLi[6a] supports this interpretation.

Isotope Effect in the ET Process. There may be an argument against the conclusion that the carbonyl-^{14}C KIE for the ET process is near unity. The argument is based on the expectation that an electron transferred to benzophenone has to be accommodated in the π^* orbital, which should result in a weakening of the C–O bond. Thus the total bonding to the carbonyl carbon of benzophenone radical anion can be weaker than that of the neutral ketone, giving a normal ET equilibrium isotope effect of considerable magnitude. One might also expect that the C–O bond weakening occurs at the TS of the ET process and therefore the ET KIE is of significant magnitude. It may be assumed, however, that these expectations are not applicable to the present case. The reasons are twofold.

First, the total bonding to the carbonyl carbon of benzophenone radical anion is actually not very much decreased as expected because the decrease of the C–O bonding is partly compensated for by the increase of conjugation between the phenyl rings and the carbonyl carbon. On the analogy of small carbon KIEs observed for S_N1 solvolyses, which have been interpreted by additional conjugative or hyperconjugative delocalization of the incipient positive charge on the α-carbon by adjacent phenyl or alkyl groups,[17] the SET equilibrium IE for benzophenone can be small. This can be seen in the MNDO calculations[18] of the SET equilibrium IE for $H_2C{=}O$ and $Ph_2C{=}O$. Geometries were fully optimized and vibrational frequencies were calculated for both carbonyl ^{12}C and ^{14}C compounds. The optimized geometries were shown in Figure 6. Benzophenone calculated with the MNDO method is known to have the twist angle at the Ph–C bonds that is too large (~75°)[19] compared to that calculated with the ab initio MO method (32°)[20] or determined by X-ray analysis (30.5°).[21] Since this angle is important in governing the degree of conjugation and hence the bonding at the carbonyl carbon, further calculations were carried out to determine the geometry and the vibrational frequencies in which the twist angle was fixed at 30.5°.

As can be seen in Figure 6, electron attachment to the ketone resulted in the lengthening of the C–O bonds by ca. 0.04–0.05 Å. Accordingly, the C–O stretching vibrational frequencies were reduced from 2114 to 1895 cm^{-1} for formaldehyde and from 2115 cm^{-1} (2082 cm^{-1}, twist angle fixed at 30.5°) to 1902 cm^{-1} for benzophenone. The important point is that the two phenyl groups of benzophenone radical anion are not equivalent in sharp contrast to the case of neutral benzophenone, in which the molecule has the C_2 symmetry. While one phenyl group of the radical anion is perpendicular to the CCO plane, the other phenyl group is coplanar with the CCO plane, allowing conjugation between the carbonyl carbon and the phenyl ring. The conjugation results in a shorter C–Ph bond length (1.430 vs 1.521 Å) and a greater negative charge (−0.61 vs −0.14 e) for the phenyl group.

The geometrical features described above are reflected in the calculated IE. The carbonyl-^{14}C equilibrium IE for SET to

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(18) Dewar, M. J. S.; Thiel, W. *J. Am. Chem. Soc.* **1977**, *99*, 4899. Thiel, W. *QCPE* **1978**, *11*, 353. Beppu, Y.; Ninomiya, I. *QCPE* **1981**, *14*, 409. Sasaki, Y.; Takagi, T.; Tanaka, A.; Tokura, R. *Bull. Comput. Center Osaka Univ.* **1985**, *14*, 103.
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(21) Fleischer, E. B.; Sung, N.; Hawkinson, S. *J. Phys. Chem.* **1968**, *72*, 4311.

formaldehyde was calculated to be 1.075 at 0 °C, consistent with the C–O bond lengthening in the anion radical. The size of this IE is similar to that determined by the ab initio HF/3-21G calculations (1.071 at 25 °C).[22] The equilibrium IEs for benzophenone were, on the other hand, much smaller (1.030 and 1.031 for the fully optimized geometry and for the geometry with the fixed twist angle at 30.5°, respectively); these are less than half of that for formaldehyde. This should be due in most part to the effect of conjugation as described above. Since the stretching vibrational frequencies calculated by the semiempirical MO method are overestimated by ca. 10–20%,[23] the true equilibrium IEs should be even smaller.

The second reason for the near-unity ET KIE is that the geometrical change of the ketone can be very small in the rate-determining TS of an ET process in which an ET occurs between less-polar species giving a very polar radical ion pair. Equation 3 shows a schematic representation of the ET process. Here the

$$A + D \overset{k_a}{\rightleftharpoons} \underset{R}{A\cdots D} \overset{k_b}{\rightleftharpoons} \underset{TS1}{[A\cdots D} \leftrightarrow \underset{TS2}{A^{\bullet-}\cdots D^{\bullet+}]^{\ddagger}} \overset{k_c}{\rightleftharpoons} \underset{P}{A^{\bullet-}\cdots D^{\bullet+}} \overset{k_d}{\rightleftharpoons} A^{\bullet-} + D^{\bullet+} \quad (3)$$

actual ET step includes two forms of TS, TS1 and TS2, both with the same nuclear structure. In the absence of solvent, the structure of the TS should simply be governed by the endothermicity of the reaction as expected by the Leffler–Hammond principle. In solution, on the other hand, the situation is different. It is well recognized that the solvent reorganization is the dominant factor in ET reactions in terms of energetics. An important point is the sudden polarity change which happens upon electron transfer. This means that the solvent reorganization can not be synchronized with the geometrical change of the substrate throughout the reaction. In eq 3, ET gives sudden increase in polarity, from less polar R to polar P. It can be expected that the solvent molecules have an orientation which stabilizes more polar TS2 than less polar TS1 in the TS in order to reduce the total activation energy of the ET process. Thus, the reaction first involves the solvent reorganization as the main activation process. Then fast ET occurs, and the geometrical change of the substrate follows. Therefore, the TS is very reactant-like in terms of the substrate geometry, and this is the reason for very small IEs and substituent effects in the forward ET step in sharp contrast to the positive values in the ET equilibrium.[24]

***tert*-Butyl Grignard Reagent.** There are now two types of Grignard reagents; one gives a large KIE, a large Hammett ρ value, and large steric rate retardation (MeMgX, ArMgBr, and $PhCH_2MgBr$; R transfer rate determining) and the other gives a near-unity KIE, a small ρ value, and negligible steric rate retardation (allylic MgBr; SET rate determining). However, it can be seen in Table I that *t*-BuMgCl shows a different pattern, i.e., a small KIE, a large ρ value, and no steric rate retardation. The large ρ value and the absence of steric effect on reactivity reported by Holm were interpreted in terms of the rate-determining SET mechanism.[4] We believe, however, that the Hammett ρ value for the SET step is small as observed in the reactions of allylic Grignard reagents and MeLi. The large ρ value of 3.0 reported for *t*-BuMgCl is rather indicative of the presence of electron-transfer equilibrium prior to a rate-determining step.

It is assumed that in the *t*-BuMgCl reaction the product formation from the first intermediate, I, is slowed down compared to the Me case because of the steric bulkiness of *t*-Bu, and another route via the second intermediate, II, becomes important. The rate-determining step of the reaction is then the isomerization of I to II. This interpretation is consistent with the large ρ value as well as a small KIE observed for this reaction.

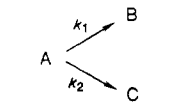
Table II. Isomerization of Cis Enone (3) during the Reaction with Grignard Reagents[a]

reagent	% recovered 3		% product		
	cis	trans	1,2-cis addition	1,2-trans addition	1,4-addition
t-BuMgCl	4.0	96.0	7.7	62.8	29.5
MeMgBr	83.1	16.7	18.9	40.2	40.9
$CH_2{=}CHCH_2MgBr$	99.2	0.8	99.3	0.7	0.0

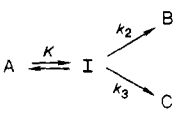
[a] Data taken from ref 26.

MeMgI + $FeCl_3$. The influence of transition-metal additives on product distribution was thoroughly investigated by Ashby and his co-workers.[25] While MeMgX prepared from pure Mg gave the normal 1,2-adduct exclusively, benzopinacol became a major product when various kinds of metal salts were added. The relative amount of pinacol to the 1,2-adduct was found to depend on the concentration of the added salt. It was suggested that the two pathways, one for the 1,2-adduct and the other for pinacol, are competing in the reaction of benzophenone with MeMgX containing transition-metal salts, and that the reduction of ketone to ketyl is catalyzed by the transition-metal salts.

We have determined the carbonyl carbon-14 KIE for both pathways in the reaction of benzophenone with MeMgI containing 5 mol % $FeCl_3$ by isolating unreacted benzophenone, 1,2-adduct, and pinacol from the reaction mixture and by measuring their specific radioactivities. The KIEs were calculated by using Tong–Yankwich type[26] equations derived for competitive reaction schemes (eq 4 and 5). Although the error limits are larger than



(4)



(5)

those for the other reactions with a single product, the results show that the KIE for the 1,2-adduct formation is large and comparable to that observed for the reaction without $FeCl_3$. This suggests that the reaction mechanism for the 1,2-adduct formation is essentially unchanged by the $FeCl_3$ added. The KIE for the pinacol formation is small, which indicates that little bonding change is occurring in the TS.

There are two possible mechanisms for the reaction of MeMgI containing $FeCl_3$ as shown in eq 4 and 5; in the first mechanism, the 1,2-adduct formation and the pinacol formation are independent pathways (eq 4), and in the second one the two pathways share the common intermediate as shown in eq 1 (also eq 5). Although the large uncertainty involved in the KIE does not allow definite conclusion, the present as well as the available experimental results can reasonably be interpreted by the reaction

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(24) (a) It should be noted that the assumption of a small ρ value for the SET process is applicable only to an ET process in which ET between less polar molecules (or fragments) gives rise to polar products. Ordinary ET process between an anion (or radical anion) and a neutral molecule does not fall into this category. This type of SET should have a significant geometrical change at its TS and should give a large substituent effect. (b) A referee pointed out that the absence of KIEs and substituent effects may arise from initial complex formation which is irreversible and rate determining. We have considered this possibility previously for the reaction of MeLi.[6a] Although this possibility cannot completely be eliminated on the basis of the present results, we feel it less probable since the complex formation is likely to be a fast and reversible step. Furthermore, the substituent effect is expected to give some negative ρ values if the complex formation is rate determining, which is not the case. However, it may be possible that a certain step such as the formation of a stronger DA complex accompanied by solvent reorganization precedes the actual ET and it is rate limiting. (c) Maruyama et al.[8] have reported that the rate of accumulation of the first radical ion pair intermediate in the Grignard reaction of benzophenones is highly dependent on the reduction potential of ketone (on a substituent of benzophenone). These appear to suggest that a large ρ value should be observed for the rate process. However, it should be noted that the observed rate is not simply an ET rate but is complicated by the back ET process.

(25) (a) Ashby, E. C.; Wieseman, T. L. *J. Am. Chem. Soc.* **1974**, *96*, 7117. (b) Ashby, E. C.; Buhler, J. D.; Lopp, I. G.; Wiseman, T. L.; Bowers, J. S., Jr.; Laemmle, J. T. *J. Am. Chem. Soc.* **1976**, *98*, 6561.

(26) Tong, J. Y.; Yankwich, P. E. *J. Phys. Chem.* **1967**, *61*, 540.

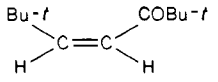
Table III. Reaction Sequences and the Rate-Determining Step of the Reactions of Benzophenone with Various Grignard Reagents

reagent	reaction sequence	rate-determining step
MeMgI	a→c	c
PhMgBr	a→c	c
CH_2=$CHCH_2MgBr$	a→c	a
CH_3CH=$CHCH_2MgBr$	a→c	a
t-BuMgCl	a→b→(d,e,f)	b
MeMgI + $FeCl_3$[a]	a→c	c
MeMgI + $FeCl_3$[b]	a→b→f	b

[a] For 1,2-adduct formation. [b] For pinacol formation.

scheme in eq 1. Added $FeCl_3$ catalyzes the isomerization from I to II as well as the initial SET, thus making the pinacol formation competitive with the 1,2-addition. The reported enhancement in the 1,2-addition rate by the addition of $FeCl_3$ in the reaction of *o*-methylbenzophenone with MeMgBr[25b] is consistent with this scheme. The fact that the product distribution in the reaction of benzophenone with *t*-BuMgCl is independent of the concentration of transition-metal salts added indicated that the pinacol formation pathway in the "catalyzed" *t*-BuMgCl reaction is the same as the "uncatalyzed" one,[25b] which also supports this mechanism.

Enone Probe. Ashby et al. carried out the enone probe experiments with various Grignard reagents and found that cis enone (**3**) when treated with *t*-BuMgCl gave more trans 1,2-adduct than



3

the cis 1,2-adduct and that the recovered enone was isomerized to a great degree to trans (Table II).[27] The results were taken as an evidence for the SET mechanism. It should be noted here that the great degree of isomerization in the recovered enone appears to suggest that considerable degree of back ET occurs and therefore a subsequent step is rate determining in the overall reaction scheme, as in the reaction of benzophenone with *t*-BuMgCl. The reaction of cis enone with allyl-MgBr gave no isomerization either in the recovered enone or in the 1,2-adduct. The results were explained by the polar mechanism at that time. It can now be considered to result from relatively slow initial SET followed by a fast decomposition of the radical ion pair intermediate; thus the lifetime of the intermediate is too short to allow the cis–trans isomerization. The MeMgBr reaction lies in an intermediate region, which suggests significant lifetime of the radical ion pair.

Concluding Remarks

All KIEs and substituent effects determined in the present study can successfully be interpreted by eq 1. The reaction route and the rate-determining step are different depending on the type of the Grignard reagent as summarized in Table III.

It was reported that the pseudo-first-order rate constants for various Grignard reagents are linearly related with E_{OX}(RMgX), the oxidation potential of RMgX,[28] and the large dependence of rates on E_{OX} is often taken as an evidence of the rate-determining SET mechanism. However, it seems that this dependence is rather indicative of the presence of ET preequilibrium; thus, the overall rate constant can be expressed as $k_0 = K_{ET}k$ and the reactivity is primarily determined by K_{ET}. The fact that *t*-BuMgBr is 1000 times more reactive than MeMgBr suggests a large radical character in the TS of the *t*-BuMgBr reaction, consistent with the presence of the ET preequilibrium.[28] The point for allyl-MgBr deviates upward from the correlation line,[28] which is in accord with the shift of the rate-determining step from R transfer to ET; the R-transfer step is extremely fast for allyl-MgBr because a sterically favored six-membered TS is possible in the C–C bond formation step for the reagent.

It should be emphasized that the carbon IE is positive and the substituent effect is of considerable magnitude in the ET equilibrium while they are very small in the forward ET step. One might ask, then, what will happen if two significantly different ketones were allowed to react with, for example allyl-MgBr; do they always react in similar rates? The answer is as follows. When the electron-accepting ability of a ketone is lowered by any perturbation, the barrier of step a becomes only slightly higher and the barrier of step b (or c) rises rapidly. As far as SET is the rate-determining step for both ketones, the reactivity difference would be small. However, when the barrier of step b (or c) becomes high enough, the back ET becomes significant and then the reactivity difference of the two ketones becomes larger. Further decrease in the electron-accepting ability of the ketone makes step b (or c) the rate-determining step. Finally the radical ion pair intermediate becomes too unstable to exist in a meaningful lifetime and the mechanism merges with the polar one. The identification of the rate-determining step for reactions of different ketones is interesting in this context and will be the subject of further study.

Experimental Section

Materials. Diethyl ether and THF were dried over $LiAlH_4$ and distilled before use. Substituted benzophenones and benzophenone-*carbonyl*-^{14}C were prepared as described previously.[6a] All glassware was flame-dried, and the ethereal solution was handled under dry nitrogen by using the Schlenk tube technique.[29] MeMgBr and *t*-BuMgCl were purchased from Aldrich. Other Grignard reagents were prepared from the appropriate halides (purified by distillation) and doubly sublimed Mg (Ventron). The Grignard reagents were standardized by using 2,2′-biquinoline as described in the literature.[30]

Competition Experiments and Determination of KIEs. For all Grignard reagents but two cases (*t*-BuMgCl and MeMgI containing $FeCl_3$), the reactions gave the normal 1,2-adducts exclusively. Products were identified by isolation and/or comparison of their GLC retention time with the authentic samples. All isolated products gave satisfactory analytical and spectroscopic data. The material balance was confirmed for the unsubstituted benzophenone and was excellent in these reactions. The relative reactivities of the substituted benzophenones were determined at 0.0 °C by the competition experiments. Typically, 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 solvent. Half of the solution was withdrawn and used for calibration in the GLC analysis. To the rest of the solution 0.1 mmol of a reagent was added by means of a hypodermic syringe, and the solution was worked up in the usual manner and subjected to GLC analysis (glass column, PEG HT 2 m, 200 °C). The relative intensities of the ketones to the internal standard were used to determine the fraction of reaction, *f*, and the rate ratio was calculated according to eq 6. The experiments were repeated two to six times and the results were averaged.

$$k_A/k_B = \log (1 - f_A)/\log (1 - f_B) \quad (6)$$

Carbonyl-^{14}C KIEs for these reagents were measured in a usual manner.[9] Typically, ^{14}C-labeled benzophenone (1.8 mmol in 1.8 mL of solvent) was allowed to react with a preset amount of a Grignard reagent (0.3–0.7 equiv) at 0.0 °C for 30 min. After the usual workup, the fraction of reaction was determined by GLC, and the unreacted ketone and the product were isolated by preparative TLC and purified by recrystallizations. The same procedure was repeated usually four to five times with a different ratio of the reagent to the ketone. Molar radioactivities were measured by a liquid scintillation counter (Beckman LS 9000),[31] and KIEs were calculated from the variation in radioactivities of the recovered ketone and the product by using the four equations of Tong and Yankwich.[26] In the cases of allylic Grignard reagents, KIEs were calculated only from the variation of radioactivity of the ketone because the product alcohols were not crystalline and the radioactivities could not be measured accurately. The KIE for PhMgBr, on the other hand, was calculated on the basis of the radioactivity of the product because the recovered ketone could not be purified for accurate ra-

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dioassay due to contamination by the product.

In the case of MeMgI + 5 mol % $FeCl_3$, two products, 1,2-adduct and benzopinacol, were formed. Since benzopinacol was liable to decompose under the practical GLC conditions (column temperature >150 °C) used in this experiment,[32] the amount of pinacol was determined by HPLC (reverse phase C18, MeOH-H_2O) by calibrating its sensitivity with an internal standard. The amounts of benzophenone and the 1,2-adduct were measured by GLC (PEG 20M, 0.5 m) with the column temperature of 145 °C. The material balance of the reaction was excellent. In the case of the reaction of the radioactive material, the molar fraction of pinacol was calculated from those of the unreacted ketone and the 1,2-adduct which could accurately be determined by GLC. To determine the KIEs, unreacted benzophenone and the two products were isolated by TLC and purified by recrystallizations, and their radioactivities were measured. The KIEs for the two reaction channels were calculated by using Tong-Yankwich type equations for competitive reaction schemes (see the supplementary material).

For the *t*-BuMgCl reaction, the typical workup procedure could not be used since the 1,6-adduct present in the reaction mixtue decomposed competitively to *tert*-butylbenzophenone and benzophenone during the workup procedure.[4] The GLC analysis (PEG 20M, 0.5 m, 145 °C) of the reaction mixture after the workup gave recovered benzophenone, 1,2-adduct, and *tert*-butylbenzophenone as major components (pinacol did not decompose but could not be detected under the GLC conditions due to a long retention time), but the ratio of benzophenone to *tert*-butylbenzophenone was variable from run to run. In order to determine the KIE, the unreacted benzophenone must be isolated without contamination due to the reversal from the 1,6-adduct. This was realized by adding 2 equiv of MeLi (Merck) into the reaction mixture prior to the usual workup. The unreacted benzophenone was isolated as 1,1-diphenylethanol. The addition reaction of MeLi to benzophenone is known to give the 1,2-adduct exclusively without a carbonyl-^{14}C KIE.[6a] The absence of the reversal from the 1,6-adduct during the procedure was confirmed by carrying out the Grignard reaction of benzophenone with excess *t*-BuMgCl followed by the addition of MeLi; this control experiment gave no 1,1-diphenylethanol. The KIE for the *t*-BuMgCl reaction was calculated from the variation in radioactivity of 1,1-diphenylethanol with the fraction of reaction.

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Supplementary Material Available: Relative reactivities of benzophenones with various Grignard reagents, radioactivity data, and Tong-Yankwich type equations for competitive reaction schemes (8 pages). Ordering information is given on any current masthead page.

Investigation of the Relationship between Rates of Base-Catalyzed Hydrogen Exchange and Anesthetic Potency for Some Halohydrocarbons

A. L. Brown, Y. Chiang, A. J. Kresge,* Y. S. Tang, and W.-H. Wang

Contribution from the Department of Chemistry, University of Toronto, Toronto, Ontario M5S 1A1, Canada. *Received October 31, 1988*

Abstract: Rates of detritiation of the inhalation anesthetics halothane ($CF_3CHClBr$), methoxyflurane ($CH_3OCF_2CHCl_2$), and enflurane (CHF_2OCF_2CHFCl) were determined in dilute aqueous sodium hydroxide solutions; rates for halothane were also measured in six amine buffer solutions. The latter give a Brønsted relation with unit slope, $\beta = 0.92 \pm 0.11$, suggesting that halothane is showing normal acid behavior. The hydrogen bond donating ability of these anesthetics, taken to be proportional to pK_a's estimated from these rate data, does not correlate with their anesthetic potency, and it is therefore suggested that hydrogen bond *accepting* ability is also important in governing anesthetic potency.

Anesthetics are believed to operate by disrupting molecular associations that give nerve cell membranes the structure they need to transmit nerve impulses. Both polar and nonpolar interactions appear to be involved, and prominent among the former are hydrogen-bonding forces. This is apparent from correlations of the potency of anesthetics[1] and especially from an extensive series of spectroscopic investigations[2] which have been supplemented by theoretical calculations.[3] These spectroscopic studies have shown that anesthetics disrupt hydrogen bonds in model systems and that the extent of disruption correlates well with the potency of the anesthetic.[4]

It is thought that anesthetics exert their hydrogen bond disruptive action by forming hydrogen bonds themselves with cell membrane constituents, in competition with the intramembrane hydrogen bonds that give membranes their requisite structure. Some of the most effective anesthetics in general use today, such as halothane (**1**), methoxyflurane (**2**), and enflurane (**3**) have both

$CF_3CHClBr$	$CH_3OCF_2CHCl_2$	CHF_2OCF_2CHFCl
1	**2**	**3**

hydrogen bond donor sites (C-H bonds) and hydrogen bond acceptor sites (oxygen and halogen atoms), and this competitive

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