C1), 143.5 (C5a), 157.9 (C7). IR (KBr): 3100–3000, 3000–2750, 1610, 1583, 1506, 1267, 738, 699 cm^{-1}. Mass spectrum: *m/z* 267 (M^+, 60), 266 (24), 252 (20), 190 (12), 176 (36), 148 (20), 135 (68), 134 (35), 132 (21), 91 (100). High-resolution mass spectrum calcd for $C_{18}H_{21}NO$ 267.1617, found 267.1620.

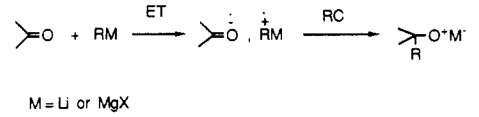
Electron Transfer in the Additions of Organolithium Reagents to Benzophenone and Benzaldehyde

Hiroshi Yamataka,* Yukie Kawafuji, Katsushi Nagareda, Nobutaka Miyano, and Terukiyo Hanafusa

The Institute of Scientific and Industrial Research, Osaka University, Ibaraki, Osaka 567, Japan

Received March 6, 1989

The mechanism of addition reactions of organolithium and organomagnesium reagents to ketones has recently been shown to differ in spite of the fact that the two types of reagents react in a similar manner to give 1,2-addition products.[1,2] For example in the reaction with benzophenone, MeLi exhibited no carbon kinetic isotope effect (KIE, $^{12}k/^{14}k = 1.000$) for the carbonyl ^{14}C-labeled compound and only very small electronic and steric effects of substituents on reactivity,[1a] while MeMgI showed a large KIE (1.056) and considerable substituent effects both electronically and sterically.[1b] These results were interpreted by assuming a rate-determining electron transfer (ET) mechanism for MeLi and a fast ET process followed by a slow rate-determining C–C bond formation (RC) for MeMgI (eq 1). The interpretation for the MeMgI reaction



(1)

is consistent with the current view that the Grignard reaction proceeds via an ET mechanism with aromatic ketones.[3] However, the conclusion for MeLi might be controversial because (1) there are no reports indicating an ET mechanism for the addition of MeLi to ketones and (2) there are only a few examples of ET processes which give very small KIE and substituent effects.

We have recently reported that the reaction of benzophenone with allylmagnesium bromide proceeds with a carbonyl carbon KIE of unity as well as with small steric and electronic substituent effect as for the MeLi system.[1c] These results can be interpreted as indicating a rate-determining ET mechanism, and thereby provide indirect support for the earlier conclusion of an ET mechanism for MeLi. Furthermore, the results indicated that the barrier heights of the two steps, ET and RC, are so comparable in the Grignard reaction that the rate-determining step could easily be shifted by the change in the structure of RMgX. In the present study, we measured KIEs and substituent effects for two different lithium reagents and two different substrates in order to see whether the reactions of lithium reagents other than MeLi may also proceed via an ET mechanism (eq 1) and whether the rate-determining step could be varied with a change in the R group of the lithium reagent as in the Grignard reaction. The reactions we examined are (1) benzophenone/PhLi, (2) benzophenone/allyllithium, and (3) benzaldehyde/PhLi. The results are compared with those observed with the benzophenone/MeLi system.

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

substrate	reagent	solvent	$^{12}k/^{14}k$
$(C_6H_5)_2CO$	PhLi	cyclohexane–Et_2O (7:3)	1.003 ± 0.001
$(C_6H_5)_2CO$	allyllithium	Et_2O	0.994 ± 0.003
C_6H_5CHO	PhLi	cyclohexane–Et_2O (7:3)	0.998 ± 0.003

[a] Reactions were carried out at 0.0 °C.

Table II. Relative Reactivities of Substituted Carbonyl Compounds with Various Lithium Reagents at 0.0 ± 0.1 °C[a]

	k_X/k_H		
substituent	$Ph_2C{=}O$/PhLi[b]	$Ph_2C{=}O$/allyllithium[c]	PhCHO/PhLi[b]
2,4,6-Me_3	0.06 ± 0.03	0.39 ± 0.04	*d*
o,p-Me_2	*d*	*d*	0.91 ± 0.05
p-MeO	1.03 ± 0.03	0.83 ± 0.02	0.96 ± 0.01
m-MeO	1.03 ± 0.02	*d*	1.17 ± 0.08
p-Me	1.06 ± 0.01	0.91 ± 0.06	0.85 ± 0.03
m-Me	0.94 ± 0.05	0.96 ± 0.01	0.95 ± 0.01
o-Me	0.56 ± 0.03	0.79 ± 0.03	0.91 ± 0.04
p-F	1.18 ± 0.01	1.15 ± 0.12	1.03 ± 0.09
m-F	*d*	*d*	1.03 ± 0.03
p-Cl	1.10 ± 0.05	0.99 ± 0.06	1.21 ± 0.09
m-Cl	1.26 ± 0.04	1.20 ± 0.13	1.09 ± 0.01
o-Cl	0.81 ± 0.03	0.93 ± 0.07	1.13 ± 0.03
m-CF_3	1.48 ± 0.03	*d*	*d*

[a] Listed values are averages of two to four determinations. Error limits are the standard deviations. [b] In cyclohexane–ether (7:3). [c] In ether. [d] Not determined.

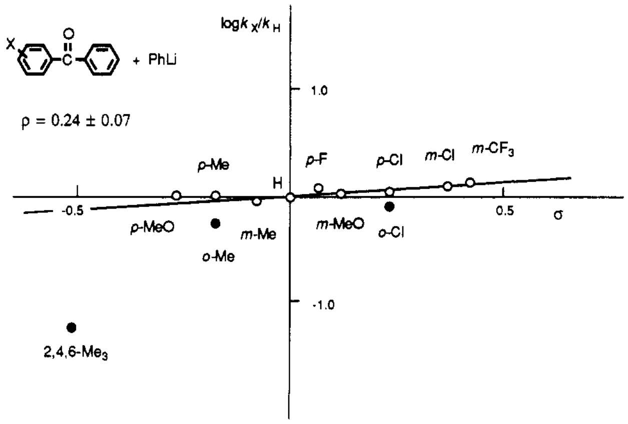


Figure 1. Variations of reactivity with σ values for the reactions of substituted benzophenones with PhLi.

The carbonyl carbon-^{14}C KIEs for the three reactions were determined as described previously[4] and are listed in Table I. In the case of reaction 1, both unreacted benzophenone and product alcohol could be isolated from the reaction mixture and purified by preparative TLC and recrystallization. The standard Tong–Yankwich equations[5]

---

[1] (a) Yamataka, H.; Fujimura, N.; Kawafuji, Y.; Hanafusa, T. *J. Am. Chem. Soc.* **1987**, *109*, 4305. (b) Yamataka, H.; Matsuyama, T.; Hanafusa, T. *Chem. Lett.* **1987**, 647. (c) Matsuyama, T.; Yamataka, H.; Hanafusa, T. *Chem. Lett.* **1988**, 1367.

[2] Ashby, E. C.; Wieseman, T. L. *J. Am. Chem. Soc.* **1978**, *100*, 3101.

[3] See for example: Ashby, E. C.; Bowers, J. R., Jr. *J. Am. Chem. Soc.* **1981**, *103*, 2242; Ashby, E. C.; Goel, A. B. *J. Am. Chem. Soc.* **1981**, *103*, 4983; Maruyama, K.; Katagiri, T. *J. Am. Chem. Soc.* **1986**, *108*, 6263; Yamataka, H.; Matsuyama, T.; Hanafusa, T. *J. Am. Chem. Soc.* **1989**, *111*, 4912.

[4] Yamataka, H.; Hanafusa, T. *J. Am. Chem. Soc.* **1986**, *108*, 6643.

[5] Tong, J. Y.; Yankwich, P. E. *J. Phys. Chem.* **1967**, *61*, 540.

0022-3263/89/1954-4706$01.50/0

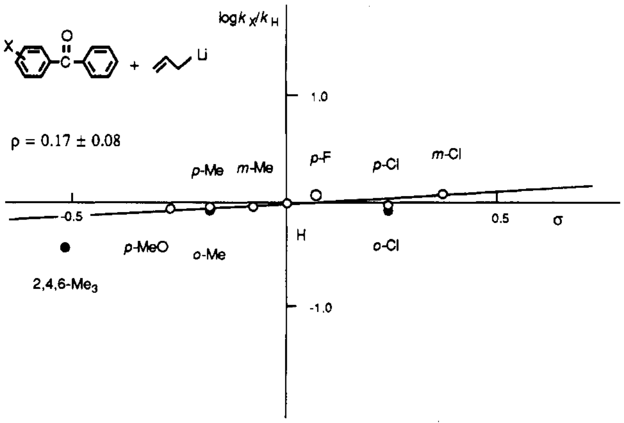


Figure 2. Variations of reactivity with σ values for the reactions of substituted benzophenones with allyllithium.

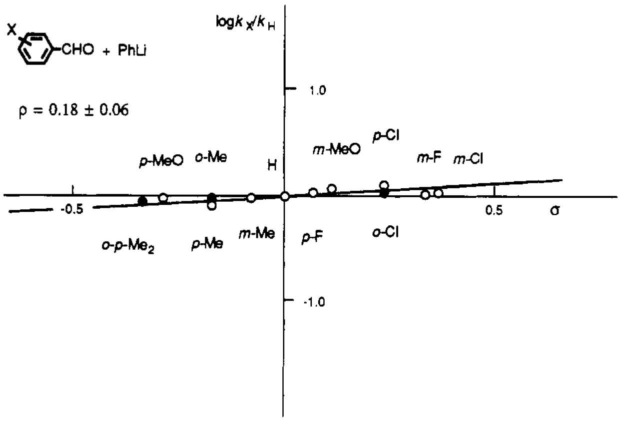


Figure 3. Variations of reactivity with σ values for the reactions of substituted benzaldehydes with PhLi.

could then be used to calculate the KIE from the fraction of reaction and radioactivities of the starting materials, the recovered ketone, and the product alcohol. For reaction 2 the KIE was calculated from the variation of radioactivity of benzophenone, and for reaction 3 the KIE was determined by following the radioactivity change of the product alcohol. It is clear from Table I that in all cases the carbonyl-^{14}C KIEs are close to unity. The results indicate that there is no bonding change at the carbonyl carbon in the rate-determining transition state of these reactions as in the cases of benzophenone/MeLi and allylmagnesium bromide. The relative reactivities of substituted benzophenones and benzaldehydes were determined as described previously and listed in Table II.[1a] Figures 1–3 show the Hammett plots for these reactions. Since no σ constants were available for ortho substituents, the $\log(k_X/k_H)$ values for the ortho derivatives were plotted against the corresponding σ_p constants and indicated by filled circles. The substituent effects determined in the present study are similar to those for benzophenone/MeLi and allylmagnesium bromide. It can be concluded, therefore, that all of the reactions of RLi examined proceed via the same mechanism, i.e., rate-determining ET followed by a fast subsequent step. The large downward deviation for 2,4,6-trimethylbenzophenone observed in the benzophenone/PhLi reaction is explained by the shift of the rate-determining step from ET to RC due to the steric hindrance of the mesityl group as in the benzophenone/MeLi case.[1a]

The product analysis of some reactions of RLi with benzophenone derivatives supports the reaction scheme shown in eq 1. In the reaction of 2,4,6-trimethylbenzophenone with PhLi, we observed the 1,4-addition product, which probably arose from the radical ion pair intermediate, in addition to the normal 1,2-adduct. Similar abnormal products have been detected in the reactions of sterically crowded benzophenone derivatives with PhLi.[6] We also observed a considerable amount of 1,6-adduct as a byproduct in the reaction of benzophenone with t-BuLi (eq 2). The situation is similar to the reaction of benzophenone with t-BuMgCl[7] and strongly suggests the involvement of the ET process.

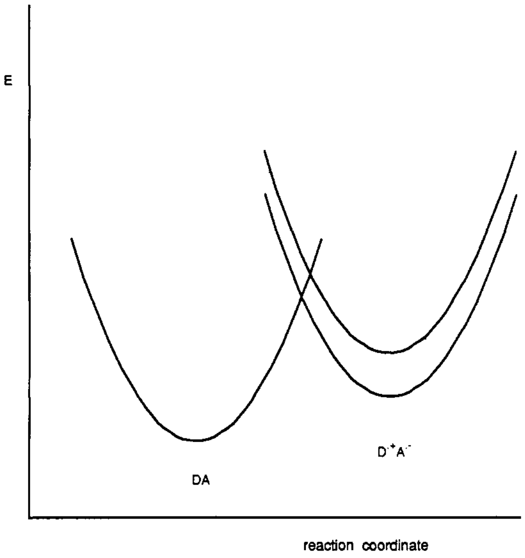
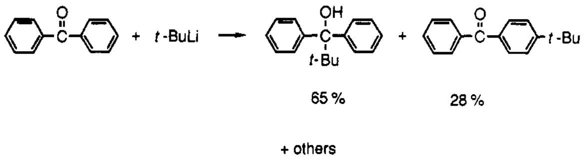


Figure 4. Potential energy curves of DA and $D^{\bullet +}A^{\bullet -}$.



(2)

The absence of a carbonyl carbon-^{14}C KIE in the rate-determining ET process was previously rationalized by assuming that the transition state (TS) is very reactantlike in terms of the substrate geometry but that it is productlike in terms of the solvent orientation.[1a] Here we would like to present the rationalization for the small Hammett ρ value observed in the ET process. Figure 4 illustrates the curve-crossing model for an ET process. A perturbation which stabilizes $D^{\bullet +}A^{\bullet -}$ state pulls down the potential energy curve of $D^{\bullet +}A^{\bullet -}$ and lowers the intersecting point. This explains the conventional view that the more exothermic the reaction the faster the reaction. It is interesting to point out, however, that the dependence of the reactivity on the exothermicity reflects the relative steepness of the two curves at the intersecting point. For example if the curve of DA is shallow and the curve of $D^{\bullet +}A^{\bullet -}$ is very steep, substantial lowering of the $D^{\bullet +}A^{\bullet -}$ curve by any perturbation brings about only a small reduction of the activation energy. This can happen in an ET reaction. It is well known that solvent reorganization plays a dominant role in an ET reaction, and this means that the reaction coordinate can be approximated by the solvent coordinate. In a charge separation ET process as considered here, the initial DA complex is less polar and the solvent molecules surrounding the complex can move relatively freely. Therefore, the potential energy curve for

---

(6) Fuson, R. C.; Speranza, G. P.; Gaertner, G. *J. Org. Chem.* **1950**, *15*, 1155.

(7) Holm, T.; Crossland, I. *Acta Chem. Scand.* **1971**, *25*, 59.

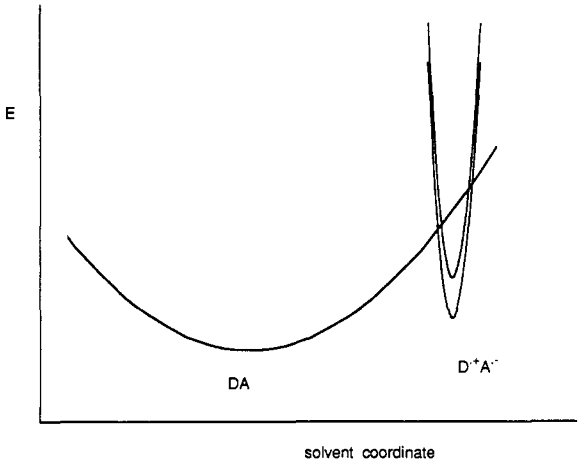


Figure 5. Possible potential energy diagram of a charge-separation ET reaction.

the DA complex should be flat. On the other hand, the solvent movement around the $D^{\bullet +}A^{\bullet -}$ complex is restricted and hence the potential energy curve of the $D^{\bullet +}A^{\bullet -}$ complex should be very sharp as illustrated in Figure 5. In such a case, the TS (intersecting point) lies late along the solvent coordinate regardless of the exothermicity of the reaction, and a perturbation which stabilizes $D^{\bullet +}A^{\bullet -}$ complex results in only a minor stabilizing effect at the TS. Therefore, the ET rate can be relatively insensitive to the change in E_{red} of the acceptor, A.

In summary, the present results indicate that all the reactions of aromatic carbonyl compounds with RLi studied proceed via the same mechanism, namely the ET mechanism in which the rate-determining step is the initial ET step.

Experimental Section

Materials. Diethyl ether was dried over $LiAlH_4$ and distilled before use. Cyclohexane was dried over CaH_2 and distilled. Pentane was dried over Na and distilled. Commercial solution of PhLi (cyclohexane–ether 7:3, Merck), allyllithium (ether, Alfa), and *t*-BuLi (pentane, Aldrich) were standardized by using 2,5-dimethoxybenzyl alcohol as described in the literature.[8] Substituted benzophenones and benzophenone-*carbonyl*-^{14}C were prepared as described previously.[1a] All substituted benzaldehydes were commercially available and purified either by distillation or recrystallization before use. Benzaldehyde-*carbonyl*-^{14}C was synthesized by the tributyltin hydride reduction[9] of benzoyl-7-^{14}C chloride which was obtained by chlorination of benzoic-7-^{14}C acid (NEN) with thionyl chloride.

Reactions. All reactions with PhLi and allyllithium gave the normal 1,2-adduct exclusively except one case, 2,4,6-trimethylbenzophenone + PhLi, in which 1,4-adduct was obtained as a minor product. All products were isolated and identified by IR and NMR. The material balance was confirmed for the unsubstituted carbonyl compounds and found excellent. The reaction of benzophenone with *t*-BuLi gave four products (1,2-adduct, 65%; 1,6-adduct, 28%; benzhydrol, 5%; structure not determined, 2%).

The relative reactivities of the substituted benzophenones and benzaldehydes were determined at 0.0 °C by the competition experiments as described previously,[1a] and the carbonyl carbon-^{14}C KIEs for reactions 1–3 were measured in a usual manner.[4]

Acknowledgment. We are indebted to the Material Analysis Center of ISIR for the elemental analyses and NMR measurements.

---

[8] Winkle, M. R.; Lansinger, J. M.; Ronald, R. C. *J. Chem. Soc., Chem. Commun.* **1980**, 87.

[9] Four, P.; Guibe, F. *J. Org. Chem.* **1981**, *46*, 4439.

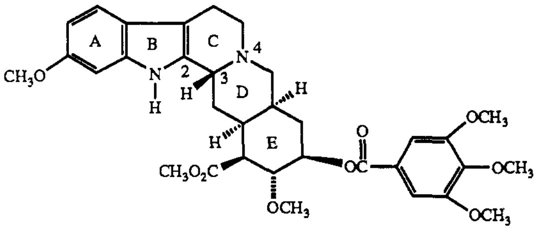
Reinvestigation of the Mechanism of the Acid-Catalyzed Epimerization of Reserpine to Isoreserpine

Lin-Hua Zhang, Ashok K. Gupta, and James M. Cook*

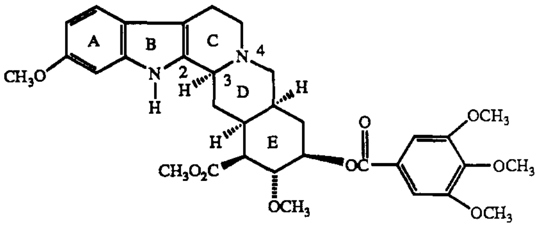
Department of Chemistry, University of Wisconsin—Milwaukee, Milwaukee, Wisconsin 53201

Received April 4, 1989

Reserpine (1) was originally isolated from the Indian snake root *Rauwolfia serpentina* Benth.[1,2] It is the preeminent member of the yohimboid class of indole alkaloids because of its structural complexity coupled with its clinical importance as a hypotensive agent. This base also exhibits significant activity as a sedative and tranquilizer.[3] Over the years, reserpine has formed the subject of extensive chemical and synthetic investigations.[4] It has been reported that the epimerization of reserpine (1) to isoreserpine (2) can be effected either under acidic or basic conditions; moreover, under acidic conditions (Δ, HOAc), 2 has been found to predominate over 1 in a ratio of 3.5:1.[4] Several mechanisms have been suggested to account for this equilibration.[2,4,5] Joule, however, concluded that the mechanism involving initial protonation at C(2) followed by reverse Mannich fission of the C(2)–C(3) bond was responsible for the isomerization between 1 and 2, as illustrated in Scheme I.[6a] This series of steps is related to



1



2

---

[1] Chatterjee, A. *Fortschr. Chem. Org. Naturst.* **1953**, *10*, 390. Chatterjee, A.; Pakrashi, S. C.; Werner, G. *Fortschr. Chem. Org. Naturst.* **1956**, *13*, 346. Schlittler, E.; Schneider, J. A.; Plummer, A. J. *Angew. Chem.* **1954**, *66*, 386. Saxton, J. E. *Quart. Rev. Chem. Soc.* **1956**, *10*, 128.

[2] Müller, J. M.; Schlittler, E.; Bein, H. J. *Experimenta* **1952**, *8*, 338.

[3] Dorfman, L.; Huebner, C. F.; MacPhillamy, H. B.; Schlittler, E.; St. André, A. F. *Experimenta* **1953**, *9*, 368.

[4] (a) Woodward, R. B.; Bader, F. E.; Bader, H.; Frey, A. J.; Kierstead, R. W. *J. Am. Chem. Soc.* **1956**, *78*, 2023 and 2657; *Tetrahedron* **1658**, *2*, 1. (b) Pearlman, B. A. *J. Am. Chem. Soc.* **1979**, *101*, 6398 and 6404. (c) Wender, P. A.; Schaus, J. M.; White, A. W. *J. Am. Chem. Soc.* **1980**, *102*, 6157; *Heterocycles* **1987**, *25*, 263. (d) Martin, S. F.; Rueger, H.; Williamson, S. A.; Grzejszczak, S. *J. Am. Chem. Soc.* **1987**, *109*, 6124.

[5] Dorfman, L.; Furlenmeier, A.; Huebner, C. F.; Lucas, R.; MacPhillamy, H. B.; Müller, J.; Schlittler, E.; Schwyzer, R.; St. André, A. F. *Helv. Chem. Acta* **1954**, *37*, 59. MacPhillamy, H. B.; Dorfman, L.; Huebner, C. F.; Schlittler, E.; St. André, A. F. *J. Am. Chem. Soc.* **1955**, *77*, 1071. Wenkert, E.; Liu, L. H. *Experimenta* **1955**, *11*, 302. MacPhillamy, H. B.; Huebner, C. F.; Schlittler, E.; St. André, A. F.; Ulshafer, R. E. *J. Am. Chem. Soc.* **1955**, *77*, 4335. Janot, M. M.; Goutarel, R.; Amin, M. *C. R. Acad. Sci., Paris* **1950**, *230*, 2541.

0022-3263/89/1954-4708$01.50/0