# Experimental Evaluation of Transition Structure Geometry for an Aryl Bromide–Alkyllithium Exchange Reaction: New Information Relevant to the Reaction Mechanism

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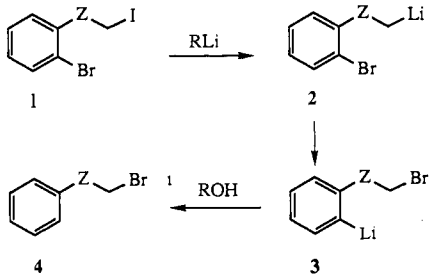
**Abstract:** The geometry of the substitution at bromine in the bromine–lithium exchange reaction between a primary alkyllithium reagent and an aryl bromide to give a primary alkyl bromide and an aryllithium reagent has been evaluated by the endocyclic restriction test. On the basis of isotopic labeling experiments the rearrangements of 3-(2-bromophenyl)-1-lithiopropane (**5**) and 5-(2-bromophenyl)-1-lithiopentane (**6**) to 3-(2-lithiophenyl)-1-bromopropane (**8**) and 5-(2-lithiophenyl)-1-bromopentane (**9**) are found to be intermolecular, while the rearrangement of 3-(2-bromophenyl)propyl 11-lithioundecanyl ether (**7**) to 3-(2-lithiophenyl)propyl 11-bromoundecenyl ether (**10**) is found to be intramolecular. A four center concerted mechanism is ruled out by these results. The geometrical dependence and the failure of external bromide to become incorporated into the products in the reactions of **5** and **6** are considered to rule out an outer sphere single electron transfer mechanism. The reaction is suggested to proceed via the trigonal bipyramid structure of a 10-Br-2 ate complex or a $S_N2$ transition state.

The bromide–lithium exchange reaction in which an aryl bromide and an alkyllithium are converted to an aryllithium and an alkyl bromide was recognized independently by Wittig and Gilman over 50 years ago.[1] The reaction has been considerably extended beyond the initial reports and is a principal method for the preparation of organolithium compounds. Four different mechanisms have been suggested for the reaction. The initial suggestion of a four center reaction has been supplemented by mechanisms involving single-electron transfer, a concerted $S_N2$ displacement, or an intermediate 10-Br-2 ate complex.[1] Each mechanism has its adherents and all possibilities appear in recent literature.

Bailey and Patricia have reviewed the data which has been used to support the different mechanisms and they note, as do most recent workers in the field, that the pathway followed may be dependent on the reactants and the reaction conditions.[2] The earliest suggestions of $S_N2$ and ate-complex mechanisms were made by Gilman and by Wittig, respectively.[3,4] More recently Winkler and Rogers have interpreted kinetic studies of organolithium aryl bromide exchange in terms of an $S_N2$ mechanism.[5] Bailey has noted the early work of Johncock can be interpreted in terms of an ate complex and such species have been firmly established as reaction intermediates in aryllithium–aryl iodide exchanges by Reich.[6,7]

The X-ray structure of a lithium bis(pentafluorophenyl)-iodinanide–TMEDA complex has been determined by Farnham and Calabrese and this 10-I-2 species has a bond angle of about 175° between the apical ligands on iodine.[8] There are many studies which establish that stable hypervalent 10-Br-2 anions have essentially a linear arrangement.[9] Structure correlation and reactivity comparisons have been taken to suggest that a linear geometry also is favored in nucleophilic substitutions at halogen.[10] The question of whether or not there is a geometrical dependence for bromine–lithium exchange and the relevance of this information to the reaction mechanism has not been addressed previously.[11]

We have evaluated the geometry at bromine in the transition structures for exchange between a primary alkyllithium reagent and an aryl bromide as a basis for making a choice between the alternative mechanisms. Our approach, which is based on the endocyclic restriction test, is illustrated by the reactions leading from **1** to **4**. The key step for our analysis is the rearrangement of **2** to **3**.[11,12,13] If the geometry required in the transition structure for the conversion can be achieved endocyclically, an intramolecular reaction should be favored. If the required geometry is not available within the bond angles allowed by an endocyclic ring, an intermolecular reaction would be expected. A geometrical dependence for the reaction would be established by a change between intramolecular and intermolecular pathways as the length of the tether and size of the endocyclic ring is varied. A lack of geometrical dependence could be revealed by no change in the intra- or intermolecularity with systematic variation of the tether.




(1) (a) Wittig, G.; Pockels, V.; Dröge, H. *Chem. Ber.* **1938**, *71*, 1903. (b) Gilman, H.; Langham, W.; Jacoby, A. L. *J. Am. Chem. Soc.* **1939**, *61*, 106.
(2) Bailey, W. F.; Patricia, J. J. *J. Organomet. Chem.* **1988**, *352*, 1, and references cited therein.
(3) Sunthankar, S. V.; Gilman, H. *J. Org. Chem.* **1951**, *16*, 8.
(4) Wittig, G.; Schöllkopf, V. *Tetrahedron* **1958**, *3*, 91. Wittig, G. *Angew. Chem.* **1958**, *70*, 65.
(5) (a) Winkler, H. J. S.; Winkler, H. *J. Am. Chem. Soc.* **1966**, *88*, 964. Winkler, H. J. S.; Winkler, H. *J. Am. Chem. Soc.* **1966**, *88*, 969. (b) Rogers, H. R.; Houk, J. *J. Am. Chem. Soc.* **1982**, *104*, 522.
(6) Johncock, P. *J. Organomet. Chem.* **1964**, *14*, 257.
(7) Reich, H. J.; Green, D. P.; Phillips, N. H. *J. Am. Chem. Soc.* **1991**, *113*, 1414, and references cited therein.
(8) Farnham, W. B.; Calabrese, J. C. *J. Am. Chem. Soc.* **1986**, *108*, 2449.
(9) For cases of such arrangements about bromine see Crowston, E. H.; Lobo, A. M.; Prabhakar, S.; Rzepa, H. Z.; Williams, D. J. *J. Chem. Soc.* **1984**, 276. Blair, L. K.; Parris, K. D.; Hill, P. S.; Brock, C. P. *J. Am. Chem. Soc.* **1983**, *105*, 3649. Bogaard, M. P.; Rae, A. D. *Cryst. Struct. Commun.* **1982**, *11*, 175.
(10) Ramasubbu, N.; Parthasarathy, R.; Murray-Rost, P. *J. Am. Chem. Soc.* **1986**, *108*, 6308. For a review of halophilic reactions which note the analogy to $S_N2$ reactions see Zefirov, N. S.; Makhanolov, D. I. *Chem. Rev.* **1982**, *82*, 615.
(11) For a preliminary report of work closely related to the present report for **4**, Z = $CH_2$, see Beak, P.; Allen, D. J.; Lee, W. K. *J. Am. Chem. Soc.* **1990**, *112*, 1629.
(12) (a) Tenud, L.; Farooq, S.; Seibly, J.; Eschenmoser, A. *Helv. Chim. Acta* **1970**, *53*, 2059. (b) Hogg, D. R.; Vipond, P. W. *J. Chem. Soc. C* **1970**, 2142. (c) Beak, P.; Basha, A.; Kokko, B.; Loo, D. *J. Am. Chem. Soc.* **1986**, *108*, 6016, and references cited therein.
(13) It is to be noted that the information which can be obtained about the geometrical dependence of a reaction by this approach is independent of the fraction of reaction which gives rearrangement. Indeed systems which have a geometric requirement which is precluded by the endocyclic limitation could then follow other pathways so that the yields of informative products may be low. Low yields do not compromise the conclusions of this study or its applicability to the same reaction in less constrained systems.

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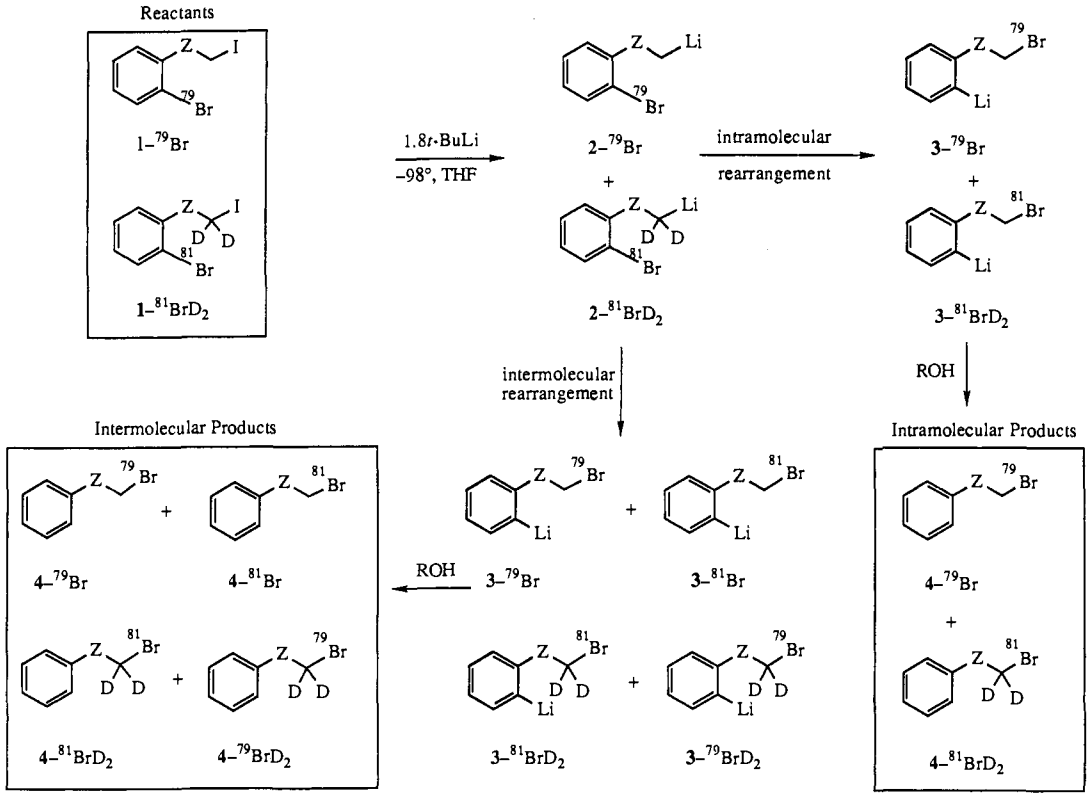
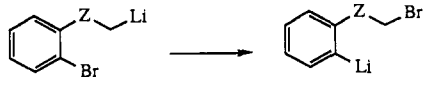
**Scheme I**




The experiments we report establish that a large carbon–bromine–carbon bond angle is required in the transition structures for these conversions. That information along with other data can be used to reach the conclusion that an ate complex or a $S_N2$ mechanism is preferred for the conversion of a primary alkyllithium reagent and aryl bromide to the corresponding alkyl bromide and aryllithium reagent.

## Results

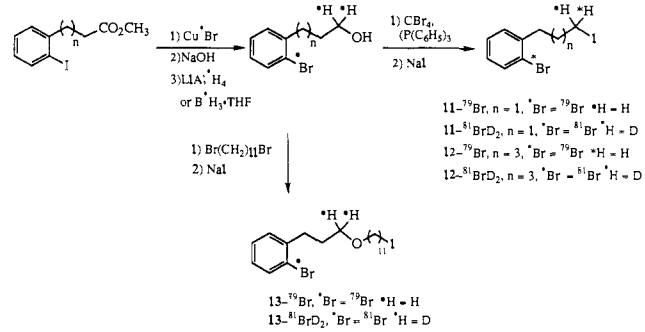
For the three cases, **5**, **6**, and **7**, which differ in the length of the tether, we have found the conversions to **8**, **9**, and **10**, respectively, can be achieved by reaction of the precursor iodides with 1.8 eq of *t*-BuLi at −98° for 20 min in THF. We have identified the products of these reactions and established the intermediacy of the organolithium reagents corresponding to **2** and **3** based on formation of the expected products on reaction with methanol and methanol-*d* (vide infra). In order to distinguish between the intramolecular and intermolecular pathways we have carried out double-labeling experiments for each case.



5, Z = $(CH_2)_2$
6, Z = $(CH_2)_4$
7, Z = $(CH_2)_3O(CH_2)_{10}$

8, Z = $(CH_2)_2$
9, Z = $(CH_2)_4$
10, Z = $(CH_2)_3O(CH_2)_{10}$

**Syntheses.** The precursor iodides were prepared as the isotopically enriched materials **11**-$^{79}$*Br*, **11**-$^{81}$*BrD*$_2$, **12**-$^{79}$*Br*, **12**-$^{81}$*BrD*$_2$, **13**-$^{79}$*Br*, and **13**-$^{81}$*BrD*$_2$ as outlined below. The deuterium labels were introduced by reduction of carboxylic acids with the deuteride reagents and the bromine labels were introduced by reactions of aryl iodides with Cu$^{79}$Br and Cu$^{81}$Br.[14] Minor amounts of $^{79}BrD_2$ and $^{81}$Br materials were present and are taken into account in the analyses. The syntheses were straightforward although we did find that hydrolysis of the methyl esters to the carboxylic acids prior to the hydride/deuteride reductions gave a more readily purified product than did direct reduction of the esters.[15] The isotopic compositions were determined by GC/EIMS for **11** and **12** and by GC/FIMS for **13**.




**Double–Double Labeling Experiments.** The reactions we have carried out to distinguish between the intramolecular and intermolecular pathways for the rearrangements of **5**, **6**, and **7** are illustrated for the conversion of the general case of **1**-$^{79}$*Br* and **1**-$^{81}$*BrD*$_2$ to **4** in Scheme I. In the first step the primary iodide undergoes preferential halogen–lithium exchange to give the organolithium reagents **2**.[16] If the rearrangement of **2** to **3** is intramolecular, the isotopic distribution in **3** and **4** will be the same as in the reactants; i.e. **4**-$^{79}$*Br* and **4**-$^{81}$*BrD*$_2$ will be the products with an isotopic distribution which is the same as the reactants. If the reaction is intermolecular, the isotopic labels will be scrambled in the products **3** and **4**; i.e. **4**-$^{79}$*Br* and **4**-$^{81}$*BrD*$_2$ will be accompanied by **4**-$^{81}$*Br* and **4**-$^{79}$*BrD*$_2$ in a statistically distributed ratio. The isotopic distribution of the labels can be determined by MS with an error of ±5%.

(14) Separate labeling with $^{79}$Br and $^{81}BrD_2$ was carried out to increase the accuracy of the distinction between the intramolecular and intermolecular reactions.

(15) The details of the syntheses are provided as supplementary material.

(16) The formations of **18** from **11**, of **22** and **23** from **12**, and of **30** from **13** indicate that halogen–lithium exchange reactions at a primary iodide and an aryl bromide are competitive. At higher temperatures the precursors to **18**, **23**, and **30** might be expected to cyclize but we did not observe such products. Brewer, P. D.; Tagat, J.; Hergrueter, C. A.; Helquist, P. *Tetrahedron Lett.* **1977**, 4573.

Table I. Composition of **15** from Isotopic Labeled **11**

| isotopic composition[a] | reactant **11** | product **15** | intramolecular reaction[b] | intermolecular reaction[b] |
|---|---|---|---|---|
| $^{79}Br$ | 45 | 24 | 45 | 25 |
| $^{81}Br$ and $^{79}BrD_2$ | 10 | 52 | 10 | 50 |
| $^{81}BrD_2$ | 45 | 24 | 45 | 25 |

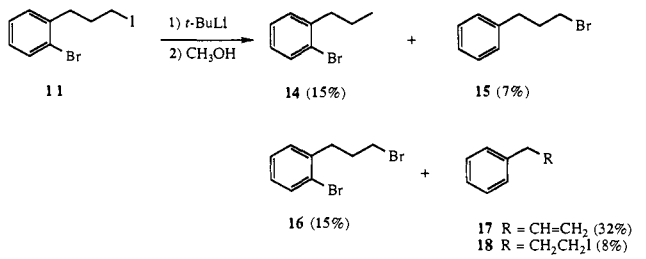
[a] Error is ±5%. [b] Expectation based on reactant labeling.

Table II. Composition of **20** from Isotopic Labeled **12**

| isotopic composition[a] | reactant **12** | product **20** | intramolecular reaction[b] | intermolecular reaction[b] |
|---|---|---|---|---|
| $^{79}Br$ | 45 | 28 | 45 | 25 |
| $^{81}Br$ and $^{79}BrD_2$ | 10 | 50 | 10 | 50 |
| $^{81}BrD_2$ | 45 | 22 | 45 | 25 |

[a] Error is ±5%. [b] Expectation based on reactant labeling.

**Intermolecular Reactions.** The reaction of **11** with 1.8 equiv of *t*-BuLi followed by addition of methanol provided **14**, **15**, **16**, **17**, and **18** in the yields indicated, along with 23% recovered **11**. The products were identified and quantified by GC/EIMS procedures using authentic compounds as standards. The isotopically labeled products **14**, **15**, and **16** were obtained from a reaction of a mixture of 0.1 M **11**-$^{79}Br$ and **11**-$^{81}BrD_2$ accompanied by minor amounts of **11**-$^{81}Br$ and **11**-$^{79}BrD_2$ as indicated in Table I. As can be seen from the label distribution of **15** also as shown in the table, the rearrangement of **5** to **6** is an intermolecular reaction. In accord with a process which could proceed via the dibromide **16** with one bromine scrambled, that compound from the same experiment has an isotopic composition of **16**-$^{79}Br^{79}Br$, **16**-$^{79}Br^{79}BrD_2$ and **16**-$^{79}Br^{81}Br$, **16**-$^{81}Br^{81}Br$ and **16**-$^{79}Br^{81}BrD_2$, and **16**-$^{81}Br^{81}BrD_2$ of 21%, 29%, 26%, and 24% in accord with the expected values of 22%, 27%, 28%, and 23% for an intermolecular reaction (vide infra). The isotopic composition of **14**-$^{79}Br$, **14**-$^{81}Br$, and **14**-$^{79}BrD_2$ and **14**-$^{81}BrD_2$ of 47%, 11%, and 43% and of recovered **11** are consistent with that of the starting mixture.




The reaction of 0.1 M **12** with *t*-BuLi was investigated also. The products of the reaction are **19**, **20**, **21**, **22**, and **23** along with 27% unreacted **12**. The products were identified and quantitated by comparison with authentic compounds by GC/EIMS procedures. Reaction of a mixture of **12**-$^{79}Br$ and **12**-$^{81}BrD_2$ accompanied by minor amounts of **12**-$^{81}Br$ and **12**-$^{79}BrD_2$ provided an isotopic distribution for **20** consistent with an intermolecular conversion of **6** to **9** as shown in Table II. The dibromide **21** from this experiment has an isotopic composition of $^{79}Br^{79}Br$, $^{79}Br^{79}BrD_2$ and $^{79}Br^{81}Br$, $^{81}Br^{81}Br$ and $^{79}Br^{81}BrD_2$, and $^{81}Br^{81}BrD_2$ of 25%, 28%, 27%, and 28% in accord with the values of 23%, 28%, 27%, and 22% expected for replacement of the iodide by an intermolecular reaction. The isotopic composition of **19** of 49%, 10%, and 41% and that of recovered **12** are consistent with that of the reactant.

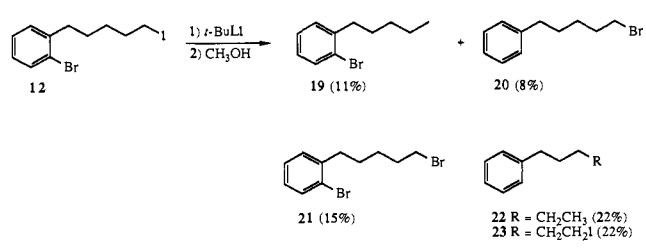



Table III. Composition of **26** from Isotopic Labeled **13**

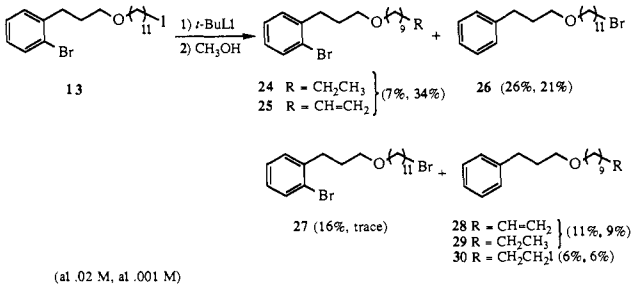
| isotopic composition[a] | reactant **13** | product **26**[b] | product **26**[c] | intramolecular reaction[d] | intermolecular reaction[d] |
|---|---|---|---|---|---|
| $^{79}Br$ | 48 | 34 | 47 | 48 | 28 |
| $^{81}Br$ and $^{79}BrD_2$ | 11 | 32 | 13 | 11 | 50 |
| $^{81}BrD_2$ | 42 | 34 | 41 | 42 | 22 |

[a] Error is ±5%. [b] The values expected for a reaction at 0.02 M which is 45% intramolecular and 55% intramolecular are $^{79}Br$, $^{81}Br$ and $^{79}BrD_2$, and $^{81}BrD_2$ 36:33:30. [c] At 0.001 M. [d] Expectation based on reactant labeling.

When the reactions of **11** and **12** were carried out at higher dilutions, the products **15** and **16** and **20** and **21**, respectively, were not obtained. These observations also support an intermolecular course for these reactions.

**Intramolecular Reaction.** The reaction of **13** with 1.8 equiv of *t*-BuLi was carried out at 0.02 M because of the insolubility of **13** at higher concentrations. The products **24** and **25**, **26**, **27**, **28** and **29**, and **30** were obtained in the yields indicated along with 31% of recovered **13**. The mixtures of **24** and **25** and of **28** and **29** were inseparable by capillary GC or HPLC and are assigned on the basis of GC/FIMS and spectral properties. Reaction of a mixture of **13**-$^{79}Br$ and **13**-$^{81}BrD_2$ with minor amounts of **13**-$^{81}Br$ and **13**-$^{79}BrD_2$ give **26** with the isotopic composition indicated in Table III. This distribution is intermediate to the expectations for either the purely intramolecular or intermolecular reactions and consistent with a conversion which is ca. 45% intramolecular and 55% intermolecular. Analyses of the isotopic composition of the dibromide **27** is also consistent with the operation of two pathways. The observed isotopic composition of $^{79}Br^{79}Br$, $^{79}Br^{81}Br$ and $^{79}Br^{79}BrD_2$, $^{79}Br^{81}BrD_2$ and $^{81}Br^{81}Br$, and $^{81}Br^{81}BrD_2$ of 25%, 28%, 27%, and 20% is consistent with a reaction which is 45% intramolecular and 55% intermolecular. The recovered reactant **13** had unchanged isotopic composition.

When the reactions of **13**-$^{79}Br$, **13**-$^{81}BrD_2$, and **13**-$^{81}Br$ and **13**-$^{79}BrD_2$ were carried out at 0.001 M, the same products were obtained as before with the exception of **25**, which was shown to be absent by GC/FIMS. The dibromide **27**, however, was reduced to a trace amount after correction for 4% dibromide present in the starting material.[17] The isotopic labeling in recovered **13** and **14** is the same as in the reactant **13**. The isotopic composition of **26** obtained is the same as that of **13** as shown in Table III. Clearly the integrity of the labels has been retained in the higher dilution experiment and the transfer of bromine in the conversion of **7** to **10** is an intramolecular process under these conditions.



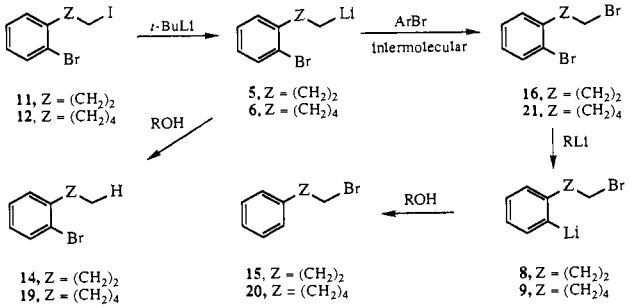

**Attempted Incorporation of Bromide.** Bromide ion could be involved in the intermolecular conversions of **5** and **6** to **8** and **9**, respectively. In order to test for that possibility, we have carried out the lithiations of 90% enriched **11**-$^{79}Br$ and **12**-$^{79}Br$ in the presence of 1 equiv of 1:1 $Li^{79}Br/Li^{81}Br$ obtained from the reaction of ethylene dibromide containing the natural abundance of the bromine isotopes with *n*-butyllithium. The expectation is that if free bromide were involved, it should mix with the bromide of LiBr and the products should contain at least 30% $^{81}Br$. However, mass spectral examination of the products shows less than 5% $^{81}Br$ from

(17) The dibromide is presumably carried over in the synthesis of **13**. This source also makes a minor contribution to the dibromide found in the 0.02 M reaction.

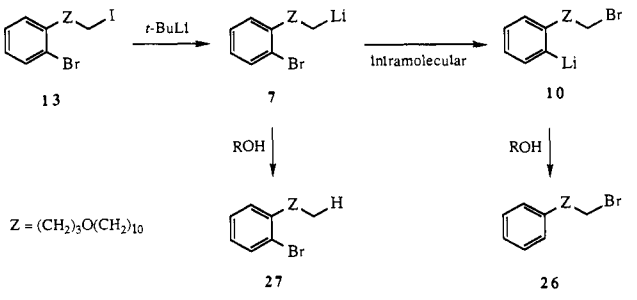
the LiBr is incorporated into **15** and **20**.

## Discussion

**Evaluation of Transition Structure Geometries for These Aryl Bromide–Alkyllithium Exchanges of 5, 6, and 7.** The above results establish that the conversions of **5** to **8** and **6** to **9** occur by an intermolecular process. An economical scheme for these reactions is provided below. The initial reaction of **11** or **12** is iodine–lithium exchange with *t*-BuLi to give **5** and **6**, respectively. The organolithium reagents **5** and **6** react intermolecularly with an aryl bromide to give the dibromides **16** and **21** which then react intermolecularly with an alkyllithium to give **8** and **9**. The products obtained after addition of methanol are the phenalkyl bromides **14** and **19**, respectively, the *o*-bromophenalkanes **15** and **20**, respectively, and the dibromides **16** and **21**, respectively. The significant conclusion about these reactions is that the bond angles required to transfer bromine from the aromatic carbon to the terminal methylene cannot be attained intramolecularly in either a six- or eight-membered endocyclic ring.

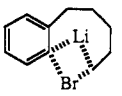



On the other hand, the conversion of **7** to **10** can proceed intramolecularly as shown below. The pathway for the reaction begins with the conversion of **13** to **7** with *t*-BuLi which is followed by its intramolecular rearrangement to **10**. The products **26** and **27** result from reactions of **7** and **10** with methanol. The isotopic labeling shows the transfer of bromine between the aromatic carbon and the methylene group can occur through an 18-membered endocyclic ring at an appropriate concentration. In contrast (vide supra) when the reactions of **11** and **12** are carried out at comparable dilution, the bromine transfer products are not observed. These results establish that there is the geometric requirement in the mechanisms of these reactions that the entering and leaving groups in the exchange be at an angle approaching linearity.




**Consideration of Mechanistic Alternatives for Aryl Bromide–Alkyllithium Exchange.** The conclusions which can be drawn about the reaction pathway from the demonstration of a geometrical dependence for the conversion of a primary alkyllithium–aryl bromide to an aryllithium–primary alkyl bromide depends on the expectations for the alternative mechanisms. We assume the conversions of **5**, **6**, and **7** to **8**, **9**, and **10**, respectively, proceed by a common mechanism.

The earliest mechanism suggested for lithium–bromine exchange was the four center reaction. A transition structure for a four centered mechanism is illustrated for **6** by **31**. Under this mechanism the carbon–bromine–carbon bond angle would be small and an intramolecular reaction should be more favorable for **5** and **6** than for **7**. Since this is not observed, the four center mechanism can be discounted.



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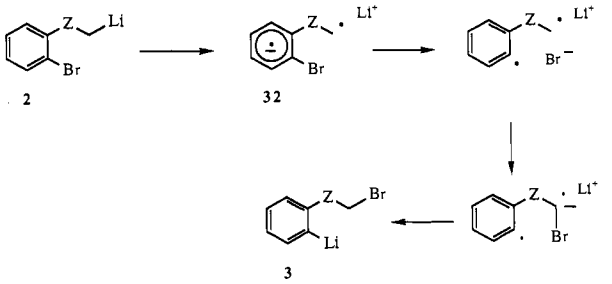
Single electron transfer (SET) has been suggested in bromide–lithium exchanges initiated by alkyllithium reagents for a number of systems and supported by different criteria.[2] Although radicals have been observed to be present in such reactions, it also is the case that none of the tests has been definitive with respect to the involvement of radicals in the actual bromine transfer.[18,19]

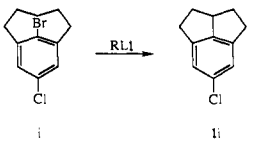
Two reasonable mechanisms involving single electron transfer in the conversions of **2** to **3** can be envisioned. One possibility shown below involves internal electron transfer within **2** to generate a radical anion **32** which loses bromide to give a biradical lithium bromide complex. Bromide bonding to the methylene within the solvent cage could generate another radical anion which could undergo electron transfer and bond reorganization to give **3**. For a process involving essentially internal return by bromide, this sequence would be expected to be intramolecular, particularly for **5** and **6**. Since that is not the case, this version of an SET mechanism can be ruled out.




A SET mechanism which could be intermolecular is also possible. In this case initial electron transfer from **2** could generate **33** and **34**. The latter could lose bromide which then escapes from its solvent cage and reacts with **33** to generate a radical anion that loses an electron to give the dibromide. Repeating the cycle, which is shown for convenience to involve a dilithio species, would give **3**. Under this mechanism **5**, **6**, and **7** would be expected to be intermolecular. However, the reaction of **7** is intramolecular, and in the case of **5** and **6**, LiBr, which is presumed to provide free bromide, is not incorporated into the product. Accordingly, neither

(18) In this discussion we use single electron transfer to refer to an outer sphere electron transfer in which the electron transfer reaction is separated from the bond breaking and bond making by a detectable energy barrier. Our work does not provide a distinction between a concerted two-electron process and sequential inner sphere electron transfers in which electron transfer and bond breaking and bond making are concerted. For a comprehensive discussion see Saveant, J. *Adv. Phys. Org. Chem.* **1990**, *2*, 61, and references cited therein.

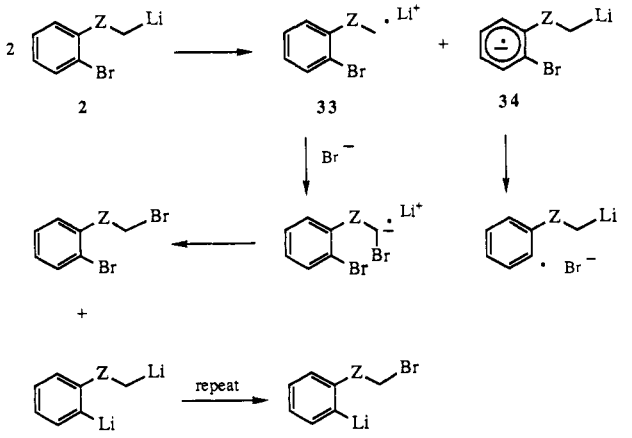
(19) It is possible to accommodate the present results in an single electron transfer mechanism by adding steps invoking radicals for which bromine transfer occurs only with large bond angles. Such advocacy would have to claim that the failure to incorporate external bromide is due to a lack of equivalence of bromide generated in the reaction to lithium bromide initially present. The fact that radicals can be produced in aryl bromine–lithium exchange is shown by reactions of metacyclophanes reported by Bickelhaupt and by Hirano (Jennesbens, L. W.; de Boer, H. J. R.; Wolf, W. H. de; Bickelhaupt, F. *J. Am. Chem. Soc.* **1990**, *112*, 8941. Hirano, S.; Hara, H.; Higama, T.; Fujita, S.; Nozaki, H. *Tetrahedron Lett.* **1975**, 2219). The conversion of i to ii is illustrative. We suggest that the structure of the




i ii

metacyclophane precludes a reaction pathway in which the entering and leaving groups can be linear thereby allowing a reaction pathway which is normally not operative to be available. Bickelhaupt et al. note that whether the radical involved in the conversion of i to ii is an intermediate in the bromine–lithium exchange or the result of an alternative SET is an open question.

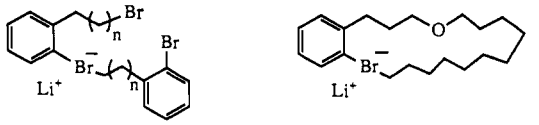
intramolecular nor intermolecular versions of single electron transfer mechanisms are consistent with the geometrical requisites for bromine–lithium exchange which are revealed by the conversions of **5**, **6**, and **7** to **8**, **9**, and **10**, respectively.[20]



2 33 34

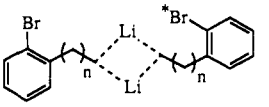
3

The two remaining mechanistic possibilities, reaction via a 10-Br-2 ate complex which has large bond angles or a $S_N2$ reaction, are consistent with our experimental results.[21] These transition structures are shown for **5** and **6** as the ate complex **35**. In these cases the reaction must be intermolecular in order to achieve the angle required for bromine transfer. In the case of **7**, an intramolecular reaction can be achieved via ate complex **36** which has the required large bond angles. If the mechanism involves an ate complex, these species are intermediates. If the mechanism is an $S_N2$ process, **35** and **36** should be redrawn as transition states.[22] To the best our knowledge this is the first direct experimental demonstration of a geometric requirement in a formal nucleophilic substitution at bromine.[9,10] The requirement of a large bond angle for these bromine transfers is consistent with established donor–acceptor interactions, Frontier MO theory, VSEPR analysis, and two of the previous mechanistic suggestions.[2,10,23,24]



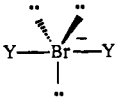
35 36

**Consideration of Aggregation.** The preceding discussion of endocyclic rings is framed in terms of a monomeric organolithium unit. However, this unit could exist as part of an aggregated species in which intraaggregate reactions may occur.[25] This possibility does not compromise the analysis; the case of **4**, Z = $CH_2$, is illustrative. Structure **37** represents a dimeric aggregate of **4**, Z = $CH_2$.[11,26] For an intramolecular monomeric reaction involving *Br a six-membered endocyclic ring would be required. If, however, the reaction were intraaggregate and involved *Br and the methylene of the other unit, an eight-membered endocyclic ring would be required. If the latter pathway were followed, it might be expected that for reaction of **6** in which an eight-membered endocyclic monomeric ring could be involved in an intramolecular reaction that the intramolecular pathway would be followed. However, since **6** reacts intermolecularly, the reaction of **4**, Z = $CH_2$, can be suggested not to have a viable intraaggregate pathway via a formal eight-membered ring. Thus an intraaggregate pathway for associated organolithium species can be discussed in terms of endocyclic rings of $n + 6$ atoms as well as for the $n + 4$ endocyclic ring used for analysis of the monomeric series. The conclusions about the geometry of the transition structures for bromine transfer based on endocyclic ring size for intramolecular reactions are not subverted by the effects of organolithium aggregation.



37 n = 2

**Summary.** In the present work we have shown that the aryl bromide–primary alkyllithium exchange reaction does not take place intramolecularly through six- or eight-membered endocyclic transition structures but can proceed intramolecularly through an 18-membered endocyclic transition structure. This demonstration of a geometrical requirement for large bond angles around the entering and leaving groups for a nucleophilic substitution at bromine is interpreted to favor a mechanism in which bromine is at the center of a trigonal bipyramid with apical ligands and equatorial electron pairs as shown for **39**. This transition structure is either an intermediate 10-Br-2 ate complex or a transition state in a $S_N2$ reaction. A four-centered mechanism is ruled out by these results and a single-electron transfer process is not required. While this mechanistic conclusion should be applied only to similar reactants, we note the general approach is broadly applicable to other systems.



39

## Experimental Section

**Reaction of 11-$^{79}Br$ and 11-$^{81}BrD_2$ with *tert*-Butyllithium, 0.1 M. Endocyclic Restriction Test of 11.** To a solution of 5.2 mg of **11**-$^{79}Br$ and 5.4 mg of **11**-$^{81}BrD_2$ (0.0325 mmol total) in 0.32 mL of THF, cooled to −98 °C by the use of a 50:50 methanol:pentane/$N_2$ bath, was added 0.043 mL of *tert*-butyllithium (1.35 M in pentane, 0.058 mmol). The solution was held at −98 °C for 20 min, and 0.1 mL (2.5 mmol) of methanol was added. The solution was stirred at −98 °C for an additional 20 min, after which the cooling bath was removed. After the solution was warmed to room temperature, water was added, and the THF/methanol was removed in vacuo. The aqueous mixture was extracted with $Et_2O$ (three 5-mL portions), and the combined organic extract was washed with brine and dried with $MgSO_4$. The drying agent was removed by filtration, and the solvent was removed in vacuo to yield 8.2 mg of a pale yellow oil. The crude product mixture was analyzed by capillary GC for its composition of **11** and **14–18** and by GC/EIMS for the isotopic composition of **14–16** and recovered **11**. The GC/EIMS peak intensities for **14–16**, and recovered **11**, as well as the peak intensities for the starting material mixture are given as supplemental material.

**Reaction of 11-$^{79}Br$ in the Presence of LiBr.** To a solution of 0.09 mL (1.0 mmol) of 1,2-dibromoethane in 10 mL of THF at −78 °C was added 1.8 mL of *n*-butyllithium (1.80 M in hexanes, 1.0 mmol). The solution

(20) The lack of bromide incorporation also rules out the possibility that the isotopic scrambling in the phenalkyl bromide and dibromide products from **5** and **6** are due to adventitious bromide displacement of iodide.

(21) These results also rule out an ate complex which has bond angles smaller than ca. the 160° carbon–bromine–carbon bond angles which could be achieved intramolecularly in an eight-membered ring from **6**.

(22) Since bromine–lithium exchange does show a leaving group effect,[2] i.e., more stable carbanions are formed more rapidly, this could be taken to favor an $S_N2$ mechanism. However, a pathway in which decomposition of a rapidly formed ate complex is the slow step or in which the apical ligand affects the rate of formation of the ate complex could also rationalize the leaving group effect.

(23) Huheey, J. E. *Inorganic Chemistry*; Harper and Row: New York, 1983; pp 207–218.

(24) Bent, H. A. *Chem. Rev.* **1987**, *87*, 587.

(25) The assumption is that similar aggregation effects would be involved in the series studied. While difference in concentration for these reactions raises concern about this assumption, it is to be noted that the systems **11** and **12** are different in behavior from **13**. Thus, while the latter involves intramolecular reaction at 0.001 M, **11** and **12** did not give bromine transfer products under these conditions.

(26) These species can be considered to represent any two adjacent units in a tetramer, hexamer, or other aggregate. The closest analogy to these structures with an established aggregation is *n*-butyllithium which is a mixture of dimer and tetramer in THF. Bauer, W.; Winchester, W. R.; Schleyer, P. R. *Organometallics* **1987**, *6*, 2371, and references cited therein.

was allowed to warm to 0 °C, and stirring was continued for 30 min. A 0.64-mL aliquot of this solution was removed and added to 20.6 mg (0.064 mmol) of **11**-$^{79}Br$. The solution was cooled to −98 °C by the use of a 50:50 methanol:pentane/$N_2$ bath; 0.070 mL of *tert*-butyllithium (1.65 M in pentane, 0.115 mmol) was added. The solution was held at −98 °C for 20 min, and 0.1 mL (2.5 mmol) of methanol was added. The solution was stirred at −98 °C for an additional 20 min, after which the cooling bath was removed. After the solution was warmed to room temperature, water was added, and the THF/methanol was removed in vacuo. The aqueous mixture was extracted with $Et_2O$ (three 5-mL portions), and the combined organic extract was washed with brine and dried with $MgSO_4$. The drying agent was removed by filtration, and the solvent was removed in vacuo to yield 13.5 mg of a pale yellow oil. The crude product mixture was analyzed by GC/EIMS for the isotopic composition of **15**. The GC/EIMS peak intensities for **15** as well as the peak intensities for the starting material **11**-$^{79}Br$ are given in the supplemental material.

**Reaction of 12-$^{79}Br$ and 12-$^{81}BrD_2$ with *tert*-Butyllithium, 0.1 M. Endocyclic Restriction Test of 12.** To a solution of 8.0 mg of **12**-$^{79}Br$ and 7.6 mg of **12**-$^{81}BrD_2$ (0.0441 mmol total) in 0.44 mL of THF, cooled to −98 °C by the use of a 50:50 methanol:pentane/$N_2$ bath, was added 0.055 mL of *tert*-butyllithium (1.42 M in pentane, 0.079 mmol). The solution was held at −98 °C for 20 min, and 0.1 mL (2.5 mmol) of methanol was added. The solution was stirred at −98 °C for an additional 20 min, after which the cooling bath was removed. After the solution was warmed to room temperature, water was added, and the THF/methanol was removed in vacuo. The aqueous mixture was extracted with $Et_2O$ (three 5-mL portions), and the combined organic extract was washed with brine and dried with $MgSO_4$. The drying agent was removed by filtration, and the solvent was removed in vacuo to yield 14.0 mg of a pale yellow oil. The crude product mixture was analyzed by capillary GC for its composition of **19–23** and **12** and by GC/EIMS for the isotopic composition of **19–21** and recovered **12**. The GC/EIMS peak intensities for **19–21** and recovered **12**, as well as the peak intensities for the starting material mixture, are given in the supplemental material.

**Reaction of 12-$^{79}Br$ in the Presence of LiBr.** To a solution of 0.09 mL (1.0 mmol) of 1,2-dibromoethane in 10 mL of THF at −78 °C was added 1.68 mL of *n*-butyllithium (1.68 M in hexanes, 1.0 mmol). The solution was allowed to warm to 0 °C, and stirring was continued for 30 min. A 0.37-mL aliquot of this solution was removed, and added to 11.4 mg (0.037 mmol) of **12**-$^{79}Br$. The solution was cooled to −98 °C by the use of a 50:50 methanol:pentane/$N_2$ bath; 0.037 mL of *tert*-butyllithium (1.80 M in pentane, 0.067 mmol) was added. The solution was held at −98 °C for 20 min, and 0.1 mL (2.5 mmol) of methanol was added. The solution was stirred at −98 °C for an additional 20 min, after which the cooling bath was removed. After the solution was warmed to room temperature, water was added, and the THF/methanol was removed in vacuo. The aqueous mixture was extracted with $Et_2O$ (three 5-mL portions), and the combined organic extract was washed with brine and dried with $MgSO_4$. The drying agent was removed by filtration, and the solvent was removed in vacuo to yield 8.2 mg of a pale yellow oil. The crude product mixture was analyzed by GC/EIMS for the isotopic composition of **20**. The GC/EIMS peak intensities for **20** as well as the peak intensities for the starting material **12**-$^{79}Br$ are given in the supplemental material.

**Reaction of 13-$^{79}Br$ and 13-$^{81}BrD_2$ with *tert*-Butyllithium, 0.02 M. Endocyclic Restriction Test of 13.** To a solution of 21.9 mg of **13**-$^{79}Br$ and 21.4 mg of **13**-$^{81}BrD_2$ (0.107 mmol total) in 5.4 mL of THF, cooled to −98 °C by the use of a 50:50 methanol:pentane/$N_2$ bath, was added 0.12 mL of *tert*-butyllithium (1.55 M in pentane, 0.19 mmol). The solution was held at −98 °C for 30 min, and 0.1 mL (2.5 mmol) of methanol was added. The solution was stirred at −98 °C for an additional 20 min, after which the cooling bath was removed. After the solution was warmed to room temperature, water was added, and the THF/methanol was removed in vacuo. The aqueous mixture was extracted with $Et_2O$ (three 5-mL portions), and the combined organic extract was washed with brine and dried with $MgSO_4$. The drying agent was removed by filtration, and the solvent was removed in vacuo to yield 35.2 mg of a pale yellow oil. The crude product mixture was analyzed by capillary GC for its composition of **24–30** and **13** and by GC/FIMS for the isotopic composition of **24**, **26**, **27**, and recovered **13**. The GC/FIMS peak intensities for **24**, **26**, **27**, and recovered **13** as well as the peak intensities for the starting material mixture are given in the supplemental material.

**Reaction of 13-$^{79}Br$ and 13-$^{81}BrD_2$ with *tert*-Butyllithium, 0.001 M. Endocyclic Restriction Test of 13.** To a solution of 8.1 mg of **13**-$^{79}Br$ and 8.1 mg of **13**-$^{81}BrD_2$ (0.0327 mmol total) in 32.7 mL of THF, cooled to −98 °C by the use of a 50:50 methanol:pentane/$N_2$ bath, was added 0.038 mL of *tert*-butyllithium (1.55 M in pentane, 0.059 mmol). The solution was held at −98 °C for 40 min, and 0.5 mL (12.5 mmol) of methanol was added. The solution was stirred at −98 °C for an additional 20 min, after which the cooling bath was removed. After the solution was warmed to room temperature, water was added, and the THF/methanol was removed in vacuo. The aqueous mixture was extracted with $Et_2O$ (three 5-mL portions), and the combined organic extract was washed with brine and dried with $MgSO_4$. The drying agent was removed by filtration, and the solvent was removed in vacuo to yield 5.1 mg of a pale yellow oil. The crude product mixture was analyzed by capillary GC for its composition of **24–30** and **13**, and by GC/FIMS for the isotopic composition of **24**, **26**, **27**, and recovered **13**. The GC/FIMS peak intensities for **24**, **26**, **27**, and recovered **13**, as well as the peak intensities for the starting material mixture are given in the supplemental material.

**Acknowledgment.** We are grateful to Dr. Richard Milberg and the Mass Spectrometry Facility at UIUC for analyses of isotopic composition. We are grateful to the National Science Foundation and the National Institutes of Health for support of this work.

**Supplementary Material Available:** The data for the mass spectral analyses and the syntheses of isotopically substituted **11**, **12**, and **13** (36 pages). Ordering information is given on any current masthead page.

# Reaction of (*E*)-*O*-Arylbenzaldoximes with Sodium Methoxide in Methanol. Effect of Leaving Group upon Nitrile-Forming Transition State

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**Abstract:** Reactions of (*E*)-*O*-arylbenzaldoximes **1–3** with MeONa–MeOH have been studied kinetically. The reactions proceed via competing E2 and $S_NAr$ reactions, in which the first step is rate-determining. Although the reactions were strongly influenced by the electronic effect of the β- and *O*-aryl substituents, they were insensitive to the steric effect of the *O*-aryl group, except that the $S_NAr$ reaction was retarded by the $CF_3$ group of **2**. For eliminations from **1–3** promoted by MeONa–MeOH, the $k_H/k_D$ value increased and the Hammett ρ value decreased with better leaving groups. From these results, the effect of leaving group variation upon the nitrile-forming transition state is assessed.

Recently we reported a kinetic investigation of the nitrile-forming elimination from (*E*)-*O*-arylbenzaldoximes promoted by tertiary amines in MeCN.[1] The reactions proceeded via an E2 central type of transition state with similar extents of $C_\beta$–H and

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