The Addition of Phenyllithium to Benzonitrile in Diethyl Ether

A Mechanistic Study

TORKIL HOLM

Department of Organic Chemistry, Technical University of Denmark, DK-2800 Lyngby, Denmark

The reactivity of solutions of 0.01 M to 0.72 M phenyllithium toward 0.01 M benzonitrile in diethyl ether at 20° was studied by means of a thermographic method. The reaction was 0.67 order with respect to phenyllithium. Likewise, the reactivities of seven substituted phenyllithiums were investigated at a concentration of 0.15 M, and a Hammett plot showed extremely low effect of polar substituents. This result was confirmed in a competition experiment. The operation of a concerted electrophilic aromatic substitution is suggested. The heat of reaction was dependent on the substituent and was 45 % larger for *p*-dimethylamino- than for *m*-trifluoromethylphenyllithium.

Reactivity studies involving lithium reagents have received less attention than those of Grignard reagents and have been limited mainly to reactions with hydrocarbons, *e.g.* triphenylmethane,[1] 1,1-diphenylethylene,[1] styrene,[2] fluorene,[3] *etc.* Reactions of butyllithium with 1,1-diphenylethylene and benzonitrile in ether have been shown to be 0.30 and 0.33 order, respectively, with respect to the lithium reagent.[1,4] Since butyllithium is tetrameric in ether[1] it is assumed that a rapidly established monomer-tetramer equilibrium exists and that the extremely low concentration of monomer is responsible for the total reaction. Phenyllithium is dimeric in THF and in ether,[1] and its reaction with triphenylmethane in THF was found to be 0.64 order with respect to the lithium reagent.[5] It appeared of interest to investigate the concentration dependence of the rate of reaction of phenyllithium in ether with a non-hydrocarbon substrate, but also to seek information about the effect of substituents on the reactivity of phenyllithium toward a given substrate. Because of our previous kinetic experience with benzonitrile as a substrate for butyllithium[4] and of the amount of facts known about the reaction of the latter with various Grignard reagents,[6,7] benzonitrile was found to be a natural choice.

Reactivity measurements were carried out, using the flowing stream termo-graphic method.[8] A standard concentration of 0.010 M benzonitrile in ether was used in all experiments. The reaction was conveniently fast (half lives of the order of 20 ms) to permit optimum reproducibility of the results which is within ± 2 − 3 %. Using concentrations of phenyllithium in ether, ranging from 0.01 M to 0.72 M, the reaction was found to be of 0.67 order with respect to lithium reagent (Fig. 1).

The consistency in the concentration-reactivity relations for a given lithium reagent, when changing the substrate, indicates that the same reactive species is involved in the various reactions, e.g. with triphenylmethane (metallation), 1,1-diphenylethylene (C=C addition), or benzonitrile (C≡N addition).

Edelstein and Becker [6] investigated the kinetics of the reaction of benzo-nitrile with p-substituted phenylmagnesium bromides and obtained a linear Hammett plot with a reaction constant $\varrho = -2.85$. Similarly, reactivity measurements of substituted phenyl Grignard reagents with acetone,[9] benzo-phenone,[9] and 1-hexyne [10] confirm the strongly activating effect of electron donating substituents in aromatic Grignard reagents.
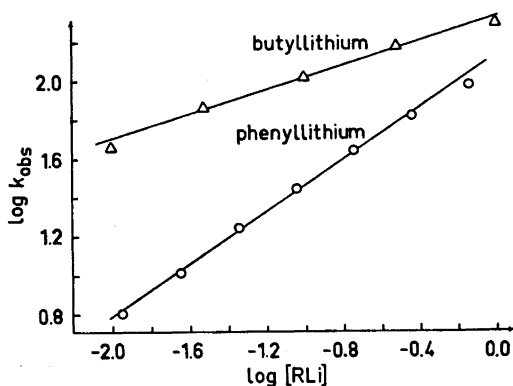

Fig. 1. log k_{obs} for reaction in diethyl ether at 20° of 0.01 M benzonitrile with butyl-lithium (triangles) and phenyllithium (circles) versus log [RLi].
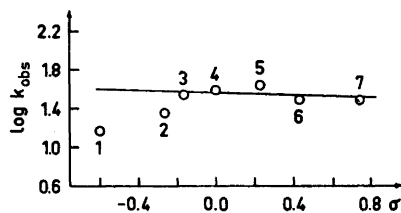
Fig. 2. log pseudo first order rate constant for the reaction in diethyl ether at 20° of 0.01 M benzonitrile with various substituted phenyllithiums versus Ham-mett sigma values for the substituents. Numbers refer to Table 1.

In order to study the substituent effects in the aromatic lithium reagents, a series of substituted phenyllithiums, varying from 3,5-dichloro ($\sigma = 0.746$) to 4-dimethylamino ($\sigma = -0.60$), was prepared by the convenient method of Schlosser and Ladenberger.[11] At a concentration of 0.15 M, the rates of addition of these aryllithiums to benzonitrile (0.01 M) were measured in ether solution at 20°. Whereas the corresponding Grignard reagents theoretically would vary in reactivity by a factor of approximately 10 000 ($\varrho = -2.85$), the reactivity of the lithium reagents in the present investigation varied only by a factor of 2.

Table 1. Pseudo first order rate constants and heats of reaction for the reaction of substituted phenyllithiums (0.15 M) with benzonitriles (0.010 M) in diethyl ether at 20°. Numbers refer to Fig. 2.

No.	Substituent(s) ϕ-Li	Substituent ϕ-CN	k_{obs} sec^{-1}	ΔH kcal/mol	σ
1	4-(CH$_3$)$_2$N-		14.8	32.2	− 0.60
2	4-CH$_3$O-		23.0	30.3	− 0.268
3	4-CH$_3$-		35.2	29.6	− 0.17
4	Unsubstituted		39.3	28.5	−
	Unsubstituted	4-Cl	177.0	29.4	−
	Unsubstituted	4-CH$_3$	22.6	27.6	−
5	4-Cl-		43.6	26.1	0.227
6	3-CF$_3$-		31.1	22.0	0.54
7	3,5-Di-Cl-		30.5	22.2	0.746

The measured rates for seven substituted phenyllithiums, shown in Table 1 and Fig. 2, do not fit a regular Hammett plot, unless the *p*-methoxy and the *p*-dimethylamino substituents are omitted. In so doing, a line with a negative slope of − 0.035 is obtained. The presence of substituents with strong donor properties may allow the formation of aggregates in ether solution of a type different from the usual dimer, causing a decrease in the concentration of the reactive monomer.

The lack of effect of polar substituents might conceivably be the result of two equally large but opposing effects, such as a negative reaction constant for reactivity of the monomer, but, at the same time, a negative ϱ for the equilibrium constant for the monomer-dimer equilibrium. That this explanation hardly is true, appears from the following experiment: phenyllithium was mixed in equal concentrations with *p*-methyl and *p*-chlorophenyllithium, and competition reactions were then effected by addition of a small amount of benzonitrile. After work up, it was shown that reaction had occurred in accordance with the reactivity of the individual aryllithiums as measured directly. Since redistribution within the dimeric complexes most likely occurs by mixing, it must be concluded from this result that neither the monomer-dimer equilibrium nor the monomer reactivities are sensitive to polar substituents.

A mechanistic interpretation of the observed lack of polar effects seems to require the operation of a *concerted* electrophilic aromatic substitution at the lithium-carrying carbon. If the carbon-carbon bond formation is synchronous with the breaking of the carbon-lithium bond, the stability of the transition state should be insusceptible to the effect of substituents. On the other hand, substituents in the benzonitrile caused a considerable change in reaction rate, the latter being 8 times higher for the *p*-chloro- than for the *p*-methyl-benzonitrile (Table 1). This observation is analogous to the results from the reaction of phenylmagnesium bromide and substituted benzonitriles.[12] One must therefore assume that both in the lithium and in the magnesium case, a negative charge is built up in the nitrile part of the transition state in such a way as to allow stabilization by electron withdrawing substituents. Hence,

the important difference between the lithium and the Grignard reagent in their behaviors towards benzonitrile is that the lithium ion as leaving group may be displaced in a concerted reaction by the electrophilic nitrile carbon without the development of charge, whereas magnesium ion is a less effective leaving group and is displaced only after the development of charge has started.

Somewhat similar observations were reported by Eaborn and Walton [13] who found no effect of substituents in the reaction of aryllithiums with chlorotrialkylsilane, although minor effects were noted in the reactions with the parent trialkylsilane. Apparently, the concerted mechanism does not apply, if the activity of the electrophile falls below a certain limit.

The overall increase in temperature for the reaction of 0.01 M benzonitrile with the various aryllithiums is given in Table 1. The values vary from a minimum of 0.571° in 3-trifluoromethylphenyllithium ($\sim \Delta H = 22.2$ kcal/mol) to 0.833° for 4-dimethylaminophenyllithium ($\sim \Delta H = 32.2$ kcal/mol). It is worth noting that no obvious correlation exists between the thermodynamic data and the observed reactivities.

EXPERIMENTAL

Materials. All solvents were freshly distilled from lithium aluminium hydride and handled under vacuum or dry argon. Aryllithiums were prepared from the analogous iodobenzenes by halogen-metal exchange with butyllithium in benzene-petroleum ether. They were washed with petroleum ether, dried in vacuum, and recrystallized from ether as described.[11] The iodides were prepared by Sandmeyer reaction or by reaction of the corresponding phenylmagnesium bromides in ether with iodine. They were purified by distillation and recrystallization. 3-Trifluoromethylphenyllithium and 3,5-dichlorophenyllithium in the dry state exploded violently at slightly elevated temperature and had to be kept cool and preferentially moist with solvent. p-Dimethylaminophenyllithium was too soluble, and p-methoxyphenyllithium too little soluble to be conveniently crystallized from ether. The pure aryllithiums were dissolved in ether to a concentration of 0.30 M, and the solutions kept at $-25°$ until use. Benzonitrile, p-chlorobenzonitrile, and p-tolunitrile were redistilled and checked by GLC. 0.020 M solutions were prepared in ether immediately before use.

Kinetics. The temperature of the 1 : 1 mixture of phenyllithium reagent and benzonitrile solution was measured at 0.5, 4, 8, 16, 32, 64, and 500 ms reaction time by means of the flowing stream equipment described.[4,8] The liquid speed in the 0.8 mm polyethylene reaction tube was 2380 mm/s. Pseudo first order rate constants were derived from the first order plots obtained. For less than 10 times excess of lithium reagent k_{obs} was derived graphically from the initial phase of the reaction.

Competition experiment. To 30 ml of diethyl ether, containing 10 mmol each of phenyllithium, 4-chloro-, and 4-methylphenyllithium, was added slowly with stirring a solution of 2 mmol benzonitrile in 40 ml of ether. Water and 6 M hydrochloric acid were added slowly, and after evaporation of the ether, acid hydrolysis of the ketimines was carried out on the steam bath for 2 h. The organic material was extracted with ether and analysed by GLC (silicone column, 200°). By comparison with a standard mixture of the respective substituted benzophenones, the relative reactivities of the three aryllithium reagents were determined to be 98 : 100 : 103, as compared to the ratios 90 : 100 : 111 derived from the direct rate measurements for the 4-methyl-, the unsubstituted, and the 4-chlorophenyllithium, respectively.

REFERENCES

1. West, P. and Waack, R. *J. Am. Chem. Soc.* **89** (1967) 4395.
2. Worsfold, D. J. and Bywater, S. *Can. J. Chem.* **38** (1960) 1891.
3. Evans, A. G. and Rees, N. H. *J. Chem. Soc.* **1963** 6039.

4. Holm, T. *Acta Chem. Scand.* **23** (1969) 1829.
5. West, P., Waack, R. and Purmort, J. I. *To be published.*
6. Edelstein, H. and Becker, E. I. *J. Org. Chem.* **31** (1966) 3375.
7. Gilman, H., St. John, N. B. and Lichtenwalter, M. *Rec. Trav. Chim.* **55** (1936) 577.
8. Holm, T. *Acta Chem. Scand.* **21** (1967) 2753.
9. Holm, T. *Acta Chem. Scand.* **23** (1969) 579.
10. Dessy, R. E. and Salinger, R. M. *J. Org. Chem.* **26** (1961) 3519.
11. Schlosser, M. and Ladenberger, V. *J. Organometal. Chem.* **8** (1967) 193.
12. Swain, C. G. *J. Am. Chem. Soc.* **69** (1947) 2306.
13. Eaborn, C. and Walton, D. R. M. *J. Chem. Soc.* **1963** 5626.