THE EFFECT OF LITHIUM ALKOXIDES ON DEPROTONIZATIONS BY SUPERBASES MADE FROM BUTYLLITHIUM AND POTASSIUM tert-PENTOXIDE*

Lubomír LOCHMANN[a], Hana JAKUBŮV[a] and Lambert BRANDSMA[b]

[a] *Institute of Macromolecular Chemistry,*
Academy of Sciences of the Czech Republic, 162 06 Prague 6, The Czech Republic
[b] *Department of Preparative Organic Chemistry,*
University of Utrecht, 3584 CH Utrecht, The Netherlands

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The presence or absence of lithium tert-pentoxide (t-PeOLi) in Superbases, prepared from butyllithium (BuLi) and potassium tert-pentoxide (t-PeOK), affects the metallation rate of toluene only slightly, the rate factors being between 1.0 and 0.3. Thus, lithium alkoxide is not essential for the high reactivity of Superbases. However, the ring-to-side chain metallation ratio is increased in the presence of t-PeOLi. On the other hand, an excess of t-PeOK (molar ratio t-PeOK/BuLi ≥ 3) considerably increases the rate and yield of the side chain metallation of toluene and suppresses its ring metallation. In this way, alkoxides enable some control on regioselectivity in Superbase reactions

Superbases (SB) prepared from alkyllithiums and alkoxides of heavier alkali metals are very reactive and useful reagents in organic synthesis, especially in deprotonations[1 – 3]. In this system the lithium–heavier alkali metal exchange proceeds according to the general scheme:

$$\mathrm{RLi} + \mathrm{R'OM} \longrightarrow \mathrm{RM} + \mathrm{R'OLi} \qquad (1)$$

(M = Na, K, Rb, Cs; R = primary alkyl; R′ = preferably tertiary alkyl).

The compound RM can then react with a substrate producing the heavier alkali metal derivative of the substrate[4 – 7], in many cases in good yields. Stoichiometric participation of potassium alkoxide in these metallations has been proved[7]. It follows therefore that in the metallation of toluene with SB, the potassium alkoxide is an essential reaction component and it does not act merely as a catalyst or activator of butyllithium.

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* Part XXI in the series Interactions of Alkoxides; Part XX: see ref.[11].

While the first reports[5,8] of such systems already appeared in 1964, the mechanism of the metallation has not been fully explained as yet.

Recently, second generation SB have been described[9 – 11]. They are characterized by the use of heavier alkali metal alkoxides with bulkier alkyl group than tert-butyl which are added to the organolithium compound in a 2 – 3 molar excess. Better properties of these modified SB indicate some influence of a heavier alkali metal alkoxide excess in reactions of SB. Specific information on the effect of lithium alkoxides, generated in SB by reaction (*1*), is still lacking, however.

EXPERIMENTAL

All operations with organic compounds of alkali metals were carried out in an atmosphere of purified argon. Crystalline lithium and potassium tert-pentoxides were prepared by reaction of tert-pentyl alcohol with the respective metal in heptane[7]. Methyl iodide was purified and dried by distillation with calcium hydride.

Determination of Metallation Rate

Method A. SB were prepared in reaction ampoules by mixing butyllithium (BuLi) and potassium tert-pentoxide (t-PeOK), in heptane solutions at 20 °C and stirring for 5 min. Toluene was added to SB and then, after various time intervals, methyl iodide at –50 °C. The unreacted toluene and products of the reaction of the metallated toluene with methyl iodide were determined by GC using tridecane as internal standard.

Initial concentration of BuLi was 0.26 mol/l, the molar ratio BuLi : t-PeOK : toluene being 1 : 1 : 1 or 1 : 3 : 1. In some experiments, a mixture of BuLi and 3 or 6 equivalents of lithium t-pentoxide (t-PeOLi) was used instead of BuLi only. In some experiments, t-PeOLi formed in SB through reaction (*1*) was removed from the mixture prior to the addition of toluene by repeated washing with heptane under rigorously inert conditions.

Method B. BuLi or its mixture with t-BuOLi in heptane was mixed with toluene prior to the addition of t-PeOK. The other operations were the same as in Method *A*.

As SB form sometimes heterogeneous systems in heptane, the same type of shaking was used in both Method *A* and *B*. Most experiments were carried out twice or three times; the metallation half-times differed within 20% relative.

Reaction of BuLi with t-PeOK in Excess

To 10 ml of a heptane solution of BuLi (11 mmol) 25.8 ml of heptane solution of t-PeOK (33.5 mmol) was added dropwise under stirring at ambient temperature. The white precipitate formed was isolated, yielding 92% of pure BuK. Metal contents (AAS) calculated: 40.64% K; found: 41.02% K, 0.12% Li. GC (after hydrolysis): butane 85 mole %, tert-pentyl alcohol 1.1 mole %.

Reaction of BuLi with t-PeOK in the Presence of Excess of t-PeOLi

To a mixture of 4 ml of a heptane solution of BuLi (4.4 mmol) and 10.3 ml of a heptane solution of t-PeOLi (8.9 mmol), 3.4 ml of a heptane solution of t-PeOK (4.4 mmol) was added dropwise under stirring at ambient temperature. A whitish precipitate, which was first formed upon contact with the drops, dissolved immediately by stirring. The initially light yellow solution became dark within about 2 h, after which a microcrystalline beige precipitate was isolated. The yield was 0.31 g. Metal contents (AAS) found: 18.50% K, 4.62% Li. GC (after hydrolysis): butane 55.2 mole %, tert-pentyl alcohol 44.8 mole %.

RESULTS AND DISCUSSION

Dependence of Rate and Regioselectivity of Toluene Metallation on Alkoxide Concentration in the Superbase

The metallation of toluene by BuLi only, or by the mixture of BuLi and t-PeOLi (molar ratio 1 : 3) proceeded extremely slowly, as expected. The results in Table I indicate that the reaction half-time was much longer than 10 000 h.

When t-PeOK was added to BuLi or its mixture with lithium alkoxide, thus the Superbase (SB) being formed, the rate of toluene metallation increased dramatically, by a factor of more than 10^6 (Table I). This enhancement of the reaction rate is evidently associated with the transformation of BuLi to BuK (Eq. (*2*)). The greatest and decisive change in the reactivity of the base was caused only by the first equivalent of t-PeOK; additional increase in the concentration of t-PeOK did increase the reactivity of SB, but only within one order of magnitude.

In preparation of SB according to Eq. (*1*) one equivalent of lithium alkoxide is formed. The influence of lithium alkoxides in the reaction of SB with toluene – as a model substrate – is investigated in this paper.

Two methods were used for the preparation of SB. In Method *A*, heptane solutions of BuLi and t-PeOK were mixed first, before the addition of toluene. The precipitate formed was characterized as pure butylpotassium in its common aggregated form[6] (BuK(aggreg)) (Eq. (*2*)).

$$C_4H_9Li + t\text{-}C_5H_{11}OK \longrightarrow C_4H_9K(aggreg) + t\text{-}C_5H_{11}OLi \qquad (2)$$

After subsequent addition of toluene and methyl iodide, the following reactions take place.

$$C_4H_9K + C_6H_5CH_3 \longrightarrow C_4H_{10} + mC_6H_5CH_2K + nC_6H_4KCH_3 \qquad (3)$$

$$C_6H_5CH_2K + CH_3I \longrightarrow C_6H_5CH_2CH_3 + KI \qquad (4)$$

$$C_6H_4KCH_3 + CH_3I \longrightarrow C_6H_4(CH_3)_2 + KI \qquad (5)$$

As the solubility of BuK(aggreg) in heptane is very low, its reaction with toluene can in principle proceed either on its surface or in solution at extremely low concentration. The actual reaction way is not known yet.

TABLE I
Metallation of toluene by Superbases made from butyllithium and alkali metal alkoxides (heptane, 20 °C) followed by the reaction with methyl iodide

Starting base system (molar ratio)	Actual base system[a] (molar ratio)	Method/ base form[b]	Conversion[c], %	$t_{1/2}$, h	Rate factor[d] F	Product yield[e], %		
						PhEt	xylenes	others[f]
BuLi	BuLi	*A*/sol	0	$>>10^4$	$<<10^{-6}$	0	0	0
BuLi–t-PeOLi (1 : 3)	BuLi–t-PeOLi (1 : 3)	*A*/sol	0	$>>10^4$	$<<10^{-6}$	0	0	0
BuLi–t-PeOLi–t-PeOK (1 : 6 : 1)	BuK–t-PeOLi (1 : 7)	*A*/sol	67	0.13	0.3	44	21	2
BuLi–t-PeOLi–t-PeOK (1 : 3 : 1)	BuK–t-PeOLi (1 : 4)	*A*/sol	67	0.072	0.5	46	21	0
BuLi–t-PeOK (1 : 1)	BuK–t-PeOLi (1 : 1)	*A*/insol	73	0.036	1.0	43	18	12
BuLi–t-PeOK (1 : 1)	BuK[g]	*A*/insol	71	0.057	1.0	54	8	9
BuLi–t-PeOK (1 : 3)	BuK–t-PeOLi–t-PeOLi (1 : 2 : 1))	*A*/insol	96	0.005	7.2	86	2	8
BuLi–t-PeOK (1 : 1)	–	*B*/sol	76	0.017	2.1	39	17	20
BuLi–t-BuOLi–t-PeOK (1 : 3 : 1)	–	*B*/sol	77	0.10	0.4	32	13	32

[a] After reaction (*1*); [b] solution or insoluble; [c] toluene conversion after 30 min; [d] $F = t_{1/2}(\text{standard})/t_{1/2}$; [e] reaction mixture quenched by methyl iodide 30 min after toluene addition; [f] 100 – (unreacted toluene + ethylbenzene + xylenes); [g] t-PeOLi removed before toluene addition by washing with heptane under strictly inert conditions.

In our study the molar ratio t-PeOLi/BuLi was varied from 7 to 0 either by adding more t-PeOLi or by reducing its amount by repeated washing of the BuK(aggreg) precipitate with heptane. Using SB modified in this way the overall rate of toluene metallation was measured under otherwise identical conditions. The mixture BuLi + t-PeOK (molar ratio 1 : 1) was used as a standard in the calculation of the rate factors (*F*). It was found (Table I) that in the concentration range investigated t-PeOLi has only a small negative effect on the overall metallation rate of toluene, exhibiting a value of *F* between 1.0 and 0.3, i.e. the reaction rate was slightly decreased in the presence of t-PeOLi. Thus, in the mixture with BuLi the effect of the lithium alkoxide on the reactivity is negligible and opposite when compared with that of the potassium alkoxide. Similarly, the reactivity of BuK(aggreg) is slightly decreased in the presence of the lithium alkoxide and increased using an excess of the potassium alkoxide.

In Method *B*, the SB was formed in the presence of the substrate (toluene) and in this case the reaction rate was found about twice ($F = 2.1$) as high as in Method *A* under the same conditions. This difference in reaction rates can be explained by a higher reactivity of butylpotassium reacting here with toluene "in statu nascendi" in less aggregated form (cf. ref.[12]). The retarding effect of lithium alkoxide on the reaction rate was observed also with Method *B* ($F = 0.4$), similarly to Method *A* (Table I). This finding agrees well with the observed higher stability of the BuK + t-BuOLi mixture towards THF when compared with BuK alone[12].

As shown in Table I, the overall toluene metallation rates do not depend substantially on the nature of the reaction mixture, i.e. the rate factors are almost the same regardless of the heterogeneous (Method *A* with low t-PeOLi content) or homogeneous reaction conditions (Method *A* with an excess of t-PeOLi or Method *B*). It should be stressed that all these data compare overall reaction rates, i.e. including the effect of the reaction mixture composition as well as other effects, such as solubility changes of BuK(aggreg) caused by the alkoxides.

In addition to the reaction rates, the presence of alkoxides also affected the distribution of the reaction products (Table I). In the presence of t-PeOLi the yield of ring-metallated derivatives (yielding mostly *m*- and *p*-xylene after reaction with methyl iodide) was higher and the yield of the expected side chain derivative (ethylbenzene) was lower than in its absence, i.e. in the metallation with pure BuK(aggreg). On the other hand, an excess of t-PeOK roughly doubled the yield of the side chain derivative (ethylbenzene) (cf. ref.[11]) and the amount of the ring-metallated derivative became negligible. These results are of importance for the synthesis as they enable a better control of the regioselectivity in the SB reactions and thus, improve the yield of the desired product.

From the rate comparisons in Table I it follows that the presence of lithium alkoxide is not essential for the high reactivity of the SB and that the important species is the organopotassium compound. This conclusion was recently supported by HOESY-NMR spectra and MNDO calculations of the system made from (triphenylmethyl)lithium and cesium 3-ethyl-3-heptoxide[13]. On the other hand, the alkoxides are not without influence on the reactions of SB and this suggests some participation of them in these reactions. Generally speaking, this participation may be of very different kind, like formation of a new species, probably in a very low concentration. However, it may be also of mere physical nature like an increase of the Li–K exchange rate due to a higher potassium alkoxide concentration and/or a change in the solubility or aggregation degree of the organopotassium compound. For this reason, the interaction of organopotassium compounds with alkali alkoxides was investigated in more detail.

Interaction of Organopotassium Compounds with Alkali Metal Alkoxides

The behaviour of t-PeOLi and t-PeOK towards BuK(aggreg) on the one hand and towards arylpotassium (e.g. benzylpotassium) on the other hand, is very different. In the reaction of BuLi with one equivalent of t-PeOK pure BuK(aggreg) is produced (Eq. (2)). However, after mixing BuLi with one equivalent of t-PeOK in the presence of three equivalents of t-PeOLi in heptane at room temperature a clear solution is formed first, from which a microcrystalline precipitate separates after about 2 h. When isolated, this compound appeared to be an adduct of an organometallic compound with an alkoxide containing both metals in the molar ratio K/Li = 0.71. In contrast, analytically pure BuK(aggreg) was isolated in a 92% yield from a mixture of BuLi and t-PeOK in the molar ratio 1 : 3; upon hydrolysis it produced only 1.1 mole % of tert-pentyl alcohol. Hence, BuK(aggreg) prepared in this way does not form any adduct with the potassium alkoxide.

With benzylpotassium and other arylpotassium compounds, however, t-PeOLi and t-PeOK behave just in the opposite way. Benzylpotassium forms easily a mixed aggregate with t-PeOK of the type $C_6H_5CH_2K \cdot x$ t-$C_5H_{11}OK$, whereas a similar adduct with t-BuOLi is not obtained[7]. As a consequence, the product formed in the metallation of an aromatic hydrocarbon (e.g. benzylpotassium) is stabilized by the coordination with potassium alkoxide. Formation of this adduct is probably an important support for the high yield and regioselectivity in the metallation reactions.

It follows from the above results that the interaction of organopotassium compounds with alkali alkoxides considerably depends on the structure of the reactants. Further investigation of these processes is in progress.

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