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The Influence of Aggregate Composition on Relative Reactivities of Alkyllithiums

WARREN PEASCOE AND DOUGLAS E. APPLEQUIST*

Department of Chemistry, University of Illinois, Urbana, Illinois 61801

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Studies of the competitive metalation of indene by *tert*-butyllithium and isopropyllithium in pentane have shown that the reactions are first order in alkyllithium and that the relative reactivities of the two alkyllithiums depend upon the compositions of the aggregates in the mixture, pure *tert*-butyllithium tetramer being an order of magnitude less reactive than *tert*-butyllithium in mixed aggregates with isopropyllithium.

An important clue to the mechanism of any reaction of an organolithium compound could be the relationship of the rate of that reaction to the stabilities or inherent basicities of the organolithiums. The latter may be assumed to bear some relationship to the aqueous acidities (pK_a) of the corresponding hydrocarbons, and, in part by such an assumption, Cram[1] has combined various kinds of kinetic and equilibrium data into an internally consistent scale ("MSAD scale") of hydrocarbon acidities. We have sought correlations of MSAD acidities with the rates of the simplest possible organolithium reactions, and here report the results of some such studies on the metalation of the acidic hydrocarbon indene by two alkyllithium compounds.

In this study, a limiting amount of indene was added to a mixture of two alkyllithiums in pentane at room temperature. After a reaction period of 1-2 hr, the reaction was quenched with D_2O and the extent of deuterium incorporation in each of the resulting alkanes was determined by quantitative infrared analysis. If undeuterated alkane arose exclusively from the reaction of RLi with indene, then the relative rates of reaction of the two alkyllithiums with indene were thus determined. The determination of the relative rate constants (k/k') from the data using eq 1 requires

$$\frac{d(\mathrm{RLi})}{d(\mathrm{R'Li})} = \frac{k(\mathrm{RLi})^m}{k'(\mathrm{R'Li})^n} \qquad (1)$$

assumption or prior determination of values for the exponents m and n. The literature reveals fractional orders for the very similar metalation of fluorene in benzene[2] and for metalation of triphenylmethane in THF.[3] Other reactions of alkyllithiums sometimes exhibit fractional order[4] or first order[5] or are reactions with induction periods.[5a,6]

The determination of the reaction orders m and n in a competitive study such as this one is complicated by the fact that if a fractional order arises from the commonly accepted mechanism (eq 2), and if the two lithium reagents in the competitive mixture have formed a statistical array of mixed aggregates, then analysis of the data using eq 1 will give constant values for k/k' only for $m = n = 1$, regardless of the fact that the rate law for reaction of an isolated RLi would be of fractional order.[7] The values of "k/k'" thus obtained will not be the ratios of rate constants for the proton-abstraction steps, but will be related to the dissociation constants of the aggregates (eq 3), where

$$\begin{gathered}(\mathrm{RLi})_n \overset{K}{\rightleftharpoons} n\mathrm{RLi} \\ \mathrm{RLi} + \text{substrate} \xrightarrow[k]{\text{slow}} \text{product}\end{gathered} \qquad (2)$$

$$\left(\frac{k}{k'}\right)_{\mathrm{obsd}} = \left(\frac{K}{K'}\right)^{\frac{1}{n}}\left(\frac{k}{k'}\right) \qquad (3)$$

K and K' are the equilibrium constants for the two alkyllithiums in the first step of mechanism 2. Competitive rate studies thus cannot be interpreted in purely kinetic terms if mechanism 2 is operative *and* if the alkyllithiums have formed a statistical mixture of aggregates.

In the present work it has been found that alkyllithiums in pentane react with indene in a process which is first order in alkyllithium, not fractional order, so that mechanism 2 is not operative here. Rather, indene apparently reacts directly with the undissociated RLi aggregate. The means by which the true first-order dependence was established was to investigate

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[7] A simple proof was presented by D. E. Applequist and D. F. O'Brien, *J. Amer. Chem. Soc.*, **85**, 743 (1963), that the ratio of two monomeric alkyllithium species in such a statistical array is directly proportional to the ratio of the total stoichiometric concentrations of the two alkyllithium compounds.

competitive reactions of a mixture of *tert*-butyllithium and isopropyllithium which were freshly mixed and therefore had not had time to form mixed aggregates.[8] Only the assumption of first-order reactions ($m = n = 1$) in alkyllithium gave constant values of $k_{i\text{-PrLi}}/k_{t\text{-BuLi}}$ from integrated forms of eq 1, as shown in Table I.

TABLE I

CALCULATED VALUES OF $k_{i\text{-PrLi}}/k_{t\text{-BuLi}}$ FOR VARIOUS VALUES OF m (ORDER IN *i*-PrLi) AND n (ORDER IN *t*-BuLi) WITH VARIOUS INITIAL MIXTURES OF HOMOGENEOUS AGGREGATES OF *i*-PrLi AND *t*-BuLi[b,c]

$X_{t\text{-BuLi}}$[a]	$m = 1$ $n = 1$	$m = 1/2$ $n = 1/2$	$m = 1/4$ $n = 1/4$	$m = 2$ $n = 2$	$m = 1/4$ $n = 1$
0.843	11.3	3.8	2.2	112	54
0.572	15.1	9.1	7.3		107
0.215	13.6	21	26	6.5	114
0.151	11.5	23	32		146

[a] Stoichiometric mole fraction of *t*-BuLi in the alkyllithium mixture. [b] The estimated maximum errors in the calculated ratios (from experimental errors) are 25–50%. [c] All alkyllithium mixtures were allowed to stand together for 18 min before addition of indene.

Since both *t*-BuLi and *i*-PrLi in their homogeneous aggregates (tetramers in the case of *t*-BuLi and a mixture of tetramers and perhaps hexamers in the case of *i*-PrLi)[9] react with indene by processes first order in alkyllithium, it seems safe to infer that mixed aggregates of these two alkyllithiums also react by such first-order processes. It was next of interest to determine the effect upon $k_{i\text{-PrLi}}/k_{t\text{-BuLi}}$ of allowing the mixture of alkyllithiums to stand long enough[8] to form a statistical mixture of aggregates before the indene was added. The results of a set of such experiments are shown in Table II.

TABLE II

RATIO OF PSEUDO-FIRST-ORDER RATE CONSTANTS AS A FUNCTION OF THE TIME THE ALKYLLITHIUMS WERE ALLOWED TO STAND PRIOR TO ADDITION OF INDENE[a]

Time, hr	$k_{i\text{-PrLi}}/k_{t\text{-BuL}}$
0.3	15 ± 4
11	3.2 ± 0.4
24.8	1.9 ± 0.4
42.8	1.6 ± 0.2
93	1.3 ± 0.2

[a] The mole fraction of *t*-BuLi was 0.572 in these runs.

The conclusion from the data of Table II is that the relative reactivities of the two alkyllithiums in the reaction with indene are markedly dependent upon the composition of the aggregate which reacts with the indene. It is clear that *tert*-butyllithium in its homogeneous tetramer is particularly unreactive, whereas *tert*-butyllithium and isopropyllithium show nearly equal reactivities toward proton abstraction when they are in mixed aggregates (presumably tetramers).

It must be concluded that simple correlations of alkyllithium reactivities with the MSAD or other scale of inherent basicities cannot be expected when the alkyllithiums react in aggregated form. Indeed the data comprising the MSAD scale could themselves be biased by steric effects within the aggregates, as we have earlier pointed out.[10]

In spite of the difficulty of quantitative interpretation of data that has been demonstrated above, measurements have been made of relative reactivities of a number of alkyllithiums (equilibrated mixtures) with indene and fluorene in pentane, benzene, or ether–pentane, and crude linear correlations with MSAD[1] or K_ϕ[10] basicity scales have been obtained. The data are recorded elsewhere.[11]

Experimental Section

Materials.—Commercial indene was repeatedly crystallized from pentane at Dry Ice temperature until it was better than 99% pure by glpc analysis on an FFAP column. It was then vacuum distilled through a 127-cm tantalum-wire column and stored in a freezer until used.

Bulk pentane was washed several times with concentrated sulfuric acid and then with water, dried ($MgSO_4$), distilled from calcium hydride, and stored over Dri-Na (sodium–lead alloy).

tert-Butyllithium in pentane was obtained from Alfa Inorganics, Inc. Isopropyllithium was prepared by the general method of Gilman[12] from 2-chloropropane (>99% pure by glpc) and high-sodium lithium metal from Lithium Corp. of America. The alkyllithium solutions were analyzed by the Gilman double-titration method with allyl bromide or 1,2-dibromoethane,[13] and in general contained less than 2% of base other than alkyllithium. All volumetric measurements of alkyllithium compounds were made with pipets inside an argon atmosphere glove box from which traces of oxygen and water were removed by continuous circulation of the atmosphere through columns packed with molecular sieves and MnO. All solutions were flushed with argon before transfer to the glove box or before addition to alkyllithium compounds.

Competitive Reactions with Indene.—Quantitives of *i*-PrLi and *t*-BuLi in pentane were pipetted into a reaction flask to give solutions *ca.* 0.3 *M* in total alkyllithium and were allowed to stand for a measured time. The solvent was removed under vacuum and replaced with *ca.* 50 ml of pentane.

The flask, which was equipped with a stopcock and also with a septum, was removed from the glove box. Two dewar traps, one above the other, were flushed with argon, attached above the stopcock of the flask, and cooled with Dry Ice. The stopcock on the reaction flask was opened, and a positive pressure of argon was maintained in the system throughout the reaction. Enough indene (generally 11–20 mmol) in *ca.* 50 ml of pentane was added through the septum to leave convenient amounts of *i*-PrLi and *t*-BuLi unreacted after *ca.* 60–90% of the indene reacted. The reaction mixture was stirred magnetically at room temperature for 2 hr for freshly mixed solutions and for 1 hr for equilibrated solutions, during which time a white precipitate presumed to be indenyllithium formed. In order to analyze for unreacted alkyllithium, the reaction flask was cooled with an ice bath, and 6 ml of D_2O was carefully added through the septum to the rapidly stirred mixture. The precipitate dissolved within a few minutes of the D_2O addition, indicating that the precipitate was indenyllithium rather than an indene polymer. The lower dewar trap was warmed to 0° and a collecting flask at the top of the lower dewar trap was cooled with Dry Ice. The reaction solution was distilled and the fraction with a boiling point less than 0° was collected. The isobutane and propane in this concentrated sample were purified to greater than 99% purity by preparative glpc using a 20-ft 20% diisodecyl phthalate on Chromosorb P column at room temperature. Only traces of products with retention times identical with those of propene and isobutene were observed in addition to the expected peaks of propane, isobutane, and solvent on both diisodecylphthalate and Porapak Q columns. The purified hydrocarbons were transferred to a vacuum line and transferred through a Dry Ice cooled trap to remove any nonvolatile impurities. Fixed amounts of

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hydrocarbon as determined by pressure were transferred to a 10-cm gas ir cell, and the ir spectrum was determined under standard conditions. The ir spectrum of propane showed bands at 2860–3000, 1480, 1470, 1450, 1390, and 1380 cm^{-1}; the ir spectrum of 2-deuteriopropane showed bands at 2860–3000, 2170, 1480, 1470, 1390, 1380, and 1142 cm^{-1}; the ir spectrum of isobutane showed bands at 2850–3000, 1482, 1380, 1330, and 1175 cm^{-1}; and the ir spectrum of 2-deuterioisobutane showed bands at 2860–3000, 2155, 1482, 1380, 1242, and 1232 cm^{-1}. The ratio of absorbance at 2170 to that at 1480 and at 2170 to that at 1380 cm^{-1} for partially deuterated propane and the ratio of absorbance at 2155 to that at 1380 and at 1242 to that at 1482 cm^{-1} for partially deuterated isobutane were determined. Comparisons of the ratios of absorbances to the ratios of absorbances of mixtures with known mole fraction of monodeuterated hydrocarbon were made graphically, and the mole fraction of deuterated hydrocarbon was determined. The results from the two determinations for each sample were within 0.02 mole fraction units and an estimated error of ±0.02 mole fraction units from the mean was assigned as a reasonable limit of accuracy for the method. The error limits assigned in Tables I and II are based on an assumed error of ±0.02 mole fraction units in the final concentrations of the alkyllithium compounds. No fractionation of partially deuterated compound occurred during work-up, since a glpc-purified sample of propane with a known deuterium content was repurified and found to have the same deuterium content.

An alternative analytical method gave results within experimental error of those described above for equilibrated alkyllithium mixtures, and in addition was used to show that added lithium chloride, *tert*-butyl chloride, or *tert*-butyl alcohol did not change the ratio $k_{i\text{-PrLi}}/k_{t\text{-BuLi}}$, whatever effects they may have had on the absolute rates. When the reaction was complete, the solvent and volatile hydrocarbon products of the reaction were removed under vacuum with external heat. The reaction mixture was not allowed to warm above 30°. Benzene containing adamantane as an internal nmr standard was pipetted into each of the flasks. The precipitated aryllithium compound was broken up and dispersed in the liquid. The solution of unreacted alkyllithium compounds and adamantane was filtered from the precipitate using disposable pipets fitted with glass-wool plugs. The nmr resonances of the alkyllithium compounds (*t*-BuLi δ 1.00 (s); *i*-PrLi 1.36 (d)] and the resonance of adamantane (δ 1.75–1.85) were integrated five times. The ratio of the areas of the alkyllithium resonances to the area of the adamantane resonance was used to determine the concentration of the alkyllithium compounds.

Registry No.—*i*-PrLi, 1888-75-1; *t*-BuLi, 594-19-4; indene, 95-13-6; propane, 74-98-6; 2-deuteriopropane, 20717-74-2; isobutane, 78-28-5; 2-deuterioisobutane, 13183-68-1.

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The Knoevenagel Reaction. A Kinetic Study of the Reaction of (+)-3-Methylcyclohexanone with Malononitrile

FRANKLIN S. PROUT,* VICTOR D. BEAUCAIRE,[1a] GARY R. DYRKACZ,[1e] WILLIAM M. KOPPES,[1c,d] ROBERT E. KUZNICKI,[1b] THEODORE A. MARLEWSKI,[1b] JAMES J. PIENKOWSKI,[1a] AND JACQUELINE M. PUDA[1d]

Department of Chemistry, De Paul University, Chicago, Illinois 60614

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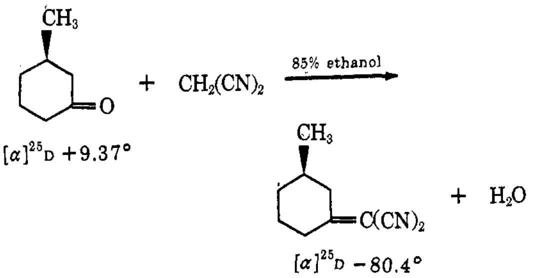
The condensation of malononitrile with (+)-3-methylcyclohexanone produced an 80–85% yield of (−)-3-methylcyclohexylidenemalononitrile. The reaction, followed polarimetrically in alcohol-water, is kinetically second order and efficiently catalyzed by weak bases (ω-amino acids, cyclic amino acids, NH_4OAc), furnishing solutions having an apparent pH of 7.5–8.0. With β-alanine as catalyst, the E_a was 7.6 kcal/mol compared to 11 kcal/mol uncatalyzed. Stronger bases (barbital, NaOAc, KOAc, KF, piperidine) effected more rapid condensation but poorer kinetics because of telemerization of malononitrile at the higher pHs.

Our earlier studies on the Knoevenagel condensation[2,3] have examined catalyst effectiveness in a heterogeneous system. Under these conditions efficiency of the largely insoluble dipolar ions was a function of an undetermined combination of pH and concentration.

A more desirable homogeneous system involved the reaction of (+)-3-methylcyclohexanone with malononitrile (eq 1). This reaction occurred slowly (when not catalyzed) and nearly quantitatively in an alcoholic solution at room temperature. The product can be isolated in 80–85% yield and is probably formed to an extent greater than 95%. The reverse reaction is very slow and can be neglected. With catalysts furnishing an apparent pH no higher than 8, no important side reactions seem to appear. Because the change in rotation during the course of this reaction is large and linear with change in concentration, the progress of the reaction can be followed polarimetrically.



(1)

An extensive series of kinetic runs were made using β-alanine as catalyst (Table I). Most runs were made with a 0.400 M concentration of reactants and the rate calculations were based on the assumption of second-order kinetics.[4,5] It is clear in runs 11, 15, 49, 50, 52, and 53 that increasing the concentration of catalyst from $6 \times 10^{-4}\ M$ to $2.5 \times 10^{-2}\ M$ increased the rate of

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[1] This investigation was supported by the National Science Foundation Grants for the Undergraduate Research Participation Program of the Science Education Section, Division of Scientific Personnel and Education in (a) 1962, (b) 1963, (c) 1964, (d) 1965, and (e) 1967.

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