

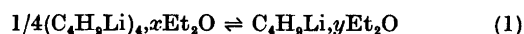
Association of Butyllithium in Diethyl Ether and in Tetrahydrofuran

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Butyllithium exists in diethyl ether and in tetrahydrofuran (THF) as an unreactive tetramer in a dynamic equilibrium with the reactive monomer. The study and interpretation of the kinetics of the reaction between butyllithium and the solvents at high dilution and between butyllithium and two selected substrates show that the equilibrium constant for the monomer-tetramer equilibrium is of the order of $10^{-4} \text{ mol}^3 \text{ l}^{-3}$ in THF and $10^{-16} \text{ mol}^3 \text{ l}^{-3}$ in diethyl ether, and that dissociation into monomer is substantial below 10^{-2} M in THF, but insignificant at 10^{-4} M in diethyl ether. The endothermicity of the dissociation of butyllithium in diethyl ether is of the order of 20 kJ mol^{-1} of monomer and ΔG° for the dissociation is of the same magnitude meaning that the $T\Delta S^\circ$ contribution is low. The high reactivity of butyllithium when dissolved in THF or other strongly coordinating solvents as compared with the ethereal solution is due to the much higher concentration of monomer obtained since a calculation shows that THF-coordinated monomer is of the order of 15–20 times less reactive toward the substrates studied than ether-coordinated monomer.

It is well-established that butyllithium exists in ether solution as a tetramer aggregate, as shown by, *e.g.*, vapor pressure measurements.¹ It is also believed that a fast equilibrium

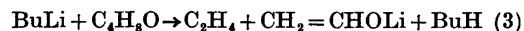
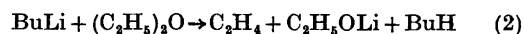


[eqn. (1)] exists between the tetramer and the monomer since a fractional kinetic order (0.25 to 0.33) with respect to butyllithium is a common finding in the reactions of the reagent with various substrates.^{2,3} This fact is explained if in eqn. (1) only the monomer has significant reactivity. For butyllithium in tetrahydrofuran traditional vapor pressure measurements are

not possible, but since fractional order kinetics have been observed it was suggested² that a tetramer-monomer equilibrium like eqn. (1) describes the situation even in this solvent.

The theory described, although very attractive, is not universally accepted⁴ and needs further experimental support. No information has been obtained about the position of a possible association equilibrium except that the concentration of monomer must be very low.

A useful route to the study of the problem seemed to be to study the reactivity of the reagent at very low concentrations since according to the laws of dilution the observed fractional order kinetics will change to first order at sufficient dilution. A serious problem in a study like this is the high reactivity of the reagent which means that an attack on the solvent is a serious side reaction if the substrate is of moderate reactivity. In the present work it was decided to bypass this dilemma by studying the attack of butyllithium on the solvent itself which occurs according to eqns. (2) and (3), respectively.



The use of the solvent as the substrate was convenient and allowed kinetic measurements at very low concentrations. Butyllithium in donor solvents has an intense absorption in UV and the absorption at 240 nm for ether and 270 nm for tetrahydrofuran varied in proportion with the concentration of butyllithium as ascertained by dilution experiments. The experimental procedure was then to prepare in

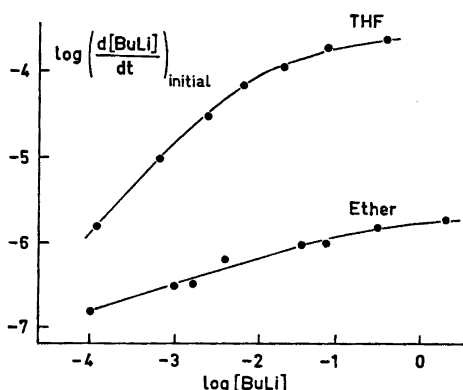
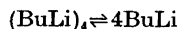


Fig. 1. \log initial rate for the reaction at 25 °C of undiluted ethers with butyllithium versus \log [BuLi]. Upper curve, tetrahydrofuran; lower curve, diethyl ether.

a flow system fresh solutions of butyllithium in the donor solvent and to record the rate of decay of the 240 nm or 270 nm absorption using a suitable UV flow cell.

The results obtained showed that for ether solutions the order of reaction with respect to butyllithium was ~ 0.30 over the range 0.0001 M to 2 M. For tetrahydrofuran, however, the reaction order was ~ 0.30 above 0.1 M, but below 10^{-2} M the slope of the \log rate versus \log concentration plot increased to ~ 1 (Fig. 1). The plot then showed a break at about 2×10^{-2} M. It seems likely that this represents the change from tetramer to monomer which should take place according to the mass equation [eqn. (4)].



$$c(1 - \alpha) = 4\alpha c$$

$$\frac{256\alpha^4 c^3}{1 - \alpha} = K \quad (4)$$

A break at the concentration mentioned corresponds to a value of K_{THF} of $ca. 10^{-4} \text{ mol}^3 \text{ l}^{-3}$.

It was found impossible to prepare and observe fresh and pure solutions of butyllithium in diethyl ether at dilutions below 10^{-4} M since the necessary 100 mm cell was too large to fit into the flow system. The break of the curve representing the transition from tetramer to monomer was not reached, and this fact may be used to calculate an upper limit to the

Table 1. Pseudo first-order rate constants (s^{-1}) for the reaction of 0.16 M butyllithium in diethyl ether with 0.02 M benzonitrile at the temperature indicated.

20 °C	40 °C	-80 °C
148	324	0.006
75 (0.22 M LiBr added)		

equilibrium constant K_{ether} . If at 0.0001 M less than 10 % of the reagent is dissociated into the monomer the maximum value of the equilibrium constant is calculated to be $ca. 10^{-14} \text{ mol}^3 \text{ l}^{-3}$.

It seems possible to combine this upper limit to the equilibrium constant with a lower limit by the interpretation of the kinetics obtained with some highly reactive substrates.

The condition necessary for the observation of fractional order kinetics with butyllithium is that the equilibrium is fast compared with the test reaction (Table 1). Benzonitrile reacts 10^{10} times faster with butyllithium in diethyl ether than does the solvent, but the kinetics are still fractional. There are substrates, however, which react so fast that they interfere with the adjustment of the equilibrium.

It has been shown that reaction of methyl trifluoroacetate with butyllithium in ether is extremely fast and that the reaction is first order in butyllithium and zero order in substrate.³ This kinetic picture was interpreted as indicating that with this substrate the rate determining step is not the reaction of monomer with substrate, but rather the formation of monomer by dissociation of tetramer. The rate constant was 18.5 s^{-1} at -28 °C. In the present work this reaction was studied at -82 °C (Table 2) and from the two rate measurements

Table 2. First-order rate constants (s^{-1}) for the reaction of 0.16 M butyllithium in diethyl ether with 0.1 M methyl trifluoroacetate.

20 °C	-28 °C	-82 °C
2000 (calc.)	18.5 (Ref. 3)	0.007 (pure) > 0.14 (0.4 M LiBr added)

the activation energy was calculated to be 57.7 kJ mol^{-1} . The rate at 20°C may then be estimated to be $2 \times 10^3 \text{ s}^{-1}$. Experiments at -80°C furthermore showed a 20-fold increase in rate when a salt like lithium bromide was added (Table 2). Since the salt addition lowers the reactivity of the reagent toward benzonitrile and toward ether (Table 1), its effect is to be interpreted as an increase in both the forward and the reverse reaction in eqn. (1). Assuming a salt effect of equal magnitude at 20°C leads to a calculated rate constant of 4×10^4 at room temperature. To effect this reaction rate using 0.1 M butyllithium and *ca.* 10 M ether requires, assuming the maximum, diffusion controlled rate constant $10^9 \text{ l mol}^{-1} \text{ s}^{-1}$ a minimum concentration of monomer of $4 \times 10^4/10^9 = 4 \times 10^{-5} \text{ M}$ leading to a lower limit for K_1 of 2.6×10^{-17} . This equals $\Delta G_1(1) = 92.9 \text{ kJ mol}^{-1}$ or 23.4 kJ mol^{-1} of monomer.

The rationalization of the kinetic results with butyllithium and methyl trifluoroacetate does not prove that a monomer is the reactive species toward all substrates. Dissociation to ions, *e.g.*, might be of importance. Evidence that the same reactive species is involved in the reactions with benzonitrile and with methyl trifluoroacetate was obtained from kinetic experiments performed at -80°C . The use of very high concentrations of benzonitrile led to a low reaction order with respect to substrate and the rate tended to be identical with that

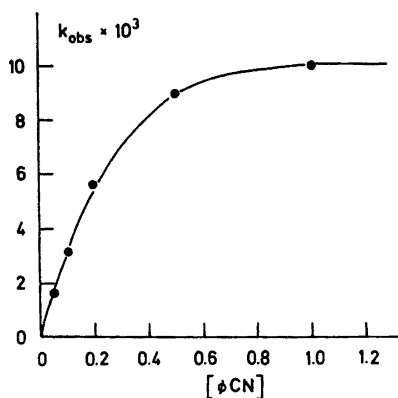


Fig. 2. Initial reaction rate given as $k_{\text{obs}} = (d[\text{BuLi}]/dt)(1/[\text{BuLi}])$ for the reaction of 0.06 M butyllithium in diethyl ether at -80°C with benzonitrile versus $[\phi\text{CN}]$.

obtained using methyl trifluoroacetate as a substrate at the same temperature. (Fig. 2).

The change in the rate determining step is therefore obtained equally well by using low concentrations of a highly reactive substrate as by using high concentration of a less reactive substrate.

As described above kinetics may yield information about the position of equilibrium (1). It is possible also to obtain a crude estimate of the enthalpy and entropy balance of the equilibrium. From measurements carried out at 20 , 25 , 30 , and 40°C the temperature dependence of the reaction between butyllithium and ether was found and the activation energy was determined. An Arrhenius treatment gave $E_A = 89.5 \text{ kJ mol}^{-1}$ (Fig. 3).

While diethyl ether reacts rather slowly with butyllithium, a substrate like benzonitrile as mentioned above reacts 10^{10} times faster (Table 1). Since the reaction order with respect to butyllithium is almost the same using the two substrates it is very probable that the reactive species is the same also in these two cases. If the entropy of activation for the two reactions is of the same magnitude the relation between the observed rates indicates a 56.5 kJ mol^{-1} higher energy of activation for the attack on ether [eqn. (2)]. By a direct measurement of E_A (Table 1) for the reaction with benzonitrile a value of 31.4 kJ mol^{-1}

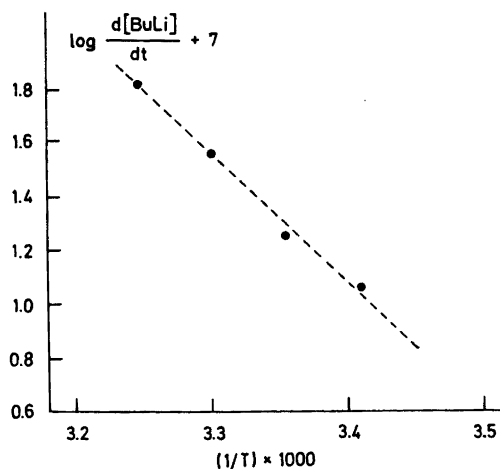


Fig. 3. Arrhenius plot. $\log 10^7 \times d[\text{BuLi}]/dt$ versus $1000 \times (1/T)$ for the reaction of 2.0 M butyllithium with the solvent diethyl ether at various temperatures.

was found which means that the difference is actually 58.2 kJ mol⁻¹.

It must be assumed that the activation energy measured in the systems mentioned is the sum of the enthalpy of reaction ΔH_r [eqn. (1)] when forming 1 mol of monomer from 1/4 mol of tetramer and the activation energy E_A [eqn. (2)] of the reaction between monomer and substrate. This leaves a rather narrow margin for the possible values of ΔH_r (1) since even though benzonitrile and monomeric butyllithium react extremely fast the energy of activation must be about 10 kJ mol⁻¹ meaning that ΔH_r (1) is ~ 21 kJ mol⁻¹. This value may seem low, but it must be considered that the enthalpy of breaking the electron-deficient bonding in the tetrameric aggregate is partly compensated for by the enthalpy of coordination between monomeric butyllithium and ether.

For the attack of butyllithium on THF the Arrhenius energy of activation was found to be 71 kJ mol⁻¹. This is an indication that equilibrium (1) is less endothermic in THF than in diethyl ether. The reason for this might be the strong and exothermic coordination between lithium compounds and THF as compared with ether. The high reactivity of butyllithium when dissolved in THF is the result of the relatively very high concentration of monomer and not an 'enhancement of the nucleophilicity' as often stated in the literature. Actually a calculation of the reactivity of monomeric butyllithium in the two solvents using the parameters obtained in the present work shows that the THF coordinated monomer is 15–20 times less reactive than the ether-coordinated monomer. In concordance with this the reactivity of dibutylmagnesium toward many substrates is lowered very substantially when changing from ether to THF.⁵

EXPERIMENTAL

Materials. Butyllithium, 15 % in hexane, was supplied by Metallgesellschaft A. G. Benzonitrile, Riedel-de Haën A. G., was distilled b.p. 91–92°C/10 mmHg.

Methyl trifluoroacetate was distilled from phosphorus pentoxide. Diethyl ether was distilled from sodium benzophenone ketyl. Tetrahydrofuran was distilled from butylmagnesium chloride.

Thermography. A lightweight 50 ml Dewar flask with an 8 mm wide and 200 mm long inlet tube was fitted with a copper constant thermocouple and closed with a rubber stopper. The flask was evacuated and filled with 40 ml of freshly distilled ether. It was then placed in a water thermostat at 25.00°C. The thermocouple reference junction was placed in alcohol at 25.00°C. The thermocouple was connected to a microvoltmeter, Phillips 2440, and a Servogor recorder. After obtaining temperature equilibrium between the inside and the outside of the flask the desired quantum of butyllithium was added through the stopper by means of a hypodermic syringe. The flask was shaken mildly and the temperature was recorded for 10 to 20 min. The heat of formation of lithium ethoxide in diethyl ether was determined to 204 kJ mol⁻¹ by reacting 0.200 M ethanol with 0.35 M ethereal butyllithium in the flow stream reactor⁶ which caused a temperature increase of 12.5°C. ΔH_r [eqn. (2)] was then calculated to be 162 kJ mol⁻¹ and on this basis the rates of temperature increase of the butyllithium/ether system were converted to reaction rates. The sensitivity of the method was about 0.1 μ V min⁻¹ $\sim 2.5 \times 10^{-6}$ M l⁻¹ min⁻¹.

For reactions requiring low temperature the water thermostat was substituted with a dry ice-acetone bath. In this case the obtaining of temperature equilibrium required the use of liquid nitrogen since only the stem of the Dewar flask was useful for heat exchange. The reference junction was placed in a separate Dewar flask in which the temperature was measured to $\pm 1^\circ$ C. Reactions of butyllithium with methyl trifluoroacetate in the Dewar flask were initiated by addition of undiluted ester to butyllithium of the desired concentration.

Fast reactions were measured by means of the thermographic flow stream procedure as described.⁶

Ultraviolet spectroscopy. Rate measurements were carried out using a flow system in which pure solvent and lithium reagent in hexane were mixed in a capillary stainless steel 'T' with 0.5 mm bore in the ratio 20:1 just before entering a thermostated UV flow cell (path 10, 1, or 0.1 mm as required). The absorption was monitored at 240 nm (ether) or 270 nm (THF). The flow rate was 1.31 ml s⁻¹ and the volume of the 10 mm cell was 0.5 ml. When the maximum absorption was attained the flow was stopped and initial rates were obtained from the slope of the time-absorption plot. Reactions in ether at higher concentrations were carried out in thermostated ampoules from which samples were measured in the flow cell at suitable intervals. All experiments were repeated until reproducible rates were obtained.

REFERENCES

1. West, P. and Waack, R. *J. Am. Chem. Soc.* 89 (1967) 4395.
2. Waack, R. and West, P. *J. Organomet. Chem.* 5 (1966) 188.
3. Holm, T. *Acta Chem. Scand.* 23 (1969) 1829.
4. Wakefield, B. J. *The Chemistry of Organolithium Compounds*, Pergamon, Oxford 1974, p. 14.
5. Holm, T. *Tetrahedron Lett.* 28 (1966) 3329.
6. Holm, A., Holm, T. and Høge-Jensen, E. *Acta Chem. Scand. B* 28 (1974) 781.

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