(100 ml) was added, and the aqueous layer was separated, acidified with 100 ml of 10% HCl, and extracted twice with ether. The combined ether extracts were dried over MgSO$_4$ and stripped to give 0.52 g (44%) of 3-carboxyl-*N*,*N*-diethyl-2-thiophenesulfonamide (**5**), mp 147–149°.

The original ether layer was dried over MgSO$_4$ and stripped to give 0.30 g (22% recovery) of starting material whose ir spectrum was superimposable on that of sulfonamide **4**.

The ir spectrum of compound **5** (Nujol) exhibited bands at 3000–2450, 1715 (COOH), 1340, 1140 cm^{-1} (–SO$_2$N<); nmr (DMSO-d_6) δ 1.07 (t, 6, CH$_3$), 3.40 (q, 4, CH$_2$), 7.55, 8.05 (AB, J_{AB} = 4.9 Hz, 2, aromatic CH).

Anal. Calcd for C$_9$H$_{13}$NO$_4$S$_2$: C, 41.05; H, 4.98; N, 5.32. Found: C, 41.03 (41.40); H, 5.01; N, 4.79 (4.96).

Metalation of *N*,*N*-Diethyl-2-thiophenesulfonamide.—To a solution of *N*,*N*-diethyl-2-thiophenesulfonamide (2.0 g, 0.0093 mol) in 50 ml of dry ether under argon was added 6.3 ml (0.01 mol) of 1.6 *M* *n*-butyllithium with stirring. After 1 hr, the contents of the reaction flask was quickly added to a slurry of excess Dry Ice in ether. The mixture was later hydrolyzed with 100 ml of water. Solid NaOH was added until the mixture was strongly basic. The aqueous layer was separated, washed once with ether, and then neutralized with 10% HCl. Ether extracts of the neutralized aqueous layer were dried over MgSO$_4$ and stripped to give 1.97 g (82%) of 5-carboxyl-*N*,*N*-diethyl-2-thiophenesulfonamide. Recrystallization from dry ether gave an analytical sample: mp 128–130°; ir (Nujol) 2700–2450, 1700 (COOH), 1360, 1145 cm^{-1} (–SO$_2$N<).

Anal. Calcd for C$_9$H$_{13}$NO$_4$S$_2$: C, 41.05; H, 4.98; N, 5.32. Found: C, 41.04; H, 4.89; N, 5.14.

B. Condensation with Deuterium Oxide.—Lithio intermediate **4′** was prepared as described at the beginning of this section using 2.0 g (0.007 mol) of sulfonamide **4**, 5.0 ml (0.008 mol) of 1.6 *M* *n*-butyllithium in hexane, and 0.90 g (0.008 mol) of TMEDA. After being stirred for 6 hr, the reaction mixture was hydrolyzed with 1.0 ml of D$_2$O. The ether layer was separated, washed with H$_2$O, dried over MgSO$_4$, and stripped. The resulting oil was vacuum distilled to give 1.4 g (70% recovery of material), bp 130–132° (0.65 mm). An nmr spectrum indicated that 1.0 deuterium atom was incorporated into the aromatic ring by the absence of a proton resonance corresponding to the chemical shift of the downfield ring proton (δ 7.50) in the undeuterated sulfonamide **4**. The ir spectrum of deuterated sulfonamide **4** was identical with that of the starting material. The C–D stretching vibration that should be present for this compound was not in evidence on an instrument with the sensitivity of the Infracord 137.

C. Condensation with Dimethylformamide.—To a solution of TMEDA (0.70 g, 0.006 mol) in 30 ml of dry ether was added 3.8 ml (0.006 mol) of 1.6 *M* *n*-butyllithium in hexane under argon. After being stirred for 15 min, the reaction mixture was cooled to 0°, sulfonamide **4** (1.45 g, 0.005 mol) was added, and the mixture was stirred for 24 hr at 0–4°. Dimethylformamide (0.88 g, 0.012 mol) was added to the mixture and stirred for 6 hr. After the reaction mixture was hydrolyzed, the ether layer was separated, combined with ether extracts of the aqueous layer, dried over MgSO$_4$, and stripped. Vacuum distillation of the resultant crude oil gave 0.10 g of a yellow oil boiling at 80–82° (1.25 mm) and 0.39 g of a product mixture boiling at 156° (1.25 mm). Ir and nmr spectra for the first fraction did not conform with any predicted product or products; ir spectrum showed bands at 2910, 1240, 1000, 833, and 745 cm^{-1}; nmr (CDCl$_3$) δ 1.05–1.53 (m, 8.5 H), 2.40–3.00 (m, 2.2 H), 6.76 (s, 1, aromatic CH).

An nmr analysis of the second fraction showed it to be 43% starting sulfonamide **4** and 57% 5-trimethylsilyl-3-formyl-2-*N*,*N*-diethylthiophenesulfonamide (**6**) by comparison of the relative peak areas at 7.50 ppm for **4** and 10.30 ppm for compound **6**. The nmr data corresponded to 12% recovery and a 14% yield, respectively, of the two compounds. An ir spectrum for the mixture showed bands at 1695 (C=O), 1330, and 1140 cm^{-1} (SO$_2$N); nmr (CCl$_4$) δ 0.37 [s, unresolved, Si(CH$_3$)$_3$], 1.20 (t, unresolved, CH$_3$), 3.27 (q, unresolved, CH$_2$), 7.50 (d, J_{34} = 3.5 Hz, aromatic CH), 7.58 (s, aromatic CH), 10.30 (s, CHO).

An unsuccessful attempt was made to separate the mixture on a 30-ft preparative scale gas chromatographic column containing Carbowax 4000.

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Registry No.—**1**, 41895-02-7; **2**, 41895-03-8; **3**, 41895-04-9; **3** methiodide derivative, 41895-05-0; **4**, 41895-06-1; deuterated **4**, 41895-07-2; **5**, 41895-08-3; **6**, 41895-09-4; *N*,*N*-dimethyl-2-thiophenesulfonamide, 41895-10-7; dimethylamine, 124-40-3; chlorotrimethylsilane, 75-77-4; diethylamine, 109-89-7; *N*,*N*-diethyl-2-thiophenesulfonamide, 41895-11-8; 5-carboxy-*N*,*N*-diethyl-2-thiophenesulfonamide, 41895-12-9; dimethylformamide, 68-12-2.

Complexation as a Factor in Metalation Reactions. Metalation of 1-Methoxy-2-phenoxyethane

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The effect of side-chain chelation on the rate of metalation of aryl rings by *n*-butyllithium was investigated by allowing anisole and 1-methoxy-2-phenoxyethane (MPE) to compete for excess base. The ratio of MPE to anisole metalation was found to be 13.9:1 and 14.4:1 in ether and hexane, respectively. MPE gave phenol and phenyl vinyl ether as minor products during the reaction. Labeling experiments showed the phenol to be derived from both inter- and intramolecular routes. Evidence for a 2:1 complex between *n*-butyllithium and MPE was presented.

The metalation reaction continues to attract attention both with regard to the mechanism of proton removal as well as synthetic utility.[1] In the latter context we became interested in the relative importance of heteroatom chelation as a directing and activating influence during the metalation of aromatics. Here we report a quantitation of this effect for oxygen in the metalation of benzene rings by *n*-butyllithium.

During the past few years evidence has been accumulating which clearly shows that heteroatoms either in the solvent or on reactants enhance the reactivity of lithium alkyls and influence site selection for proton removal. Thus, while generally unreactive to *n*-butyllithium, benzene can be quantitatively metalated by this base in the presence of simple tertiary amines.[2] Good chelating bases such as sparteine or

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(1) J. M. Mallan and R. L. Bebb, *Chem. Rev.*, **69**, 693 (1969).

(2) C. G. Screttas and J. F. Eastham, *J. Amer. Chem. Soc.*, **87**, 3276 (1965).

N,N,N′,N′-tetramethylethylenediamine are especially effective and the degree of enhanced reactivity was found to be proportional to base strength.[3] Similarly, chelation of ethers has been invoked to explain the fragmentation of self-associated lithium alkyls to smaller and more reactive species.[4]

Prior coordination of the lithium alkyl to a substituent heteroatom appears to explain the selective ortho metalation of γ-phenylpropyldimethylamine by *n*-butyllithium[5a] as well as similar results observed with dimethylaminomethylferrocenes,[5b] alkoxymethylferrocenes,[5c] and related thiophenes.[5d] In the case of *p*-methoxybenzyldimethylamine, proton removal occurs at the position meta to the methoxyl group in spite of the virtually selective metalation of anisole at the ortho position.[6]

This situation is not universally true, however, since triphenylamine has been shown to meta metalate[7] and ethylphenyl sulfide yielded as much as 18.5% of meta proton removal.[8] Further, while prior coordination of the base should be reflected in a steric hindrance effect due to alkyl substituents on the heteroatom, a competitive metalation of anisole and phenyl *tert*-butyl ether using *tert*-butyllithium showed no difference in metalation rate.[9] On the other hand, what appears to be a distinct steric effect in the metalation of *o-tert*-butylanisole has recently been observed.[10] Alternate explanations for site-selective metalation and increased reactivity in aromatics include enhanced inductive effects operating on the ortho carbon due to electronegative substituents[7] and a multistep free-radical mechanism.[9]

The work described here was aimied at studying the influence of chelation under careful control of variables. It was reasoned that a good measure of the effect of reagent chelation would be obtained by keeping the electronic characteristics of the aryl ring constant while varying the chelating ability of the ring substituent.

Experimental Section

Nmr spectra were obtained on a Varian A-60A instrument with chemical shifts in δ units relative to internal tetramethylsilane. Deuterium incorporation was determined by mass spectrometry using a Finnigan 1015 instrument coupled to a Varian 1700 gas chromatograph. Errors in these measurements were estimated as ±1%. Quantitative analysis of product mixtures was accomplished with a Varian Aerograph 1800 instrument with flame ionization detectors and a 6 ft × 0.125 in. 10% Apiezon L column at 200°. Infrared spectra were recorded on neat films using a Beckman IR-5A instrument.

n-Butyllithium in hexane (15.03 and 21.4%) was obtained from Matheson Coleman and Bell and Alfa Inorganics Inc., respectively. The concentration was determined by a previously described method.[11] Lithium aluminum hydride and lithium aluminum deuteride ($LiAlD_4$) were obtained from Alfa Inorganics Inc. 2-Phenoxyethanol and 2,3-benzofuran were obtained from Aldrich Chemical Co. and were purified by distillation. Phenoxyacetic acid was obtained from Eastman Organic Chemicals. Pyridine was purified before use by distillation from barium oxide.

Preparation of 1-Methoxy-2-phenoxyethane-*1,1-d*$_2$ (MPE-*1,1-d*$_2$).—To a solution of 10 g (58.0 mmol) of *p*-toluenesulfonic acid in 500 ml of benzene was added 15.2 g (0.1 mol) of phenoxyacetic acid and 17.6 ml (0.3 mol) of absolute ethanol. The reaction mixture was refluxed with continuous removal of water until no further water evolution was evident (2 hr) and then concentrated by evaporation *in vacuo*. The concentrate was added to saturated sodium carbonate and extracted twice with ether. The ether extracts were combined, dried with magnesium sulfate, and evaporated *in vacuo* until free of solvent, affording 13.6 ml (83.5 mmol, 83.5%) of phenoxyacetic acid ethyl ester which was 100% pure by glc, and characterized in the ir by the absence of a carboxylic acid peak and the presence of strong unconjugated ester peaks at 1725 and 1200 cm^{-1}.

To 50 ml of diethyl ether in a flame-dried 100-ml three-necked round-bottomed flask fitted with a reflux condenser was added 0.575 g (13 7 mmol) of $LiAlD_4$. To this mixture a 25-ml diethyl ether solution of 3 ml (18.3 mmol) of the above-prepared phenoxyacetic acid ethyl ester was slowly added *via* a dropping funnel and then allowed to reflux for 24 hr. After the reaction was complete, a saturated water solution of Rochelle salt was added dropwise to the reaction vessel until precipitation was initiated. The reaction mixture was filtered and the residue was washed twice with ether. The ether layers were combined, dried with magnesium sulfate, and evaporated *in vacuo* at room temperature until free of solvent. The crude product was redistilled under high vacuum, affording 1.952 g (76%) of 2-phenoxyethanol-*1,1-d*$_2$ which was 100% pure on glc and characterized by ir and nmr comparisons with an authentic sample of 2-phenoxyethanol.

To a flame-dried flask containing 0.70 g (16.7 mmol) of a sodium hydride suspension in oil was added 30 ml of dimethoxyethane (DME) after several prior washings of the hydride suspension with DME to remove excess oil. Once a fine suspension was achieved, a 20-ml DME solution of 1.952 g (13.9 mmol) of the above-prepared 2-phenoxyethanol-*1,1-d*$_2$ was added with an oven-dried syringe. After 1 hr a 10-ml DME solution of 1.04 ml (16.7 mmol) of iodomethane was added to the flask with an oven-dried syringe and the reaction was allowed to reflux overnight. The unreacted sodium hydride was decomposed by a dropwise addition of saturated aqueous ether. The reaction mixture was added to water and extracted three times with ether. The ether layers were combined, dried with magnesium sulfate, and evaporated *in vacuo* until free of solvent. The crude isolated product was distilled under high vacuum, affording 1.875 g (87%) of 1-methoxy-2-phenoxyethane-*1,1-d*$_2$ which was 100% pure on glc: nmr (CCl_4) δ 4.00 (s, 2, OCH_2CD_2–), 3.34 (s, 3, OCH_3), and 6.7–7.4 (m, 5, phenyl H).

The 3350-cm^{-1} band was absent from the ir spectrum. The molecular weight was determined by mass spectrometry to be 154 with nearly quantitative incorporation of two D atoms.

Preparation of 1-Methoxy-2-phenoxyethane (MPE).—Using the above procedure MPE was prepared in 90% yield from 2-phenoxyethanol. The isolated product was 100% pure by glc: nmr (CCl_4) δ 4.04 (t, 2, $C_6H_5OCH_2$–), 3.65 (t, 2, CH_2OCH_3), 3.37 (s, 3, OCH_3), 6.7–7.4 (m, 5, phenyl H). The 3350-cm^{-1} hydroxyl peak was absent from the ir spectrum.

Preparation of Coumaran (2,3-Dihydrobenzofuran).—A 5-ml solution of 0.250 g (2.12 mmol) of 2,3-benzofuran in glacial acetic acid was added to a dry 100-ml round-bottomed hydrogenation flask containing a 20-ml solution of 0.500 g of 5% Pd/C in glacial acetic acid and under hydrogen at atmospheric pressure and temperature. The reactants were stirred vigorously until 47.5 ml (2.12 mmol) of hydrogen gas was consumed (~4.5 hr). The reaction mixture was filtered through Kieselguhr, neutralized with saturated sodium carbonate, and extracted four times with ether. The diethyl ether layers were combined, dried with magnesium sulfate, and evaporated *in vacuo* at room temperature until free of solvent. The crude isolated product was distilled, affording 0.113 g (44%) of coumaran: bp 104° (0.1 mm); nmr ($CDCl_3$) δ 3.18 (t, 2, $CH_2C_6H_4$), 4.56 (t, 2, $C_6H_4OCH_2$), and 6.7–7.4 (m, 4, C_6H_4).

Anal. Calcd for C_8H_8O: C, 79.97; H, 6.71. Found: C, 79.93; H, 6.76.

Preparation of Phenyl Vinyl Ether.—(2-Chloroethoxy)benzene was prepared by a modification of the method of Brooks and

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[4] H. L. Lewis and T. L. Brown, *J. Amer. Chem. Soc.*, **92**, 4664 (1970).

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[9] D. A. Shirley and J. P. Hendrix, *J. Organometal. Chem.*, **11**, 217 (1968).

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Snyder.[12] Into a flame-dried flask fitted with a reflux condenser and containing 36.4 ml (0.29 mol) of 2-phenoxyethanol and 25.6 ml (0.32 mol) of pyridine cooled with an ice bath was slowly added 21.6 ml (0.30 mol) of thionyl chloride with an oven-dried syringe. Once addition was complete, the ice bath was removed and the reaction was allowed to proceed with continuous stirring for 12 hr. The reaction mixture was added to 300 ml of ether and washed with saturated aqueous sodium carbonate and twice with water. The ether layer was dried with magnesium sulfate and evaporated *in vacuo* until free of solvent. The crude product was distilled under high vacuum, affording 37.42 g (82.5%) of (2-chloroethoxy)benzene which was 100% pure by glc and had an nmr spectrum identical with that of a reference spectrum.[13]

This product was treated with powdered KOH according to the method of Fauer and Spielman[14] to give an oil which was purified by distillation: bp 147–153° (760 mm); nmr ($CDCl_3$) δ 4.42 (1 H, d, d, J = 6, 1.5 Hz), 4.77 (1 H, d, d, J = 14, 1.5 Hz), 6.62 (1 H, d, d, J = 14, 6 Hz), 7.15 (5 H, m); mass spectrum m/e (rel intensity) 120 (49), 91 (100), 39 (75), 27 (78).

General Metalation Procedure.—All experiments involving *n*-butyllithium were performed in flame-dried, three-neck, 100-ml, round-bottomed flasks fitted with serum caps. The reactions were run at room temperature with a positive pressure of argon being maintained in the flasks throughout the reaction period. *n*-Butyllithium in hexane solution was delivered to the flasks by means of an oven-dried standard B-D Yale type syringe. After 2 hr reactions were quenched with D_2O (99.7%, Merck and Co.) and added to 50 ml of 1 *N* HCl, then extracted four times with ether. The ether extracts were combined, dried over magnesium sulfate, and evaporated *in vacuo* at room temperature. Control experiments showed no incorporation of deuterium into phenol under these quenching conditions.

The following metalation experiments were conducted using the quantities and times indicated. The yields of isolated products were obtained by glc and combined glc–mass spectrometry.

Anisole.—Anisole (0.356 g, 3.57 mmol), ether (50 ml), and *n*-butyllithium (3 ml, 2.1 *M*, 6.2 mmol) were used. The recovered anisole (0 349 g, 97%) contained 29.5% anisole-d_1.

1-Methoxy-2-phenoxyethane (MPE) in Ether.—MPE (0.542 g, 3.57 mmol), ether (50 ml), and *n*-butyllithium (2 ml, 2.1 *M*, 4.2 mmol) were used. The product mixture (0.491 g) contained phenyl vinyl ether, 0.034 g (0.287 mmol, 8.1%), phenol, 0.039 g (0.417 mmol, 11.7%), and MPE, 0.418 g (2.74 mmol, 77%) containing 67.5% MPE-d_1. Total recovered material (mmol) was 96.8%.

MPE in Tetrahydrofuran (THF).—MPE (0.152 g, 1.0 mmol), THF (50 ml), and *n*-butyllithium (0.66 ml, 1.67 *M*, 1.1 mmol) were used. The recovered MPE (86%) contained less than 1% MPE-d_1.

1-Methoxy-2-phenoxyethane-*1,1-d*$_2$ (MPE-*1,1-d*$_2$) in Ether.—MPE-*1,1-d*$_2$ (0.432 g, 2.8 mmol), ether (50 ml), and *n*-butyllithium (2 ml, 1.67 *M*, 3.34 mmol) were used. The product mixture (0.380 g) contained phenyl vinyl ether-d_2, 0.032 g (0.264 mmol, 9.4%), phenol, 0.006 g (0.064 mmol, 2.3%) containing 15.7% phenol-d_1, and MPE, 0.341 g (2.204 mmol, 79%) containing MPE-d_2 (37.3%) and MPE-d_3 (62.7%). Total recovered material (mmol) was 90.7%.

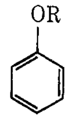
MPE-*1,1-d*$_2$ in Hexane.—MPE-*1,1-d*$_2$ (0.432 g, 2.80 mmol), hexane (50 ml), and *n*-butyllithium (2 ml, 1.67 *M*, 3.34 mmol) were used. The recovered product mixture (0.378 g) contained phenol, 0.045 g (0.48 mmol, 17.1%) containing 2.5% phenol-d_1, MPE, 0.290 g (1.90 mmol, 68%) containing MPE-d_2 (59.5%) and MPE-d_3 (40.5%), and unknown, 0.043 g. No phenyl vinyl ether was detected. Total recovered material (material balance) was 87.5%.

Competition between MPE and Anisole in Ether.—MPE (0.542 g, 3.57 mmol), anisole (0.386 g, 3.57 mmol), ether (50 ml), and *n*-butyllithium (2 ml, 2.1 *M*, 4.2 mmol) were used. The product mixture (0.750 g) contained anisole, 0.314 g (2.90 mmol, 79%) containing 4.0% anisole-d_1, phenol, 0.039 g (0.417 mmol, 11.7%), phenyl vinyl ether, 0.034 g (0.287 mmol, 8.05%), and MPE, 0.393 g (2.59 mmol, 72.6%) containing 66.0% MPE-d_1. Total recovered material (mmol) was 87%.

Competition between MPE and Anisole in Hexane.—MPE (0.425 g, 2.80 mmol), anisole (0.302 g, 2.80 mmol), hexane (50 ml), and *n*-butyllithium (2 ml, 1.67 *M*, 3.34 mmol) were used. The recovered product mixture consisted of anisole, 0.255 g (2.36 mmol, 84.3%) containing 2.0% anisole-d_1, phenol, 0.061 g (0.65 mmol, 23%), MPE, 0.310 g (2.03 mmol, 72.5%) containing 39.0% MPE-d_1, and unknown, 0.034 g. Total recovered material (mmol) was 90%.

Results and Discussion

Anisole and 1-methoxy-2-phenoxyethane (MPE, 2) were chosen for comparison in order to maintain aromatic rings which were comparable electronically while at the same time displaying differences in complexing ability of the substituent heteroatoms. The vicinal oxygen atoms in 2 might be expected to behave somewhat like 1,2-dimethoxyethane.[15] Since 1 metalates almost exclusively in the ortho position,[16] the chelation effect, if any, would be reflected in an enhanced reactivity for 2 which could be quantitated by competition with 1 for base.



1, R = CH_3
2, R = $CH_2CH_2OCH_3$

Metalation of 1.—Treatment of **1** with excess *n*-butyllithium in ether for 2 hr followed by quenching with deuterium oxide gave a 97% recovery of anisole of which 29.5% was monodeuterated. No bisdeuterated material was detected. Under the same conditions in tetrahydrofuran (THF) only a trace of metalated product was detected reflecting the competing decomposition of THF by *n*-butyllithium.

Metalation of 2.—The analogous metalation of **2** proved to be more complex than anticipated but could be analyzed to provide data for the competition study. Thus, treatment of **2** with 1.2 molar equiv of *n*-butyllithium in ether followed by quenching with deuterium oxide gave phenol and phenyl vinyl ether (**10**) as products in addition to MPE-d_1. The results are shown in Table I and the corresponding pathways are presented in Scheme I. The position of metalation in **4**

SCHEME I

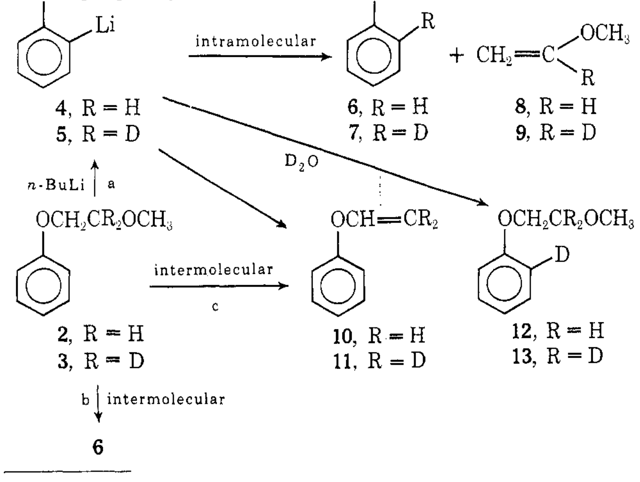


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TABLE I

METALATION OF MPE (2) AND MPE-d_2 (3)

MPE (2)		MPE-d_2 (3)		
Product	% yield (% D incorpn)[a,b] of ether	Product	% yield (% D incorpn)[a,b] Ether	Hexane
MPE	77.0 (67.5)	MPE-*1,1*-d_2	79.0 (62.7)	68.0 (40.5)
Phenol	11.7 (0)	Phenol	2.3 (15.7)	17.1 (2.5)
Phenyl vinyl ether	8.1	Phenyl vinyl ether-d_2	9.4	0

[a] The reaction was quenched with D_2O. [b] Isotope composition was determined by combined glc–mass spectrometry.

and 5 was assumed to be ortho in analogy with anisole. The structure of phenyl vinyl ether was verified by chromatographic and spectrographic comparison with an authentic sample unambiguously prepared. Since the fragmentation products could arise from either intra- or intermolecular elimination (see Scheme I) it was necessary to distinguish between these two routes. This was accomplished by metalation of the bisdeuterated analog of 2 (3). From this reaction the extent of aryl metalation was determined from the sum of all products derived from the intermediate anion 5 (*i.e.*, 7 + 13 + intramolecularly derived 11). A blank run showed that under the work-up conditions 7 could only arise *via* intramolecular deuterium exchange.

With ether as solvent, intramolecular phenol formation (3 → 5 → 7) proceeded to the extent of 15.7% and this value was accepted as valid for the same reaction with 2. The lower yield of phenol from 3 as opposed to 2 is ascribed to the deuterium isotope effect during elimination. With the compounds at hand it was not possible to determine the amount of 11 obtained from 5. However, in spite of the different transition states involved, this was taken to be comparable with that for 7 derived from 5 (*i.e.*, 15.7%). Owing to the relatively small amount of phenyl vinyl ether obtained, this assumption does not seriously affect the results. On this basis total metalation of 2 was found to exceed intermolecular elimination by a factor of 3.1. This result and those from the competition experiments below are valid only if some *n*-butyllithium remains when the reaction is quenched; otherwise 7 would continue to accumulate at the expense of 6. That this is the case is evidenced by the fact that *n*-butyllithium is stable to diethyl ether under the reaction conditions[17] and that less than 1 equiv of material was treated with the base.

When the same reaction was conducted in hexane as solvent the amount of phenol derived from intramolecular elimination was some six times less than in ether, although the overall production of phenol was greater. Interestingly, no 11 was formed but rather a small amount of a new product which was not identified. One possible product is 2,3-dihydrobenzofuran. However, comparison of the gas chromatographic retention time of the product with that of synthetically prepared material showed this not be the case. Generally however, the results in hexane were similar to those in ether.

Competitive Metalation.—The results of allowing equimolar amounts of 1 and 2 to compete for an excess of *n*-butyllithium in both ether and hexane are shown in Table II. The ratio of MPE metalation to that of anisole was found to be 13.9:1 and 14.4:1 in the respective solvents, although the presence of a small amount of unidentified product in the hexane run makes that value somewhat uncertain. It is clear, however, that the presence of the second oxygen atom in the side chain significantly influences the rate of metalation of the aryl ring.

TABLE II

COMPETITION OF ANISOLE AND MPE FOR *n*-BUTYLLITHIUM

Product	% yield (% D incorpn)[a] Ether	Hexane
Anisole	79 (4.0)	84.3 (2.0)
MPE	72.6 (66.0)	72.5 (39.0)
Phenol	11.7 (15.7)	23.2 (2.5)
Phenyl vinyl ether	8.1	0[b]
% total MPE metalation	55.6[c]	28.7[d]

[a] Yields were determined by combined glc–mass spectrometry. [b] A small amount of unidentified material was also detected. [c] Calculated as recovered MPE-d_1 + 0.157 × recovered (6 + 10) and then normalized to 100%. [d] Based on 95.7% material balance.

The change in solvent from ether to hexane does not significantly alter the ratio of metalation rates but does result in a twofold decrease in overall rate for both 1 and 2.

Evidence for Complexation.—In order to obtain evidence for a complex between *n*-butyllithium and 2, increasing quantities of 2 were added to *n*-butyllithium in hexane and the chemical shift of the methylene protons α to lithium was observed. This technique has been used to demonstrate the existence of a 1:1 complex between *n*-butyllithium and 1.[18] The results are shown in Table III. Starting from −50.5 Hz a maximum upfield shift is observed at −57.0 Hz at a molar ratio of MPE to base of 1:2. This stoichiometry has previously been observed for the complex between *n*-butyllithium and diethyl ether.[19] Unlike the latter case, further addition of MPE caused a decrease in the observed chemical shift. This is possibly due to the intervention

TABLE III

COMPLEXATION OF MPE (2) WITH *n*-BUTYLLITHIUM IN HEXANE

Expt	[MPE] × [*n*-BuLi][c]	[MPE]/[*n*-BuLi]	Observed chemical shift, Hz[a,b] *n*-BuLi	*n*-BuLi + MPE
1	0.543	0.25	−50.5	−54.6
2	0.550	0.33	−50.5	−56.5
3	0.545	0.50	−50.5	−57.0
4	0.546	1.0	−50.5	−54.0
5	0.552	2.0	−51.0	−52.5

[a] Methylene protons α to Li. [b] Relative to internal tetramethylsilane. [c] The rate of metalation (k[MPE][*n*-BuLi]) was held constant and values were read at the same time into the run.

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(17) G. E. Coates, M. L. H. Green, and K. Wade, "Organometallic Compounds, Vol. 1. The Main Group Elements," 3rd ed, Methuen, London, 1967, p 9.

(18) R. A. Ellison and F. N. Kotsonis, *Tetrahedron*, **29**, 805 (1973).

(19) Z. K. Cheema, G. W. Gibson, and J. F. Eastham, *J. Amer. Chem. Soc.*, **85**, 3517 (1963).

of new equilibria, but no further evidence is available on this point.

The rapid reaction of **2** with *n*-butyllithium was evident from observation of the nmr spectrum in the region downfield from tetramethylsilane. Shortly after addition of **2** a new singlet appeared upfield from that assigned to MPE which was attributed to the methoxyl protons of the metalated derivative. During the course of the reaction both singlets gradually moved upfield, indicating that these species were also involved in changing equilibria. Because the chemical shift of the methylene protons α to lithium also changed with time, it was necessary to adjust concentrations of *n*-butyllithium and **2** so as to maintain a constant reaction rate for all spectra and to record each at the same time into the run.

While the details are undoubtedly complex, it seems likely that the 14-fold increase in reactivity of **2** relative to **1** can be explained in part by the change in base-ether ratio from 1:1 in the case of **1** to 2:1 in the case of **2**.

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Registry No.—**1**, 100-66-3; **2**, 41532-81-4; **3**, 41894-71-7; **10**, 766-94-9; phenoxyacetic acid, 122-59-8; phenoxyacetic acid ethyl ester, 2555-49-9; 2-phenoxyethanol-*1,1*-d_2, 21273-38-1; 2-phenoxyethanol, 122-99-6; 2,3-benzofuran, 271-89-6; 2,3-dihydrobenzofuran, 496-16-2; (2-chloroethoxy)benzene, 622-86-6.

1-Butanol–Hydrogen Chloride. An Allegedly Anhydrous Esterification Reagent

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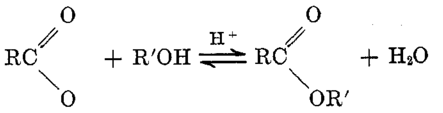
The stability of a common Fischer esterification reagent used extensively for preparation of amino acid and carboxylic acid esters, 2.1 *M* HCl-1-butanol, has been studied in detail. After 2 hr at 100 and 150°, the concentrations of 1-chlorobutane, di-1-butyl ether, and water in this reagent are 0.71, 0.04, and 0.75, and 2.36, 0.22, and 2.58 *M*, respectively. Approximate rate constants for formation of these products at 100 and 150° have been determined. It is concluded that esterifications with this reagent should be carried out below 100° to achieve best yields. An equilibrium constant of 0.15 ± 0.03 has been measured in the esterification of a typical aliphatic amino acid, leucine. The significance of the production of water in this esterification reagent is discussed especially in light of its use in amino acid esterification procedures where the carboxylic acid concentrations may be at the millimolar or lower concentration level.

The importance of amino acid chemistry and general lack of detailed quantitative studies of amino acid esterification reactions suggested to us that the latter problem deserves more extensive investigation. Herein we describe an investigation of some of the properties of the Fischer esterification reagent, 1-butanol–hydrogen chloride in our case, or in general an alcohol mixed with a strong acid, and its use for esterification of amino acids.

The Fischer esterification procedure for carboxylic acids was introduced in 1895[1] and synthetic procedures for esterification of amino acids by this method were published in 1901.[2] The mechanism of the reaction has been widely investigated and discussions of it may be found in most organic chemistry tests.[3] It is well known that, for equimolar quantities of reactant, the equilibrium in this reaction lies quite short of completion. To obviate this, an excess of alcohol or acid, product removal by distillation, or addition of a water scavenger is generally employed to shift the equilibrium in favor of the product.[3]

Recently, methods have been reported[4-8] utilizing Fischer esterification, usually with 1-butanol–HCl, and subsequent trifluoroacylation to render amino acids amenable to quantitative analysis by gas chromatography. Examination of the literature indicates that little systematic investigation has been directed toward the esterification reaction at concentration levels usually encountered in amino acid analysis. The quantitative yield of volatile amino acid derivatives is dependent upon the reproducibility and completeness of the derivatization reactions. Equilibrium constants, concomitant reactions of the esterification reagent, and the relationship of these to the total reaction become, therefore, important considerations in these analytical procedures and should be considered in any syntheses involving an expensive and/or small amount of carboxylic acid.

With few exceptions,[9,10] the esterification reagent has been generally considered anhydrous in that it contributes little or no water to the reaction. On this basis, it has been accepted that maximum water concentration at equilibrium would be equal to amino acid ester concentration according to eq 1. With a carboxylic acid



$$\mathrm{RC}\substack{/\!\!/\mathrm{O}\\ \diagdown\mathrm{O}} + \mathrm{R'OH} \overset{\mathrm{H^+}}{\rightleftharpoons} \mathrm{RC}\substack{/\!\!/\mathrm{O}\\ \diagdown\mathrm{OR'}} + \mathrm{H_2O} \qquad (1)$$

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