$(CH_3)_3CCH_2TePh$, 113303-08-5; $(CH_3)_2CHSPh$, 3019-20-3; $(CH_3)_2CHSePh$, 22233-89-2; $(CH_3)_2CHTePh$, 32343-99-0; c-$C_6H_{11}SPh$, 7570-92-5; c-$C_6H_{11}TePh$, 56950-05-1; c-$C_5H_9CH_2SPh$, 100258-36-4; c-$C_5H_9CH_2SePh$, 78872-19-2; $CH_2{=}CH(CH_2)_3CH_2SPh$, 39984-84-4; $CH_2{=}CH(CH_2)_3CH_2SePh$, 78872-18-1; $CH_2{=}CH(CH_2)_3CH_2TePh$, 113303-11-0; $CH_2{=}CH(CH_2)_3CH_2SH$, 17651-39-7; $CH_3(CH_2)_3CH_2SPh$, 1129-70-0; $(CH_3)_2CHCH_2SPh$, 13307-61-4; $(CH_3)_3CSPh$, 3019-19-0; $PhS(CH_2)_6SPh$, 55129-89-0; n-BuSePh, 28622-61-9; $(i\text{-Bu})_2Hg$, 24470-76-6; $PhCH_2HgCHPh$, 780-24-5; $PhCH_2HgSPh$, 113303-12-1; $PhCH_2HgSePh$, 113303-13-2; $PhCH_2HgCl$, 2117-39-7; $PhCH_2SePh$, 18255-05-5; $PhCH_2SPh$, 831-91-4; $PhCH_2TePh$, 32344-00-6; $PhCH_2CH_2Ph$, 103-29-7; $PhCH_2Br$, 100-39-0; (E)-PhCH=CHI, 42599-24-6; (Z)-PhCH=CHI, 57918-63-5; $Ph_2C{=}CHI$, 19997-66-1; $H_2C{=}CHI$, 593-66-8; $Me_2C{=}CHI$, 20687-01-8; (E)-$MeO_2CCH{=}CHI$, 6213-88-3; (Z)-$MeO_2CCH{=}CHI$, 6214-23-9; (Z)-$MeO_2CCH{=}CHCl$, 3510-44-9; PhC≡CI, 932-88-7; PhC≡CSPh, 35460-31-2; $PhC{\equiv}CSO_2Ph$, 5324-64-1; (E)-PhCH=CHSPh, 7214-53-1; $Ph_2C{=}CHSPh$, 13112-46-4; (E)-$PhCH{=}CHSO_2Ph$, 16212-06-9; $Ph_2C{=}CHSO_2Ph$, 26189-62-8; $MeOC(CH_2)_4HCHHgO_2CCF_3$, 720-77-4; $MeOC(Ph)HCH_2HgO_2CCF_3$, 111823-11-1; (E)-PhCH=CH-n-Bu, 6111-82-6; (Z)-PhCH=CH-n-Bu, 15325-54-9; (E)-PhCH=CH-i-Pr, 15325-61-8; (Z)-PhCH=CH-i-Pr, 15325-56-1; (E)-PhCH=CH-c-C_6H_{11}, 18869-27-7; (Z)-PhCH=CH-c-C_6H_{11}, 40132-69-2; (E)-PhCH=CH-t-Bu, 3846-66-0; (Z)-PhCH=CH-t-Bu, 3740-05-4; $Ph_2C{=}CH\text{-}n\text{-}Bu$, 1530-19-4; $Ph_2C{=}CH\text{-}i\text{-}Pr$, 35467-39-1; $Ph_2C{=}CH\text{-}c\text{-}C_6H_{11}$, 91083-83-9; $Ph_2C{=}CH\text{-}t\text{-}Bu$, 23586-64-3; $MeOC(CH_2)_4HCHCH{=}CPh_2$, 111823-12-2; $MeOC(Ph)HCH_2CH{=}CPh_2$, 111823-13-3; $Me_2C{=}CH\text{-}c\text{-}C_6H_{11}$, 89656-98-4; ($E$)-$MeO_2CH{=}CH\text{-}i\text{-}Pr$, 20515-15-5; ($Z$)-$MeO_2CCH{=}CH\text{-}i\text{-}Pr$, 20515-16-6; ($E$)-$MeO_2CCH{=}CH\text{-}c\text{-}C_6H_{11}$, 26429-99-2; ($Z$)-$MeO_2CCH{=}CH\text{-}c\text{-}C_6H_{11}$, 26429-98-1; ($E$)-$MeO_2CCH{=}CH\text{-}t\text{-}Bu$, 20664-51-1; ($Z$)-$MeO_2CCH{=}CH\text{-}t\text{-}Bu$, 57539-96-5; $PhC{\equiv}C\text{-}n\text{-}Bu$, 1129-65-3; $PhC{\equiv}C\text{-}c\text{-}C_6H_{11}$, 33414-83-4; $PhC{\equiv}C\text{-}t\text{-}Bu$, 4250-82-2; $PhC{\equiv}C\text{-}i\text{-}Pr$, 1612-03-9; $PhCH(t\text{-}Bu)CH_2SPh$, 113303-14-3; $Ph(t\text{-}Bu)C{=}CHSPh$, 113303-15-4; $Ph(t\text{-}Bu)CHCH_2SO_2Ph$, 113303-16-5; ($E$)-PhCH=CHSOPh, 40110-66-5; (Z)-ClCH=CHCl, 156-59-2; (E)-ClCH=CHCl, 156-60-5; (E)-ICH=CHI, 590-27-2; $Ph_2C{=}CHSePh$, 108365-51-1; (E)-ClCH=CHI, 28540-81-0; (E)-ClCH=CHSPh, 26620-11-1; (E)-$ClCH{=}CHSO_2Ph$, 38238-75-4; (E)-$BrCH{=}CHSO_2Ph$, 20408-25-7; (Z)-$BrCH{=}CHSO_2Ph$, 52244-26-5; (E)-$ICH{=}CHSO_2Ph$, 58202-75-8; (E)-$PhSCH{=}CHSO_2Ph$, 37530-86-2; (E)-$Bu_3SnCH{=}CHSO_2Ph$, 88486-41-3; (E)-ClCH=CH-n-Bu, 50586-19-1; (Z)-ClCH=CH-n-Bu, 50586-18-0; (E)-ClCH=CH-c-C_6H_{11}, 67404-71-1; (Z)-ClCH=CH-c-C_6H_{11}, 67404-70-0; (E)-ClCH=CH-t-Bu, 18314-62-0; (Z)-ClCH=CH-t-Bu, 18314-61-9; (E)-ICH=CH-n-Bu, 16644-98-7; (Z)-ICH=CH-n-Bu, 16538-47-9; (E)-ICH=CH-c-C_6H_{11}, 42599-23-5; (Z)-ICH=CH-c-C_6H_{11}, 67404-69-7; (E)-ICH=CH-t-Bu, 61382-45-4; (Z)-ICH=CH-t-Bu, 64245-24-5; $PhS(CH_2)_2SPh$, 622-20-8; (E)-n-BuCH=CHSPh, 62839-73-0; (Z)-n-BuCH=CHSPh, 70197-34-1; (Z)-c-$C_6H_{11}CH{=}CHSPh$, 94633-43-9; (E)-c-$C_6H_{11}CH{=}CHSPh$, 94633-42-8; (Z)-t-BuCH=CHSPh, 58431-67-7; (E)-t-BuCH=CHSPh, 53847-74-8; (E)-c-$C_6H_{11}CH{=}CHSO_2Ph$, 112863-50-0; (Z)-c-$C_6H_{11}CH{=}CHSO_2Ph$, 113303-17-6; (E)-t-$BuCH{=}CHSO_2Ph$, 68969-27-7; (Z)-t-$BuCH{=}CHSO_2Ph$, 108344-86-1; $(PhS)_2Hg$, 21514-24-9; $(PhSe)_2Hg$, 21514-25-0; $(PhSO_2)_2Hg$, 26186-79-8; $[(EtO)_2PO]_2Hg$, 74475-14-2; $(PhCOCH_2)_2Hg$, 37160-45-5; $(EtCO_2)_2Hg$, 26719-04-0; $(t\text{-}BuCO_2)_2Hg$, 32276-77-0; $(i\text{-}PrCO_2)_2Hg$, 19348-33-5; (Z)-PhCH=CHSPh, 7214-56-4; (E)-PhCH=CHSePh, 60466-40-2; (Z)-PhCH=CHSePh, 60466-30-0; (Z)-$PhCH{=}CHSO_2Ph$, 32291-77-3; (E)-$PhCH{=}CHP(O)(OEt)_2$, 20408-33-7; (Z)-$PhCH{=}CHP(O)(OEt)_2$, 25362-01-0; $Ph_2C{=}CHCH_2COPh$, 57694-83-4; $Ph_2C{=}CHP(O)(OEt)_2$, 78462-91-6; $PhC{\equiv}CP(O)(OEt)_2$, 3450-67-7; $Ph_2C{=}CHEt$, 1726-14-3; $(EtO)_2POHgCl$, 29120-01-2; 7-norbornylmercury, 83020-42-2; 1,6-dihexanediylmercury, 6675-64-5; 7-norbornylphenyl sulfide, 94110-62-0; 7-norbornylphenyl selenide, 113303-09-6; 7-norbornylphenyl teluride, 113303-10-9; 7,7′-dinorbornyl, 1712-32-9; 2-iodobenzothiazole, 120-75-2; 2-phenylsulfonylbenzothiazole, 64345-00-2; 2-butylbenzothiazole, 54798-95-7; 2-isopropylbenzothiazole, 17626-86-7; 2-cyclohexylbenzothiazole, 40115-03-5; 2-*tert*-butylbenzothiazole, 17626-88-9.

Does Formal Intramolecular Transfer of an Acidic Deuterium to a Site of Halogen–Lithium Exchange Show That Lithium–Halogen Exchange Is Faster than Loss of the Acidic Deuterium? Evidence in Favor of an Alternative Mechanism

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Abstract: Reactions in which there is formal intramolecular transfer of an acidic deuterium to a site of halogen–lithium exchange could be interpreted to show that initial halogen–lithium exchange occurs faster than loss of the acidic deuterium. However studies of the competition between halogen–metal–deuterium exchange and deuterium loss for *N*-deuterio-*N*-alkyl-*o*, -*m*-, and -*p*-halobenzimides are not consistent with that mechanism. We suggest an alternative in which initial loss of the acidic deuterium is followed by halogen–lithium exchange to give a dilithiated intermediate. Deuterium transfer to the site of halogen–lithium exchange then occurs by reaction of the dilithiated species intermolecularly with unreacted N-deuteriated amide. The halogen–lithium exchange is faster than complete mixing of the reactants and can occur either in an initially formed deprotonated complex or in a transient high local concentration of organolithium reagent. Evidence for both possibilities is provided. Two reactions from the literature in which halogen–lithium exchange appears to be faster than transfer of an acidic hydrogen have been reinvestigated and found to be interpretable in terms of similar sequences.

The relative rates of competitive reactions of organolithium compounds are important for the use and to the understanding of these reagents.[1] Particularly interesting are reactions of polyfunctional molecules in which a kinetically driven reaction takes precedence over a thermodynamically favored alternative.[2] Perhaps the most dramatic apparent examples of such reactions are those in which a highly acidic hydrogen appears not to react

(1) For a summary of pertinent literature and elegant uses of selective reactions of organolithium reagents in competitive situations, see: Cooke, M. P., Jr.; Widner, R. K. *J. Org. Chem.* **1987**, *52*, 1382. Parham, W. F.; Bradsher, C. K. *Acc. Chem. Res.* **1982**, *15*, 300 and references cited therein.

(2) A number of such reactions have been attributed to complex-induced proximity effects: Beak, P.; Meyers, A. I. *Acc. Chem. Res.* **1986**, *19*, 356.

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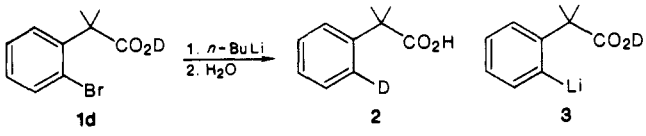
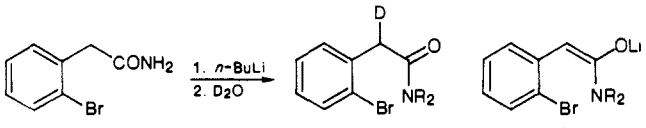
with a highly basic organolithium reagent, during the time that reagent does effect a bromine–lithium exchange.[3]

A widely quoted example of such a reaction is the conversion of deuteriodimethyl-*o*-bromophenylacetic acid (**1d**) to dimethyl-*o*-deuteriophenylacetic acid (**2**) with *n*-butyllithium.[4] The straightforward interpretation of this result is that bromine–lithium exchange to give **3** is faster than transfer of the acidic deuterium from the carboxylic acid function to the *n*-butyllithium reagent. Under this mechanism **3** subsequently undergoes deuterium transfer to give **2**.



1d **2** **3**

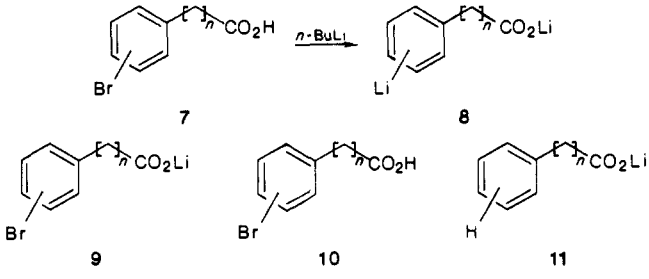
However, in unpublished work we have found that *N*,*N*-diisopropyl-*o*-bromophenylacetamide (**4**) on treatment with *n*-butyllithium followed by deuterium oxide gives *N*,*N*-diisopropyl-*α*-deuteriophenylacetamide (**5**).[5] In this case **6** is reasonably the intermediate, and bromine–lithium exchange must be slower than loss of the *α* proton to give the enolate. Comparison of the



4: R = *i*-Pr **5** **6**

reactions of **1** and **4** with *n*-butyllithium suggests a dilemma. For the reaction of **1d**, bromine–lithium exchange appears to be faster than loss of a highly acidic proton, yet for reaction of **4** bromine–lithium exchange is slower than loss of a less acidic proton.

The possibility that bromine–lithium exchange is generally faster than loss of an acidic proton also does not seem consistent with the work of Parham et al. who have reported that a number of aromatic bromo acids **7** react with 2 equiv of *n*-butyllithium to give the dilithio species **8**.[6] Most reasonably, these reactions

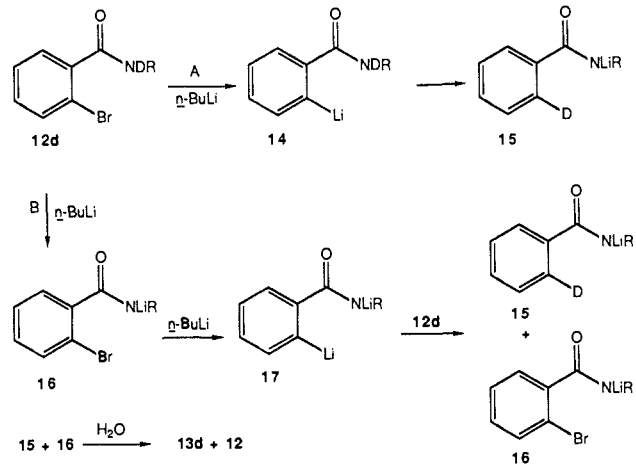


7 **8** **9** **10** **11**

involve initial loss of the acidic proton and formation of the intermediate **9** prior to bromine–lithium exchange with the second equivalent of *n*-butyllithium. If, in these cases bromine–lithium exchange occurred first, the proton of the carboxylic acid of **10** would have to be unreactive until the halogen–lithium exchange was complete. If it were not, proton transfer would be expected to give **11**, which would then be inert to ring metalation under these conditions.

In this paper we detail our suggestion that lithium–bromine exchange, while rapid, is slower than loss of an acidic hydrogen.[7]

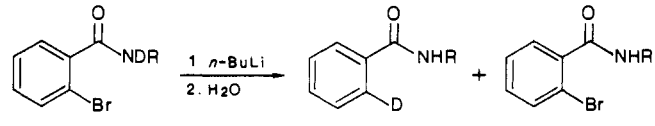
Scheme I



We have also reinvestigated two examples from the literature, which have been interpreted in favor of bromine–lithium exchange being faster than reaction of an acidic hydrogen, and find these cases to be in accord with the present proposal.

Results and Discussion

In order to illustrate the alternative possibilities, we will discuss the lithiation of *N*-deuterio-*N*-isopropyl-*o*-bromobenzamide (**12d**) with 1 equiv of *n*-butyllithium as a representative case. Treatment of **12d** with 1 equiv of *n*-butyllithium followed by water gives *N*-isopropyl-*o*-deuteriobenzamide (**13d**) in 33% yield and **12** in 33% yield. The structure is assigned to **13d** on the basis of comparison of ^{1}H NMR, ^{13}C NMR, and MS data with those of *N*-isopropylbenzamide.



12d: R = *i*-Pr **13d** **12**

A mechanism of initial bromine–lithium exchange followed by deuterium transfer would involve the initial formation of **14** and its conversion to **15** as shown in pathway A of Scheme I. Reaction of **15** with water would provide **13d** and the presence of **12** attributed to exchange with water after incomplete reaction.

An alternative shown as pathway B in Scheme I is initial reaction of **12d** by loss of an acidic deuterium to *n*-butyllithium to give **16** followed by bromine–lithium exchange with another *n*-butyllithium to give **17**. This second step must be fast with respect to mixing of the *n*-butyllithium with unreacted **12d**. Since 2 equiv of *n*-butyllithium are required to give **17**, after these steps are complete 0.5 equiv of **12d** would remain. That unreacted starting material could provide a deuterium to the 0.5 equiv of **17** formed to give **15** and **16**. The products **12** and **13d** would come from protonation of **16** and **15** on workup with water. By pathway B the initial reaction involves the most acidic proton, and the second step of bromine–lithium exchange is slower than the first, albeit, it is faster than complete mixing of *n*-butyllithium in the solution with **12d**. The formation of **12** is a necessary consequence of the mechanism.

Pathways A and B have different consequences. If bromine–lithium exchange is fastest as in pathway A, high yields of **13d** should be observable with equimolar reactants, and the yield should

(3) For a discussion of proton transfers, see: Eigen, M. *Angew. Chem., Int. Ed. Engl.* **1964**, *3*, 1. For a discussion of halogen–metal exchange, see: Bailey, W. F; Gagnier, R. P.; Patrica, R. P. *J. Org. Chem.* **1984**, *49*, 2098. Reich, H. J.; Phillips, N. H.; Reich, I. L. *J. Am. Chem. Soc.* **1985**, *107*, 4101 and references cited therein.

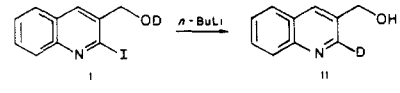
(4) Boatman, R. J.; Whitlock, B. J.; Whitlock, H. W. Jr. *J. Am. Chem. Soc.* **1977**, *99*, 4822. For other cases that could be similarly interpreted, see: Stein, C. A. Morton, T. H. *Tetrahedron Lett.* **1973**, 4933. Taylor, E. C. Vogel, D. E. *J. Org. Chem.* **1985**, *50*, 1002. Bailey, W. F.; Patricia, J. J.; Nurmi, T. T.; Wang, W. *Tetrahedron Lett.* **1986**, *27*, 1861.

(5) Beak, P.; Chin, C. W., unpublished observation, 1985.

(6) Parham, W. F.; Jones, L. D.; Sayed, Y. *J. Org. Chem.* **1975**, *40*, 2394.

(7) Beak, P.; Chen, C. W. *Tetrahedron Lett.* **1985**, *26*, 4979.

(8) Narasimhan has reported the conversion of i to ii in 90% yield, a result that is inconsistent with a reaction via a pathway analogous to pathway B: Narasimhan, N. S.; Ammaramarchi, R. *J. Chem. Soc., Chem. Commun.* **1985**, 1368. We have prepared i and are unable to repeat the conversion of i to ii in high yield, so we cannot comment on this report.



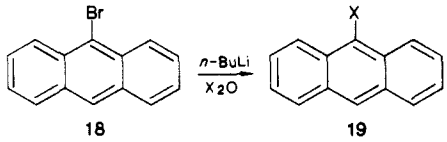
i ii

be independent of the mode of reaction. However, if deuterium loss is fastest as in pathway B and **16** and **17** are involved as suggested, the yield of **13d** could be no greater than 50% with equimolar reactants. If reaction occurs via pathway B, the ratio of bromine–lithium exchanged to nonexchanged product might be influenced by the mode of addition or by the rate of mixing (vide infra).

The normal technique for these reactions is addition of a solution of *n*-butyllithium reagent to a solution of the substrate. In this case a high local concentration of *n*-butyllithium is present transiently and pathway B could be favored. We found that when inverse addition was used for the reaction of **12d** and *n*-butyllithium, the formation of **13d** was suppressed. Specifically addition of a 0.02 M solution of **12d** at a rate of 0.1 mL/min solution to a 0.05 M solution of *n*-butyllithium at 0 °C followed by quenching with water gave only **12** in 92% yield.

Similar experiments were carried out with deuteriodimethyl-*o*-bromophenylacetic acid (**1**). Under the normal mode of addition, a 1:1 ratio of **2** and dimethyl-*o*-bromophenylacetic acid was obtained. When reaction was carried out with slow inverse addition, dimethyl-*o*-bromophenylacetic acid was obtained in 90% yield. The fact that 1:1 ratios of brominated/debrominated products are obtained in both the reactions of **1d** and of **12d** tends to discount the possibility that bromine–lithium exchange and dedeuteriation are directly competitive in the initial step. If that were the case, the different acidities of the carboxylic acid and amide functions would be expected to affect the relative rates of the dedeuteriation and lithiation reactions so that different product ratios would be expected from **1d** and **12d**.

A case in which the competition between proton transfer and dehalogenation is intermolecular is the reaction of 9-bromoanthracene (**18**) with *n*-butyllithium in the presence of isotopically labeled water to give **19**, anthracene that is labeled at the 9-position. A 70% yield of 9-tritioanthracene has been reported



for this reaction.[9] Again reaction could occur either by initial bromine–lithium exchange or by initial deprotonation of the water followed by bromine–lithium exchange in the local environment. We carried out the reaction of **18** with *n*-butyllithium in tetrahydrofuran in the presence of 1 equiv of deuterium oxide. With no stirring, a 9% yield of 9-deuterioanthracene **19d** was obtained along with 88% **18**. With magnetic stirring, 94% **18** was recovered, and with overhead stirring, 98% **18** was obtained. On the basis of these results, we suggest that with no stirring halogen–metal exchange can occur in a local environment that has been depleted of water by initial reaction of the water with the lithiating reagent. Stirring breaks up that environment and allows the more rapid deprotonation of water to predominate.

In order to gain more information about these reactions, we have investigated the extent of exchange as a function of the relative positions of the deuterium and halogen in intramolecular competitions. Our approach is shown in Scheme II for the ortho, meta, and para bromo and iodo isomers of the *N*-ethylhalobenzamides, **20d**. The first reaction is considered to be loss of the acidic deuterium from **20d** to give **21**, which is partitioned between bromine–lithium exchange to **22**, pathway C, and dissassociation from its complex or local environment, pathway E, to give "free" **21**, which does not undergo bromine–lithium exchange. The dilithiated species, from pathway C, **22** can undergo deuteriation by **20d** to give **23** and "free" **21**. On reaction with water, **21** will give **20** and **23** will give **24**. If only pathway C is followed, a 1:1 ratio of **21**/**23** would obtain. On the other hand, if only pathway E is followed, only **21** would be formed. When

(9) Taylor, R. *Tetrahedron Lett.* **1975**, 435.

Scheme II

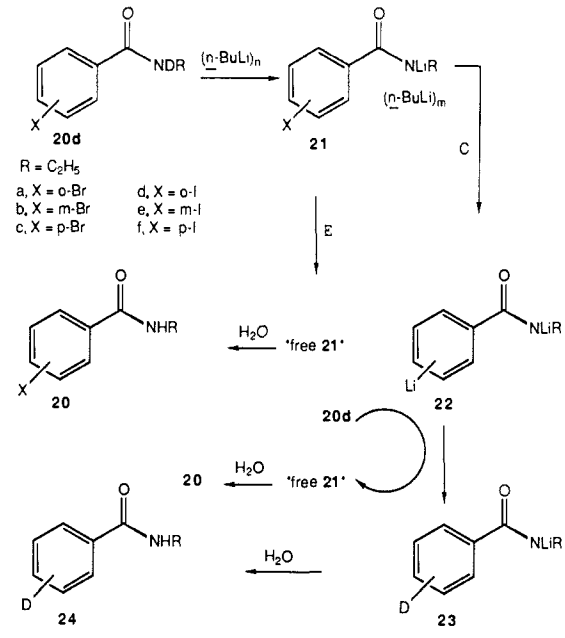


Table I. Ratio of Products **20**/**24** from the Reaction of *N*-Deuterio-*N*-Ethylhalobenzamides **20d** a–f with *n*-Butyllithium[a,b]

reactant	no stirring	slow stirring[c]	fast stirring[d]	reverse addition[e]
20d a (*o*-Br)	56:44	59:41	66:33	56:44
20d b (*m*-Br)	55:45	83:17	95:5	76:24
20d c (*p*-Br)	60:40	91:9	94:6	>98:2
20d d (*o*-I)	50:50	60:40	60:40	52:48
20d e (*m*-I)	47:53	73:26	94:5	64:36
20d f (*p*-I)	58:42	95:5	97:3	>98:2

[a] The solution of *n*-butyllithium was added at a rate of ca. 1 mL/min to a 0.05 M solution of the substrate. [b] The experimental error is ±3%. [c] Magnetic stirring was used. [d] Overhead stirring was used. [e] The substrate was added to the *n*-butyllithium

both paths are operative, the ratio 21/23 will be >1 and the ratio may be taken as a measure of the partitioning.

Reactions were carried out by addition of a solution of *n*-butyllithium to a solution of the *N*-deuteriohalobenzamides **20d**, followed by reaction with water, as shown in Table I.[10] The ratio of **21**/**23** after lithiation is complete is obtained from the ratio of *N*-ethyldeuteriobenzamide/*N*-ethylhalobenzamide (**20**/**24**).

In all cases as the reaction conditions are changed from no stirring to slow stirring to fast stirring, the ratio of **20**/**24** increases although the change ranges from slight, for the ortho-substituted cases, to large in the para-substituted compounds. In a mechanism of initial dehalogenation, pathway A of Scheme I, the ratio of **20**/**24** would be unaffected by the stirring rate and therefore can again be discounted. Under Scheme II the increased stirring could favor the dissociation of pathway E, and the observed increases in the ratios of **20**/**24** are explicable.

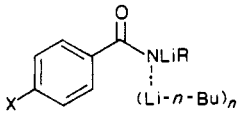
The bromine–lithium exchange of pathway B in Scheme I and pathway C in Scheme II can be concieved of as proceeding either within the general local environment of excess *n*-butyllithium provided by the normal mode of addition or more specifically within a complex that results from the initial dedeuteriation. In the former case, addition of the *N*-ethylhalobenzamide to *n*-butyllithium should lead to a decreased yield of ring-deuteriated product **24**, since the local environment would be initially enriched in unreacted **20d** relative to the customary addition. In the later case, if the complex between the associated *n*-butyllithium and **21** is tightly bound and bromine–lithium exchange occurs within

(10) The ratio of **20**/**24** may be a function of the exact way in which the reactions are carried out, so comparisons must be made under as close to identical conditions as possible. When that is done, reproducibility is observed and qualitative interpretation of the changes product ratios is justified.

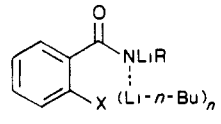
that complex, no change in the ratio would be expected on addition of the substrate to *n*-butyllithium.

Comparison of the ratios of **20/24** obtained on reverse addition, shown as the last column in Table I, with the ratios in the other columns, suggests both mechanisms are operative. Thus, the *p*-bromo, **20d** c, and *p*-iodo, **20d** f, benzamides give only the halobenzamides, **20c** and **20f**, respectively, on reverse addition. On the other hand, the *o*-bromo- and *o*-iodobenzamides **20a** and **20d**, respectively, show no change in the product ratio of **20/24** on reverse addition.

In the para-substituted cases, the first formed species may be represented as **25**. In this structure with the ionized amide bound to the lithium, the para halogen is not near the *n*-butyllithium groups in the complex, so halogen–metal exchange reasonably involves *n*-butyllithium external to the complex. Hence a high local concentration of *n*-butyllithium is needed to promote the halogen–metal exchange, and reverse addition leads to a decrease in the extent of halogen–lithium exchange. In the complex resulting from the *o*-halobenzamides, however, a potentially reactive *n*-butyllithium group in the complex is in close proximity to the halogen as suggested by structure **26**, and an essentially intramolecular reaction can ensue.[2] Thus the ortho-substituted cases are little affected by the mode of reverse addition.



25



26

The meta-substituted cases **20d** b and **20d** d show intermediate behavior. Both stirring and inverse addition have an affect on the ratio of **20/24** and both the high local concentration and the oriented complex could contribute to the halogen–metal exchange reaction.[11] The apparent small effect of stirring on the ortho-substituted cases could be due to an effect by stirring on the exchange between aggregates. In fact, when inverse addition is carried out very slowly and with high dilution as noted for the case of **12d**, bromine–lithium exchange can be suppressed. Indeed the operation of both processes would be consistent with the inter- and intramolecular exchange processes, which are well-known for organolithium reagents.[12]

We suggest that reactions that have been interpreted as demonstrating that halogen–lithium exchange is faster than reaction of an acidic deuterium because of the formal intramolecular transfer of deuterium may be proceeding by a two-step intermolecular process. The pathway of initial loss of the acidic deuterium is followed by a slower, but still rapid, halogen–lithium exchange. This exchange is promoted by a high local concentration of the lithium reagent and/or by appropriate orientation within the complex formed by the initial loss of deuterium. The latter reaction within an initially formed aggregate may be considered another example of a complex-induced proximity effect.[2]

Experimental Section

General Procedures. ^{1}H NMR spectra were recorded on Varian XL-200 (200 MHz), Nicolet NTC 360 (360 MHz), or General Electric QE-300 (300 MHz) spectrometers in deuteriochloroform with tetramethylsilane (TMS) as the internal standard. Chemical shifts are reported in parts per million relative to TMS; when peak multiplicities are given, the following abbreviations are used: s, singlet; d, doublet; t, triplet, q, quartet, m, multiplet; br, broadened. Mass spectra were obtained on a Varian MAT CH-5 spectrometer with an ionization voltage of 10 or 70 eV or on a Finnigan-MAT 731 spectrometer. Data are reproted in the form *m/e* (intensity relative to base = 100). Elemental analyses were performed by the University of Illinois Microanalytical Service Laboratory.

Analytical gas chromatography was performed on a Hewlett-Packard 5790 gas chromatograph equipped with a programmable temperature control and a flame-ionization detector. The column used was a 25-m SE 52/54 capillary column; injector temperature was 270 °C, detector temperature was 300 °C, and programs were as indicated. Retention times and peak integrals were obtained from a Hewlett-Packard 3390A recorder. Error values were determined by standard deviation calculations of repeated runs and injections. Response factors were calibrated by using known solutions of *N,N*-diisopropylbenzamide. Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Bulb-to-bulb distillations were performed on a Büchi GKR-50 Kugelrohr; boiling points refer to air–bath temperatures and are not necessarily an accurate measure of boiling points. Column chromatography was performed with silica gel of grade 0.05–0.2 mm with columns of various sizes, depending on the amount of material and ease of separation. Medium-pressure liquid chromatography (MPLC) was performed with various silica gel columns, depending on the amount of material and the difficulty of separation. Rotary chromatography was performed on a Harrison Research Chromatotron Model 7924 with either 1-mm, 2-mm, or 4-mm plates made from EM Reagents silica gel PF_{254} with $CaSO_4 \cdot {}^1/_2H_2O$ as a binder. Solvent systems were various mixtures of ethyl acetate and hexane.

Unless mentioned otherwise, all reagents were obtained from commerical sources and used without further purification. Diethyl ether (Et_2O) and tetrahydrofuran (THF) were distilled from sodium and benzophenone under a N_2 atmosphere. Dichloromethane (CH_2Cl_2), hexane, and pyridine were distilled from calcium hydride under N_2 atmosphere. Ethyl acetate (EtOAc) was distilled from potassium carbonate. Commerical solutions of *n*-butyllithium (*n*-BuLi) in hexanes titrated by using a modification of Tischler and Tischler's procedure.[13] All glassware was oven- or flame-dried prior to use, and all reactions were done under a dry nitrogen atmosphere.

Typical data will be given herein for syntheses. Data for other cases appears in the supplementary material.

Preparation of 3-Bromo-*N*-ethylbenzamide (20b). To excess (10 mL) thionyl chloride was added 1.6 g (0.0080 mol) of 3-bromobenzoic acid. The solution was heated at reflux for 2 h, at which time thionyl chloride was distilled off. Benzene was added, and the resulting azeotrope was distilled off. The remaining acid chloride was dissolved in CH_2Cl_2 and cooled to 0 °C, and 10 mL of 10% NaOH solution was added. Then, 2.5 mL of 70% $EtNH_2$ in H_2O was added dropwise with stirring. After 30 min the solution was washed with water, 10% NaOH, and 10% HCl. The organic phase was dried with $MgSO_4$ and reduced to give a white solid. It was distilled in a Kugelrohr apparatus to give 0.7388 g (0.003 24 mol, 41%) of **20b** as a white solid: mp 69–73 °C; GC (155 °C isothermal) t_R 3.60 min; ^{1}H NMR (200 MHz) δ 1.26 (t, 3 H, CH_3), 3.46 (dq, 2 H, CH_2), 6.08 (br s, 1 H, NH), 7.21–7.69 (m, 3 H, Ar H), 7.91 (s, 1 H, Ar H2); mass spectrum (FI, M^+ (relative intensity)), *m/e* 231 (1163), 230 (17 103), 229 (156 041), 228 (19 772), 227 (159 652), 226 (2466), 225 (559). Anal. Calcd for $C_9H_{10}BrNO$: C, 47.39; H, 4.42; N, 6.14; Br, 35.03. Found: C, 47.68; H, 4.39; N, 6.25; Br, 35.28.

The same procedure as above was used to prepare the amides **20** with the following analytical data. **20a**: mp 90–91 °C; GC (155 °C isothermal) t_R 2.63 min; ^{1}H NMR (200 MHz) δ 7.2–7.6 (m, 4 H, Ar H), 5.97 (br s, 1 H, NH), 3.50 (dq, 2 H, CH_2), 1.24 (t, 3 H, CH_3). Anal. Calcd for $C_9H_{10}BrNO$: C, 47.39; H, 4.42; N, 6.14. Found: C, 47.48; H, 4.38; N, 6.05.

20c: mp 122–124 °C; GC (155 °C isothermal) t_R 3.15 min; ^{1}H NMR (200 MHz) δ 7.5–7.7 (m, 4 H, Ar H), 6.09 (br s, 1 H, NH), 3.49 (dq, 2 H, CH_2), 1.27 (t, 3 H, CH_3). Anal. Calcd for $C_9H_{10}BrNO$: C, 47.39; H, 4.42; N, 6.14. Found: C, 47.59; H, 4.42; N, 6.11.

20d: mp 114–116 °C; GC (155 °C isothermal) t_R 4.31 min; ^{1}H NMR (200 MHz) δ 7.87 (d, 1 H Ar H), 7.10–7.42 (m, 3 H, Ar H), 5.75 (s, 1 H, NH), 3.45–3.79 (m, 2 H, CH_2), 1.23 (m, 3 H, CH_3). Anal. Calcd for $C_9H_{10}INO$: C, 39.30; H, 3.66; N, 5.09. Found: C, 39.38; H, 3.70; N, 4.98.

20e: mp 80–82 °C; GC (155 °C isothermal) t_R 5.48 min; ^{1}H NMR (200 MHz) δ 8.09 (s, 1 H, Ar H), 7.61–7.82 (m, 2 H, Ar H), 7.10–7.21 (m, 1 H, Ar H), 6.10 (br s, 1 H, NH), 3.47 (dq, 2 H, CH_2), 1.21 (t, 3 H, CH_3). Anal. Calcd for $C_9H_{10}INO$: C, 39.30; H, 3.66; N, 5.09; I, 46.13. Found: C, 39.40; H, 3.76; N, 5.14; I, 46.09.

20f: mp 147–149 °C; GC (155 °C isothermal) t_R 5.52 min; ^{1}H NMR (200 MHz) δ 7.78 (m, 1 H, Ar H), 7.47–750 (m, 3 H, Ar H), 6.10 (br s, 1 H, NH), 3.49 dq, 2 H, CH_2), 1.26 (t, 3 H, CH_3). Anal. Calcd for $C_9H_{10}INO$: C, 39.30; H, 3.66; N, 5.09. Found: C, 39.50; H, 3.77; N, 5.08.

Preparation of 3-Bromo-*N*-ethylbenzamide-*N*-*d* (20b). To approximately 20 mL of dry CH_2Cl_2 was added 0.3065 g (0.0134 mol) of amide **27b**, 1 mL of D_2O, and 2 drops of pyridine. The reaction was stirred for 24 h. The phases were separated, and the organic layer was dried

(11) In these cases some reorientation within the complex would be required to bring the meta halogen near a reactive *n*-butyl group.

(12) For a recent example and leading references, see: Fraenkel, G.; Henrich, M.; Hewitt, M.; Su, B. M. *J. Am. Chem. Soc.* **1984**, *106*, 255.

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($MgSO_4$) and reduced to yield 0.3041 g (0.001 33 mol, 99%) of **20b** as a white solid, which is 92.26% deuteriated: mass spectrum (FI, M^+ (relative intensity)) m/e 232 (1331), 231 (15 207), 230 (144 498), 229 (52 503), 228 (151 675), 227 (37 736), 226 (830). The same procedure was used for deuteriation of the other amides.

Reactions of Amides with *n*-Butyllithium. To a solution of amide **20** dissolved in 20 mL of dry THF at −78 °C under N_2 was added the butyllithium via a syringe pump at the rate of approximately 1 mL/min. The reaction was stirred for 30 min and then quenched with 0.5 mL of MeOH. The solution was washed with water and extracted with ether. The ether extracts were combined, washed with brine, dried over $MgSO_4$, and reduced in vacuo to yield a mixture of **20** and **24**, which was analyzed by GC, separated, and purified if necessary. "Slow stirring" reactions are conducted with the agitation of a magnetic stir bar. "Fast stirring" reactions are conducted with an overhead mechanical stirrer.

Reaction of 2-Bromo-*N*-ethylbenzamide-*N*-*d* (20a d). To 0.1201 g (0.525 mmol) of amide **20a** d dissolved in 20 mL of dry THF at −78 °C under N_2 was added 0.42 mL of 1.26 M *n*-BuLi (0.525 mmol). The reaction mixture was stirred for 30 min and quenched with 0.5 mL of MeOH. Solution was washed with water and extracted with ether. Ether extracts were combined, washed with brine, dried over $MgSO_4$, and reduced in vacuo to yield an off-white solid mixture of 58% of **20a** and 42% of **24a** according to GC. The mixture was separated by MPLC with 30% EtOAc/hexane as eluent to yield 0.0609 g (0.267 mmol, 51%) of **20a** and a 0.0344 g (0.231 mmol, 44%) of **24a**. The mass spectrum showed **24a** to 94.11% deuteriated. Data from **20a**: ^1H NMR (200 MHz) δ 7.20–7.67 (m, 4 H, Ar H), 5.94 (br s, 1 H, NH), 3.48 (dq, 2 H, CH_2), 1.28 (t, 3 H, CH_3); GC (155 °C isothermal) t_R 2.63 min; mp 92–94 °C. Data from **24a**: ^1H NMR (200 MHz) δ 7.30–7.71 (m, 4 H, Ar H), 6.11 (br s, 1 H, NH), 3.50 (dq, 2 H, CH_2), 1.26 (t, 3 H, CH_3); ^{13}C NMR (300 MHz) δ 21.41, 45.26, 125.83, 126.10, 126.23, 130.66, 131.30, 139.46, 173.60; mass spectrum, (FI, M^+ (relative intensity)) m/e 147 (525), 148 (7060), 149 (42 486), 150 (464 758), 151 (54 158), 152 (4175).

Fast stirring: 0.1183 g (0.517 mmol) of amide was treated with 0.40 mL of 1.26 M *n*-BuLi (0.504 mmol) to yield 66% **20a** and 34% **24a**.

No stirring: 0.134 g (0.134 g (0.586 mmol) of amide was treated with 0.44 mL of 1.34 M *n*-BuLi (0.590 mmol) to yield 56% **20a** and 44% **24a**.

Acknowledgment. We are grateful to the National Institutes of Health and to the National Science Foundation for support of this work.

Supplementary Material Available: Experimental data for **20b–f** and the reaction of amides **1a–f** with *n*-BuLi (2 pages). Ordering information is given on any current masthead page.

Heterogeneous Catalytic Hydrogenation of Poly(vinylethylene)

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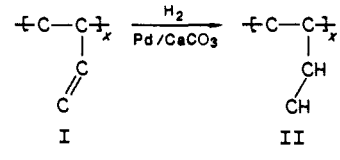
Abstract: The hydrogenation of poly(vinylethylene) in cyclohexane (1% w/v) at 70 °C with use of a calcium carbonate supported palladium catalyst has been investigated. Evaluation of partially hydrogenated polymer by size-exclusion chromatography and ^1H NMR spectroscopy reveals that this reaction initially proceeds by the concerted hydrogenation of approximately 85% of the unsaturated repeat units in individual polymer molecules during a single adsorption step from solution. This finding is qualitatively explained on the basis of the unique adsorption characteristics of polymers, in conjunction with the estimated heats of adsorption for unsaturated and saturated hydrocarbons on group VIII metal surfaces.

In recent years fully saturated hydrocarbon polymers have been recognized as outstanding materials for studying the fundamental physical properties of polymers in general. Perhaps the most successful route to obtaining monodisperse model polyolefins, which cannot be directly polymerized by any known method, is the hydrogenation of anionically polymerized dienes. This process imparts excellent oxygen, radiation, and thermal stability to unsaturated hydrocarbon polymers. Butadiene,[1-3] isoprene,[3,4] and 2-methyl-1,3-pentadiene[5] have been anionically polymerized by various researchers into a variety of microstructures, which have been shown to be easily transformable to the fully saturated form by hydrogenation in cyclohexane at approximately 70 °C, with use of a palladium catalyst supported on calcium carbonate.

We have recently implemented this hydrogenation method in our laboratory in order to prepare model saturated polymers for the investigation of isotope effects.[6] We discovered that this heterogeneous catalytic hydrogenation reaction proceeds by a mechanism that appears to be unique to polymers and describe here our initial findings concerning this mechanism, which is qualitatively shown to result from the general behavior of polymer solutions in contact with solid surfaces. We make use of the following model reaction in cyclohexane for this purpose:



I II

where I and II are referred to as poly(vinylethylene) (PVE) and poly(ethylethylene) (PEE), respectively, and x = 3070.

Experimental Section

Monodisperse poly(vinylethylene) was synthesized by using the anionic polymerization technique. Butadiene monomer (Matheson, instrument purity) was purified by successive distillation from dibutylmagnesium and *n*-butyllithium. Benzene (Aldrich) was distilled from polystyryllithium under purified argon just prior to use as the polymerization medium. The polymerization was initiated with *n*-butyllithium (Aldrich, 1.5 M) in the presence of 1,2-dipiperidinoethane (DPE) (Aldrich) at 6 °C; the ratio of DPE to lithium was 3. Polymerization of butadiene under these conditions has been shown to result in >99% 1,2 addition.[2] The reaction was terminated with degassed methanol, and the product was dried under vacuum and stored in a dark, purified argon environment.

Hydrogenation reactions were carried out in a 2-L Parr reactor at ca. 500 psi of hydrogen and at 70 °C. In all cases the concentration of PVE was 10 g/L of cyclohexane solution; the cyclohexane was distilled from potassium/benzophenone and stored under purified argon prior to use. A palladium catalyst dispersed on calcium carbonate (Strem Chemical Inc.; 5% by weight Pd; 5–10 $m^2\ g^{-1}$ active surface area) was employed at concentrations of 0.5, 1, and 1.8 g/g of polymer; these reactions will be referred to as A, B, and C, respectively. Reaction A was sampled 16

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