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Evidence for Bromine-Lithium Exchange in a Local High Concentration Gradient

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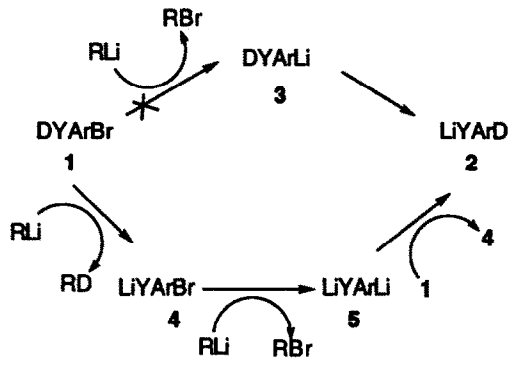
Abstract. The product ratios for bromine-lithium exchange of 3,3'-dibromostilbene (**6**) with one equivalent of *n*-butyl lithium, *s*-butyl lithium or *t*-butyl lithium in THF and in Et_2O to give after quenching with methanol 3-bromostilbene (**7**) and stilbene (**8**), have been investigated. In the most reactive cases the ratio of **8**:**7** is significantly greater than expected for a statistical reaction. The apparently accelerated exchange of **7**-Li relative to **6** is attributed to reaction in a high local concentration of the butyl lithium reagent.

INTRODUCTION

The bromine-lithium exchange reaction was discovered independently by Gilman and by Wittig in 1938.[1] The reaction has become a principle method for the preparation of aryl lithium compounds and studies of its mechanism are of current interest.[2] Winkler and Rogers measured second order kinetics for a series of exchanges and noted their results to be consistent with an S_N2 mechanism.[3] Recent work has established the reaction has a geometrical dependence which requires a large bond angle between the entering and leaving carbons consistent with either an S_N2 transition structure or an ate complex as an intermediate .[4]

Suggestions that the rate of bromine-lithium exchange could be surprisingly fast were based on observations that substrates which had both an acidic deuterium and an exchangeable bromine gave products in which the deuterium replaced the bromine. An illustration is shown in (1) for the conversion of **1** to **2**. Although the earliest interpretations of such results suggested a pathway of initial very fast bromine-lithium exchange to give **3**, a more recent interpretation is that a sequence involving an initial dedeuteration gives **4** which undergoes a subsequent rapid bromine-lithium exchange to provide **5**.[5] The dilithiated intermediate **5** then obtains a deuterium from **1** to give **2** and **4**. Under this mechanism the reaction of **4** to give **5** has to be expedited relative to mixing of the reagents. Two possibilities were suggested for the acceleration of that bromine-lithium exchange.[5] In one mechanism the complex which is formed in the dedeuteration of the first

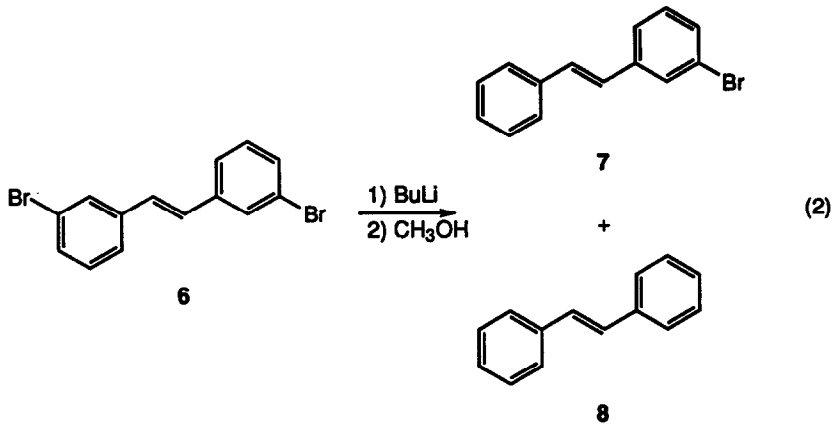
step is considered to give an organolithium aggregate which undergoes an intraaggregate reaction faster than dissociation and mixing.[6] In the other mechanism the high local concentration of the organolithium reagent which is present on addition of the organolithium to the substrate is considered to promote the rapid exchange reaction. We have undertaken the present work to evaluate the viability of this later possibility.



(1)

RESULTS AND DISCUSSION

The issue of whether a very rapid bromine-lithium exchange reaction can occur in a high local concentration has been addressed by investigation of the reaction of 3,3'-dibromostilbene (**6**) with three different butyl lithium reagents in tetrahydrofuran (THF) and diethyl ether (Et_2O). The products of the exchange after protonation will be 3-bromostilbene (**7**) and stilbene (**8**) as shown in equation (2). The corresponding mono and dilithiated species would be **7-Li** and **8-Li_2**, respectively If all bromines are replaced at the same rate independently of any transient concentration gradients, the products should be formed statistically: *i.e.*, complete reaction of one equivalent of a butyl lithium would give a ratio of **8:7:6** of 25:50:25 or an **8:7** ratio of 1:2. The relative amounts of products and reactants for reaction of up to one equivalent is shown in Figure 1.[7] If less than one equivalent of butyl lithium undergoes reaction with all bromines reacting at the same rate the ratio of **8:7** should be substantially less than 1:2 as shown in the Figure. If the ratio of **8:7** is greater than 1:2, a pathway in which bromine-lithium exchange for **7-Li** is accelerated relative to bromine-lithium exchange for **6** is indicated. In view of our previous results we might expect the results to be sensitive to stirring.[5] The location of the bromines with respect to one another in **6** should minimize the operation of a conventional complex induced proximity effect.[6] The use of a bifunctional substrate to evaluate the sensitivity of a reaction to a concentration gradient is an established approach to such questions.[7] The assumption that each functionality is sufficiently isolated that its reactivity is essentially that of a monofunctional molecule, is considered to resolve kinetic and thermodynamic questions for the present case.



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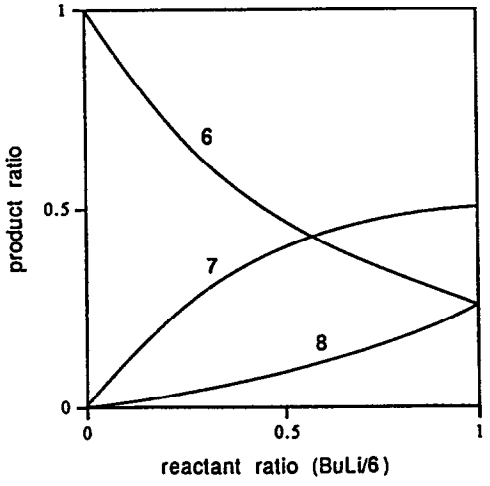

Figure 1. Reactant and Product Compositions for Bromine-Lithium Exchange of **6** with Butyl Lithium for Exchange of All Bromines at the Same Rate.

The results of bromine-lithium exchanges of **6** on additions of 1 eq of the three butyl lithium reagents in THF and Et_2O with and without stirring are shown in Table I. The uncertainties in comparing stirred and unstirred reactions and different extents of reaction allows only semi quantitative interpretations. Bromine-lithium exchange has proceeded to the largest extent for *t*-butyl lithium and to a lesser extent for *s*-butyl and *n*-butyl lithium. Most of reactions have not proceeded to completion. For all reactions in THF with no stirring the ratio of **8:7** is greater than 1:2 and with *s*-BuLi and *t*-BuLi the ratio even exceeds 1:1. For reactions in Et_2O only the reaction of *t*-BuLi without stirring has a ratio of **8:7** greater than 1:2. In Et_2O for the reactions of *n*-BuLi and *s*-BuLi, the product ratios observed are more consistent with the expectation for statistical exchange.

Table I. Treatment of **6** with Butyl Lithium Reagents to Give **7** and **8**.

RLi	Solvent	Addition mode	Composition **8: 7 :6**
n-BuLi	THF	no stirring	9 : 8 : 83
	THF	stirring	2 : 10 : 88
	Et_2O	no stirring	3 : 22 : 75
	Et_2O	stirring	1 : 12 : 87
s-BuLi	THF	no stirring	17 : 5 : 78
	THF	stirring	6 : 14 : 80
	Et_2O	no stirring	3 : 21 : 76
	Et_2O	stirring	2 : 32 : 66
t-BuLi	THF	no stirring	34 : 16 : 50
	THF	stirring	15 : 64 : 21
	Et_2O	no stirring	30 : 29 : 41
	Et_2O	stirring	14 : 49 : 37

The reactions in the Table in which a ratio of **8**:**7** is greater than 1:2 clearly are consistent with an accelerated conversion of **7-Li** to **8-Li_2** in the transient high local concentration provided when the butyl lithium reagent is added to a solution of **6**. With stirring or with the slower reactions of *s*-butyl or *n*-butyl lithiums the compositions move toward the product ratio expected for the statistical distribution of a sequential process in which all bromine-lithium exchanges occur at the same rate. The remote positions of the bromines in **6** are such that an intraaggregate reaction is not expected. Moreover, *t*-butyl lithium in THF is mostly monomeric so it is reasonable to suggest that the exchange observed in that case is not attributable to an intraaggregate reaction.[8]

This demonstration that the exchange reaction can occur in a high local concentration establishes the possibility of the first of two pathways previously suggested for apparently accelerated bromine-lithium exchanges.[5] These results should not be over generalized. The regiochemical differences in the conversions of ortho and para bromobenzamide derivatives of **1** suggest an accelerated intracomplex process also can be operative.[5] In addition it is known from a number of synthetic results that selective exchange of one bromine in a polybrominated substrate is possible.[9] Nonetheless the present results do show that a bromine-lithium exchange which is competitive with mixing can occur and the previously suggested possibility of such a pathway is established by this work.

EXPERIMENTAL

Gas chromatography/electron impact mass spectrometry (GC/MS) was performed on a Hewlett-Packard 5890 gas chromatograph coupled to a Hewlett-Packard 5970B electron impact mass selective detector using an Ultra-1 capillary column (Hewlett Packard, 30m x 0.20 mm i.d., 0.33 mm film).

All reagents and solvents were obtained from commercial sources and used without further purification, unless mentioned otherwise. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from sodium and benzophenone under nitrogen atmosphere. Commercial solutions of *n*-BuLi in hexane, *s*-BuLi in cyclohexane, and *t*-BuLi in pentane were titrated using *N*-pivaloyl-*o*-toluidine as the indicator.[10]

Preparation of 3,3'-dibromo-trans-stilbene (**6**). A mixture of 6.40 g (24.4 mmol) of triphenylphosphine and 5.00 g (24.4 mmol) of 3-bromobenzylchloride was heated at 100 °C for 15 min, then allowed to cool to room temperature. The reaction mixture was filtered and washed four times with 10 mL portions of ether to give a white solid. A mixture of 0.61 g (26.8 mmol) of Na and 50 mL of absolute EtOH was stirred at room temperature until all of the Na dissolved. To this mixture was added the above white solid in one portion. After being stirred for 20 min, a solution of 3.84 mL (24.4 mmol) of 3-bromobenzylaldehyde in 3 mL of absolute EtOH was added dropwise. The reaction mixture was concentrated to half the original volume in vacuo and then cooled in an ice bath. The crude product which crystallized was collected, washed three times with water, and dried to give a white solid. The solid was purified by flash column chromatography eluted with 5% EtOAc/hexane and recrystallization from 70% EtOAc/hexane to afford 3.04 g (38% yield) of **6** as white crystals: mp 97-99 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.65 (s, 2H), 7.40 (dd, 4H, J = 8.1 Hz), 7.23 (t, 2H, J = 8.0 Hz), 7.01 (s, 2H); ^{13}C NMR ($CDCl_3$, 70 MHz) δ 138.9, 130.8, 130.2, 129.4, 128.6, 125.5, 123.0; EIMS (70 eV) *m/z* (relative intensity) 340 (42, M^+), 338 (87, M^+), 336 (44, M^+), 178 (100). Anal. Calcd for $C_{14}H_{10}Br_2$ (338.0): C, 49.74; H, 2.98; Br, 47.28. Found: C, 49.97; H, 3.00; Br, 47.20.

Preparation of 3-dibromo-trans-stilbene (**7**). A mixture of 6.40 g (24.4 mmol) of triphenylphosphine and 5.00 g (24.4 mmol) of 3-bromobenzylchloride was heated at 100 °C for 15 min, then allowed to cool to room temperature. The reaction mixture was filtered and washed four times with 10 mL portions of ether to give a white solid. A mixture of 0.616 g (26.8 mmol) of Na and 50 mL of absolute EtOH was stirred at room temperature until all of the Na dissolved. To this mixture was added the above white solid in one portion. After being stirred for 20 min, a solution of 2.41 mL (24.4 mmol) of benzaldehyde in 3 mL of absolute EtOH was added dropwise. The reaction mixture was extracted twice with ether. The combined organic extracts were washed with water, concentrated in vacuo to give an off-white solid. The solid was purified by flash column chromatography eluted with 5% EtOAc/hexane and recrystallization from EtOAc to afford 2.04 g (33% yield) of **7** as white crystals: mp 85-87 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.67 (s, 1H), 7.53-7.23 (m, 8H), 7.09 (s, 1H), 7.05 (s, 1H); ^{13}C NMR ($CDCl_3$, 70 MH) δ 139.5, 136.8, 130.4, 130.2, 130.1, 129.2, 128.2, 128.8, 128.1, 127.1, 126.7, 125.2, 122.9; EIMS (70 eV) *m/z* (relative intensity) 261 (61, M^+), 258 (61, M^+), 179 (91), 178 (100). Anal. Calcd for $C_{14}H_{11}Br$ (259.1): C, 64.88; H, 4.28; Br, 30.84. Found: C, 65.01; H, 4.29; Br, 30.64.

General procedure for treatment of **6** *with butyl lithium reagents.* Approximately 0.9 mmol of **6** was dissolved in 20 mL of the appropriate solvent and cooled to -78 °C. To the solution was added dropwise, at the approximate rate of 1 mL per minute, a solution of 1 equivalent of the appropriate butyllithium reagent in 3 mL of the solvent precooled to -78 °C. The solution was stirred, if required, or allowed to stand without stirring for 30 min and then quenched with MeOH. Standard workup involved evaporation of the solvent and addition of water and ether to the remainder. The organic phase was separated and the aqueous layer was extracted twice

with ether. The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated in vacuo to give a mixture of products. The products **7** and **8** were identified by GC and GC/MS with comparison to authentic materials.

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