Half-Lives of Organolithium Reagents in Common Ethereal Solvents

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Received September 4, 1996

In the solid state as well as in hydrocarbon solutions polar organolithium compounds are more or less associated. The size of these aggregates is determined by structural features of the alkyl group and depends on the temperature. The degree of aggregation can further be modified by commonly used nucleophilic solvents such as diethyl ether, tetrahydrofuran (THF), or dimethoxyethane (DME) and even more effectively by some chelating additives, e.g., *N,N,N′,N′*-tetramethylethylenediamine (TMEDA),[1] a feature that strongly influences their reactive behavior. The ever-increasing knowledge in this field is very helpful to the synthetic chemist, who becomes able to choose the right alkyllithium−solvent combination with suitable properties (basicity and/or nucleophilicity) for each experiment. In practice, however, one has additionally to bear in mind that ethereal solvents react readily with organolithium bases in storage as well as under reaction conditions frequently applied in lithiation reactions, a fact often neglected even in the recent literature. Thus, low yields reported in lithiation reactions sometimes can be attributed to a side reaction in which the organolithium reagent is mainly consumed by the ethereal solvent instead of being available for the desired lithiation of the substrate.

In a model reaction, we recently were able to improve the situation in the case of *t*-BOC-protected aniline that often had caused difficulties in the literature resulting in highly varying reported yields.[2] Although there are a huge number of papers dealing with synthetic applications of lithiation reactions[3] as well as studies concerning the aggregation status of various organolithium compounds,[1] only a few papers appeared where the stabilities of frequently used lithiation reagents (*n*-, *s*-, or *t*-BuLi with or without addition of TMEDA) are determined under practical conditions (temperature range between −80 °C and room temperature in diethyl ether or THF). Apart from early data given by Gilman[4] for MeLi, *n*-BuLi, and PhLi and Honeycutt's[5] kinetic study of the cleavage of THF by *n*-BuLi, only the half-lives of DME solutions of *n*-, *s*-, and *t*-BuLi at −20 and −70 °C are available in a more recent work of Fitt and Gschwend.[6] In the course of our systematic study of the *N*-phenylcarbamic acid *tert*-butyl ester, we investigated the kinetics of some butyllithium reagents under typical reaction conditions for *ortho*-metalation.[2]

In the present paper, we wish to expand this study by adding new and summarizing all available data known to us. The prime objective of this publication is to provide the synthetic chemist with a dataset of half-lives as a tool enabling him to select the optimum storage and reaction conditions for his specific problem. We also would like to emphasize that we did not intend to carry out an exact kinetic study but rather to make available some semiquantitative correlations for the system lithiating agent, solvent, and temperature to the large group of chemists working in the area of directed metalation chemistry.

For practical reasons, we preferred a slightly modified titration technique published by Watson and Eastham[7] (titration with *sec*-butanol in toluene using 1,10-phenanthroline as indicator) over methods where the titration had to be carried out with samples taken from the cooled mixture. Control experiments on a random sample using Gilman double titration gave good agreements (error limits below 5%).

Since the solvent is present in large excess, most of the reactions show *pseudo*-first-order kinetics (indicated as I in Table 1) according to the following equation:

$$d[\mathrm{BuLi}]/dt = -k[\mathrm{BuLi}]$$

However, in some cases we could obtain a better fit using *pseudo*-second-order kinetics (indicated as II in Table 1). The fact that in some systems an arresting of the decomposition could be observed might be explained by the existence of a stable donor−acceptor complex of the solvent and the organolithium compound respectively, as has been reported for the system *t*-BuLi/ether.[8]

In the case of tetrahydropyran (THP) and *t*-BuLi, we observed an accelerating decomposition rate. After reaching approximately half of the $t_{1/2}$ derived from the first datapoints following first-order kinetics, increasing polymerization possibly initiated by a ring-opening reaction of the solvent complicated the titration process. A larger deviation of the results was caused by formation of a gel in the reaction vessel. The concentration of butyllithium decreased dramatically to almost zero. The slightly lower correlation coefficients for the system THP/*n*-BuLi at +35 and +20 °C might indicate a similar but much weaker effect.

The calculated kinetic data (rate constants k and half-lives $t_{1/2}$ as well as the regression coefficients *r*) are listed in Table 1. Table 2 provides an overview of all pertinent stability data known to us.

Experimental Section

General Methods. THF, THP, and diethyl ether were distilled from sodium benzophenone and diisopropylamine from calcium hydride immediately before use. *n*-BuLi (2.5 M in hexane), *s*-BuLi (1.3 M in cyclohexane), and *t*-BuLi (1.7 M in pentane) were purchased from Aldrich, *N,N,N′,N′*-tetramethylethylenediamine (TMEDA) and 1,10-phenanthroline from Merck. The observation temperature was maintained by a Lauda RK 20 cryostat.

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S0022-3263(96)01701-X CCC: $14.00

Table 1. Rate Constants, Half-Lives, and Correlation Coefficients of Various Lithiating Agents in Ethereal Solvents

conditions	k	$t_{1/2}$ **(min)**	r^{order}	remarks
n-BuLi/THF/+20 °C	6.46×10^{-3}	**107 ± 3**	0.999^{I}	
n-BuLi/THF/0 °C	6.67×10^{-4}	**1039 ± 37**	0.997^{I}	
n-BuLi/THP/+35 °C	2.49×10^{-3}	**278 ± 24**	0.990^{I}	
n-BuLi/THP/+20 °C	5.51×10^{-4}	**1257 ± 111**	0.990^{I}	
s-BuLi/Et_2O/0 ˚C	6.31×10^{-3}	**139 ± 10**	0.991^{II}	$t_{1/2}^{\mathrm{I}} = 149 \pm 16$, $r^{\mathrm{I}} = 0.976$
s-BuLi/Et_2O/−20 °C	5.84×10^{-4}	**1187 ± 65**	0.994^{I}	
s-BuLi/THF/−20 °C	8.85×10^{-3}	**78 ± 4**	0.997^{I}	
s-BuLi/THF/−40 °C		stabilization at $c \approx 0.4c_0$[a]		
s-BuLi/TMEDA/Et_2O/−20 °C		stabilization at $c \approx 0.5c_0$		
s-BuLi/TMEDA/THF/−20 °C	1.53×10^{-2}	**28 ± 2**	0.999^{II}	$t_{1/2}^{\mathrm{I}}=45\pm7$, $r^{\mathrm{I}}=0.983$
s-BuLi/TMEDA/THF/−40 °C		stabilization at $c \approx 0.4c_0$		
t-BuLi/THP/−20 °C		slow decomposition for ~400 min, then polymerization		
t-BuLi/THF/−40 °C	2.05×10^{-3}	**338 ± 16**	0.997^{I}	
t-BuLi/TMEDA/Et_2O/−20 °C		stabilization at $c \approx 0.8c_0$		
t-BuLi/TMEDA/THF/−20 °C	1.29×10^{-2}	**45 ± 3**	0.997^{II}	$t_{1/2}^{\mathrm{I}} = 65 \pm 10$, $r^{\mathrm{I}} = 0.974$

[a] c_0 is the initial concentration of commercially available BuLi given in the Experimental Section (General Methods).

Table 2. Summary of Half-Lives of BuLi in Ethereal Solvents

$t_{1/2}$	−70 °C	−40 °C	−20 °C	0 °C	+20 °C	+35 °C
t-BuLi DME[6]	11 min 0.18 h	<2 min <0.03 h				
s-BuLi DME[6]	120 min 2 h	2 min 0.03 h				
s-BuLi/TMEDA THF		stab. at $0.4c_0$	28 min 0.47 h			
t-BuLi THF[2]		338 min 5.63 h	42 min 0.70 h			
t-BuLi/TMEDA THF			45 min 0.75 h			
s-BuLi THF		stab. at $0.4c_0$	78 min 1.30 h			
n-BuLi DME[6]			111 min 1.85 h			
t-BuLi/TMEDA ether			stab.at $0.8c_0$			
t-BuLi ether[2]			483 min 8.05 h	61 min 1.02 h	complex kinetics	
s-BuLi/TMEDA ether			stab. at $0.5c_0$			
s-BuLi ether			1187 min 19.8 h	139 min 2.32 h		
n-BuLi/TMEDA THF[2]			3314 min 55.2 h	338 min 5.63 h	38 min 0.63 h	
n-BuLi THF				1039 min 17.3 h	107 min 1.78 h	
n-BuLi/TMEDA ether[2]					603 min 10.1 h	
n-BuLi THP					1257 min 21.0 h	278 min 4.63 h
n-BuLi ether[5]					9180 min 153 h	1860 min 31 h

Titration Procedure. A few crystals (approximately 1 mg) of 1,10-phenanthroline and a magnetic stirring bar were placed in a 50 mL round-bottom flask with a white-painted bottom dried in an oven at 110 °C. This flask was flushed with nitrogen, fitted with a septum, and equipped with a nitrogen balloon. Two mL of dry solvent (diethyl ether, THF, or THP) was charged into the flask by syringe, which then was cooled 20−30 °C below the observation temperature to avoid warming during the addition of the BuLi solution. One mL of the BuLi solution was then added by syringe (eventually followed by 1 equiv of TMEDA) and the flask placed in a cooling bath maintained at the observation temperature and stirred. The titration was carried out with a solution of *sec*-butanol in dry toluene and the flask again immersed in a cooling bath maintained at 20−30 °C below observation temperature to avoid warming during the exothermic reaction.

JO961701A