had been frozen at a concentration of 0.5 g/100 ml. With increasing protein concentration the amount of aggregate formed decreased rapidly so that in the solution containing 5 g/100 ml it was not possible to demonstrate any aggregated globulin. Solutions containing concentrations of protein higher than 5 g/100 ml did not contain aggregated globulin. 27 % of the molecules had formed aggregates in the globulin solution prepared from pooled serum the sample containing 0.5 g/100 ml protein. The amount aggregated was never below 3 % even when the concentration in the solution was 11 g/100 ml.

1. Putnam, F. W. *The proteins I*, Part B (1953) 827.
2. Kochwa, S., Smith, E., Brownell, M. and Wasserman, L. R. *Biochemistry* **5** (1966) 277.
3. Hansson, U.-B. *Acta Chem. Scand.* **22** (1968) 483.
4. Barandun, S., Kistler, P., Jeunet, F. and Isliker, H. *Vox Sanguinis* **7** (1962) 157.
5. Hansson, U.-B. *Acta Chem. Scand.* **22** (1968) 953.
6. Hansson, U.-B., Laurell, C.-B. and Bachmann, R. *Acta Med. Scand. Suppl.* **445** (1966) 89.
7. Högman, C. F. and Killander, J. *Acta Pathol. Microbiol. Scand.* **55** (1962) 357.

Reactivity of Butyllithium in Diethyl Ether Toward Benzonitrile and Methyl Trifluoroacetate

TORKIL HOLM

Department of Organic Chemistry, The Technical University, DK-2800 Lyngby, Denmark

Evidence has been accumulating in the last few years for a tetrameric structure of butyllithium in diethyl ether solution. West and Waack [1] rationalized the observation of a 0.30 order dependence with respect to butyllithium of the addition of butyllithium to 1,1-diphenylethylene as the result of insignificant reactivity of the tetramer but high reactivity of the monomer in the equilibrium:

$$(C_4H_9Li)_4 \rightleftharpoons 4\,C_4H_9Li; \quad \frac{[C_4H_9Li]^4}{[(C_4H_9Li)_4]} = K_{eq} \text{ (I)}$$
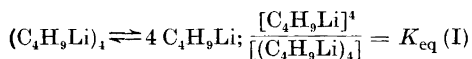
Colligative measurements by West and Waack also indicated a tetrameric structure. Various observations point to the coordination of one molecule of ether for every two equivalents of butyllithium on addition of diethyl ether to a solution of butyllithium in hydrocarbons.[2−4] This requires the tetramer to be di-solvated and excludes the possibility of a trimer.

Kinetic data obtained in the present investigation may be interpreted according to the theory described and afford further
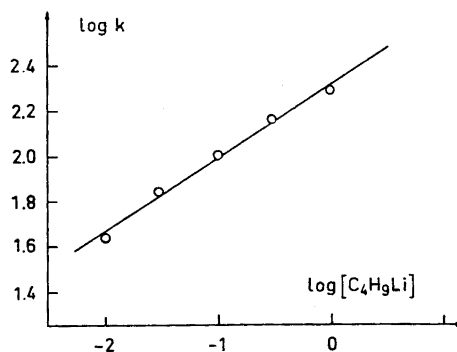
Fig. 1. log pseudo first order rate constant k for the reaction in diethyl ether at 20° of 0.01 M benzonitrile with butyllithium *versus* log $[C_4H_9Li]$.

insight into the monomer-tetramer equilibrium.

Using a thermographic method the kinetics of the reaction of benzonitrile with butyllithium at 20° in diethyl ether was investigated (Fig 1). The rate was found to be first order in benzonitrile and 0.33 order with respect to butyllithium over a concentration range from 0.01 M to 1.0 M in accordance with the kinetics obtained for the addition of butyllithium to 1,1-diphenylethylene,[1] and for the reaction of triphenylmethane with butyllithium in diethyl ether.[5] The half life of a 0.01 M solution of benzonitrile reacting at 20° with 0.10 M butyllithium was 0.007 sec.

Though benzonitrile reacts 10^6 times faster than triphenylmethane with butyllithium in ether, the observed kinetics strongly indicate that the only reactive species in both reactions is the monomeric butyllithium. It may be concluded that the equilibrium between monomer and tetramer is established fast enough to be without effect on the kinetic picture, even in the benzonitrile reaction.

The equilibrium (I) requires 0.25 order of rate with respect to butyllithium, while the observed values are 0.30—0.33. The deviation may be accounted for if K_{eq} increases at higher concentrations of butyllithium. This is not unlikely since the dielectric and other properties of the solvent are dependent on the concentration of butyllithium.

Methyl trifluoroacetate was found to react about 200 times faster than benzonitrile with butyllithium, and the kinetics of the reaction were totally different (Fig 2). It was found that the initial rate of reaction of a 0.1 M ethereal butyllithium was almost independent of the concentration of methyl trifluoroacetate, but it was close to first order with respect to the concentration of butyllithium.

An interpretation of the kinetics of this reaction may be obtained by assuming that the rate limiting step for the reaction of butyllithium with highly reactive substrates may be the formation of the reactive monomer by depolymerisation of the tetramer according to eqn. (I). The results indicate a first order rate constant for the depolymerisation reaction of 18.5 sec^{-1} at −28°.

It would seem reasonable that the equilibrium constant of eqn. (I) might be estimated by observation of the initial temperature "jump" observed by mixing methyl trifluoroacetate with butyllithium
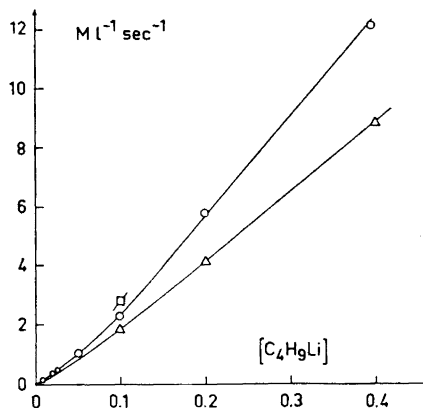

Fig. 2. Initial rates of reaction in diethyl ether at −28° of methyl trifluoroacetate 1.0 M (□), 0.10 M (○) and 0.010 M (△) *versus* concentration of butyllithium.

solutions, since the ester reacts instantly with the amount of monomer present, in accordance with the equilibrium. The initial, instant reaction observed by mixing equal volumes of 0.02 M methyl trifluoroacetate with 0.20 M butyllithium in ether corresponds to 5 % of the total reaction indicating the presence in 0.20 M butyllithium of 0.001 M monomer, corresponding to $K_{eq} = 2 \times 10^{-11}$. The estimate is tentative and the actual concentration of monomer may be lower but not higher. Uncertainty is introduced, because even the slow reacting benzonitrile produces a temperature "jump" due to initial, instant reaction at the moment of mixing.

A control of the value of the equilibrium constant would be possible if the reaction of benzonitrile (or triphenylmethane) could be followed at extremely dilute solutions of butyllithium since the reaction should then finally change to first order with respect to butyllithium. Because of the instability of such dilute ethereal solutions experiments of this type have not been performed, but rates of low order with respect to lithium reagent were observed in the reaction butyllithium with styrene at concentrations as low as 10^{-4} M in benzene solution.[6]

Benzonitrile and methyl trifluoroacetate are of low basicity and are unable to displace coordinated diethyl ether from

alkylmagnesium reagents.[7] Neither are they likely to coordinate with lithium reagents. More basic substrates, however, may coordinate with lithium bromide in ether. The carbonyl absorption of t-butyl acetate at 1634 cm^{-1} is shifted by coordination with lithium bromide to 1700 cm^{-1}, and quantitatively an equilibrium constant of approximately 0.7 may be calculated for the equilibrium in diethyl ether at 20°:

$$CH_3COO - t\text{-}C_4H_9 + LiBr \rightleftharpoons Complex$$
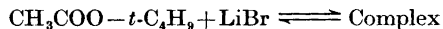
This coordination may influence the kinetics of basic substrates. For example it was found that the presence of 0.1 M LiBr in the ether solution accelerates the reaction of 0.01 M acetone with 0.1 M butyllithium by a factor 5, while the corresponding reaction with methyl trifluoroacetate is accelerated by a factor 1.7. These observations are of course very much in contrast to the inhibiting effect which is observed by the presence of magnesium halides in Grignard reactions.[7,9]

That coordination with magnesium bromide or other electrophilic magnesium compounds *inhibit* Grignard addition reaction to ketones or esters in spite of the presumably favourable polarizing effect on the carbonyl group exerted, seems to be due to a purely steric effect, which is much less pronounced in the case of lithium reagents.

Experimental. Kinetic data were obtained using a thermographic method. Freshly prepared diethyl ether solutions of substrate and butyllithium were used, taking rigorous precautions to exclude exposure to air. The solutions were delivered from motor burettes at a constant speed of 0.690 ml/sec. Temperature equilibration was obtained by leading the solutions through cooling coils of stainless steel immersed in either water at 20° or liquid ammonia, and the solutions were mixed in a "T" of stainless steel with a bore of 0.5 mm and a 2 mm exit. The polyethylene reaction tube in which the temperature was measured by means of a movable 0.1 mm copper-

constantan thermocouple junction had 0.6 mm bore, and the liquid speed was 4600 mm/sec. Parallely connected reference junctions were placed in the delivery tubes 5 mm ahead of the mixing point. EMF was registered to within ± 0.2 μV by combining a Phillips microvoltmeter and a Servogor recorder.

Reaction rates were derived graphically. Initial rates for methyl trifluoroacetate were obtained by extrapolating the time-temperature plots toward zero reaction time, while rates for benzonitrile were measured after 1.0 msec reaction time with correction for the fraction of substrate consumed at this time. All readings were corrected for the temperature increase observed when mixing pure ether with the lithium reagent, and the low temperature readings were corrected for heat exchange with the surroundings.

The increase in temperature for 100 % reaction of 0.01 M benzonitrile was 1.07° corresponding to 41.8 kcal/mole, and for the addition of 1 mole of butyllithium to methyl trifluoroacetate the temperature increase was 1.65° which equals 64.3 kcal/mole.

Relative reaction rates at various concentrations (0.001 M to 1.00 M) of butyllithium with 0.005 triphenylmethane in diethyl ether at 23° were determined by recording the rate of increase in extinction at 500 mμ ($l = 10$ mm) according to the procedure described.[8]

1. West, P. and Waack, R. *J. Am. Chem. Soc.* **89** (1967) 4395.
2. Smith, R. N., Duffield, J. P., Pierotti, R. A. and Mooi, J. *J. Phys. Chem.* **60** (1956) 495.
3. Gibson, G. W. and Eastham, J. F. *J. Am. Chem. Soc.* **85** (1963) 2171.
4. Cheema, Z., Gibson, G. W. and Eastham, J. F. *J. Am. Chem. Soc.* **85** (1963) 3517.
5. Holm, T. *Unpublished results.*
6. Worsfold, D. J. and Bywater, S. *Can. J. Chem.* **38** (1960) 1891.
7. Holm, T. *Acta Chem. Scand.* **21** (1967) 2753.
8. Waack, R. and West, P. *J. Am. Chem. Soc.* **86** (1964) 4494.
9. Holm, T. *Acta Chem. Scand.* **23** (1969) 579.