

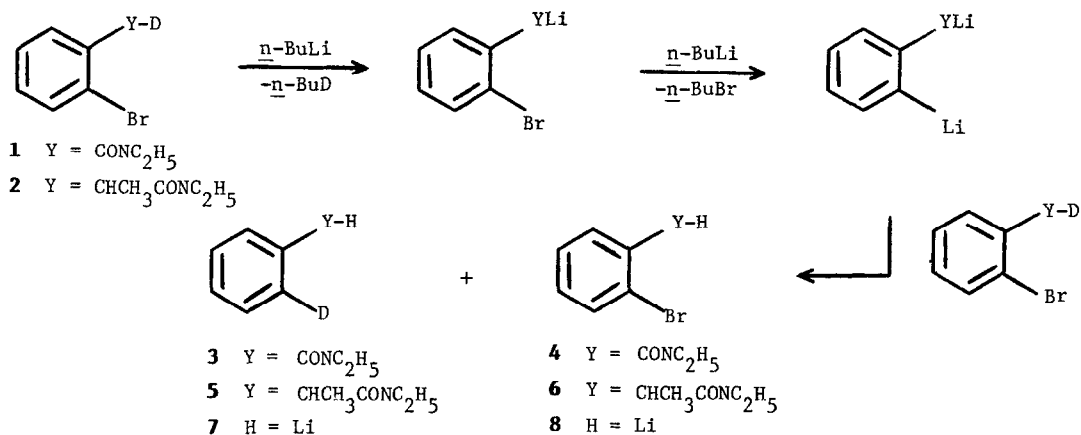
Relative Rates of Deprotonation and of Bromine-Lithium Exchange by
Organolithium Reagents: Interpretation of Some Deceptive Results

Peter Beak* and Chin-Wen Chen
Department of Chemistry
University of Illinois
Urbana, Illinois 61801

Abstract. Two reactions in which bromine-lithium exchange might be considered to be faster than deprotonation of an acidic deuterium on the basis of carbon deuterium labelling in the products, are suggested to involve initial dedeuteration followed by rapid bromine-lithium exchange and subsequent deuteration by a second molecule of deuterio acid.

Organolithium reagents are generally prepared by deprotonation of a carbon acid or halogen-metal exchange of an organohalide.¹ The relative rates of these reactions are of interest to studies of mechanism and for the synthetic use of these reactions in bifunctional molecules.² The possibility that halogen-metal exchange could be faster than deprotonation of a carboxylic acid is raised by the conversion of dimethyl-*o*-bromophenylacetic acid *O*-*d* to dimethyl-*o*-deuterophenylacetic acid on treatment with *t*-butyllithium.³ On the other hand, Parham, *et al* report that halogen-metal exchange of the rapidly formed lithium carboxylate salt of *o*-bromophenylacetic acid is slow at -100°⁴ and their other work is most consistent with deprotonation of acidic functions being faster than bromine-lithium exchange.

We have found that addition of one equivalent of *n*-butyllithium to the aryl bromide secondary amides **1** and **2**, respectively, gives the deuterioamides and aryl bromide amides **3-4** and **5-6** in 1:1 ratios and 75 and 73% yields, after aqueous work up. Our proposal for the mechanism of this conversion is shown in the reaction scheme. Initial dedeuteration at nitrogen is followed by formation of the dilithio derivative which then obtains a deuterium from **1** or **2** to give *o*-deutero and *o*-bromo lithium salts **7** and **8**, respectively. Protonation by water then provides **3-4** or **5-6**. The dilithiation appears to be promoted by a high local concentration of *n*-butyllithium. If the reaction of **1** is carried out by dilution of the *n*-butyllithium with ether prior to addition or by addition of **1** to a dilute solution of *n*-butyllithium, **4** is the sole product. The alternative of initial bromine-lithium exchange should be unaffected by dilution.



The point of present interest is that under this proposal lithiation and replacement of bromine by an acidic deuterium which is formally in the same molecule does not require that halogen-metal exchange to be faster than dedeuteration of the acidic function.⁵ While it is conceivable that halogen-lithium exchange could involve electron transfer and be faster than atom movement,⁶ until compelling evidence is presented, it appears that the deprotonation of strongly acidic functions by alkyl lithiums should be regarded as faster than bromine lithium exchange.

Acknowledgement. We are grateful to the National Institutes of Health and the National Science Foundation for support of this work and to Professor S. G. Smith for helpful discussions.

References and Notes

1. B. J. Wakefield "The Chemistry of Organolithium Compounds," Pergamon Press, Oxford, England, 1974, Chapter 2.
2. For examples of selective bromine lithium exchange in competition with potential addition reactions see: W. E. Parham and C. K. Bradsher, Accnts. Chem. Res. 1982, 15, 300.
3. R. J. Boatman, B. J. Whitlock and H. W. Whitlock, Jr., J. Am. Chem. Soc. 1977, 99, 4822.
4. W. E. Parham, L. D. Jones, and Y. Sayed, J. Org. Chem., 1975, 40, 2394.
5. In our hands, lithiation of dimethyl-*o*-bromophenylacetic acid *O*-d provides equivalent amounts of *o*-deutero and *o*-bromo acids suggesting a similar sequence.
6. Such cases may exist. Reactions in which greater than 50% yields of dehalogenated acids are obtained with 1 eq. of lithiating reagent have been reported: E. C. Taylor and D. E. Vogel, J. Org. Chem. 1985, 50, 1002 and C. D. Stein and T. H. Morten, Tetrahedron Lett. 1973, 4933. The titer of the lithiating reagent is critical in such cases.

(Received in USA 3 July 1985)