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"Super Bases" Derived from 5-Hexenyllithium and Alkali Metal Alkoxides: Rearrangements of 5-Hexenylalkalis

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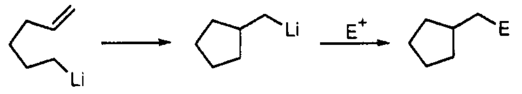
Abstract: Solutions of 5-hexenylsodium, 5-hexenylpotassium, 5-hexenylrubidium, and 5-hexenylcesium were prepared in THF at −78 °C by addition of an excess (10–20 equiv) of the approrpriate alkali metal alkoxide of 3-ethyl-3-heptanol to a solution of 5-hexenyllithium that had been generated from 6-iodo-1-hexene by lithium–iodine exchange. When allowed to stand at −52 °C for 1 h, the Na, K, Rb, and Cs 5-hexenylalkalis undergo prototropic rearrangement to give variable amounts of the isomeric 1-propylallyl species. Quench of such reaction mixtures afforded 1-hexene and (*Z*)-2-hexene as the major products along with smaller amounts of (*E*)-2-hexene; only traces of methylcyclopentane were detected. Under identical conditions, rearrangement of 5-hexenyllithium in the presence of an excess of lithium 3-ethyl-3-heptoxide affords only (cyclopentylmethyl)lithium.

The highly stereoselective "anionic" cyclization of 5-hexenyllithiums to (cyclopentylmethyl)lithiums has attracted recent attention as a convenient route to functionalized cyclopentylmethyl-containing products.[1,2] In view of the synthetic utility of the facile 5-exo isomerization of 5-hexenyllithium, it was of interest to determine whether this rearrangement is generally characteristic of the 5-hexenylalkalis or is confined to the lithium species.



Some time ago, Garst and co-workers reported that the predominant mode of rearrangement of both 5-hexenylsodium and 5-hexenylcesium in ethereal solvents involves intramolecular 1,4–proton transfer to give 1-propylallyl organometallics.[3] The Na and Cs 5-hexenylalkalis were generated by reaction of metal mirrors with 6-chloro-1-hexene, and in addition to the 1- and 2-hexenes expected upon quench of the 1-propylallyl organometallics, dimeric products and non-negligible quantities of methylcyclopentane were also detected. Indeed, methylcyclopentane was a major component of product mixtures generated from reaction of the chloride with Cs metal.[3] Since the 5-hexenyl radical is a probable intermediate in the reactions that were used to produce the Na and Cs-hexenylalkalis,[4] it is not clear whether the methylcyclopentane observed in these experiments was a result of ring-closure of the organometallic or the radical intermediate.[5] In order to address this question, it would be desirable to generate the 5-hexenylalkalis by a pathway that does not involve single-electron transer. To this end, we have investigated the preparation of Na, K, Rb, and Cs 5-hexenylalkalis by metal–lithium exchange between 5-hexenyllithium and alkali-metal alkoxides. As demonstrated by the results presented below, cyclization is unique to the lithium species; the Na, K, Rb, and Cs 5-hexenylalkalis rearrange exclusively by 1,4-proton transfer.

Results and Discussion

The enhanced reactivity of an organolithium that results upon addition of an equivalent of a sodium or potassium alkoxide was recognized independently and virtually simultaneously by the groups of Lochmann[6] and Schlosser.[7] The nature of the actual species in these mixtures, often referred to as "super bases", remains a controversial issue.[8] It has been argued that the reactive species is properly viewed as a mixed aggregate of the organometal and the alcoholate,[7] while recent evidence has been presented[8] supporting the formation of a discrete organoalkali resulting from

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[8] For a succinct discussion of the evidence for various structures proposed for the species generated upon addition of an organolithium to a heavier-alkali-metal alkoxide see: Lochmann, L.; Bauer, W. *J. Am. Chem. Soc.* **1992**, 114, 7482.

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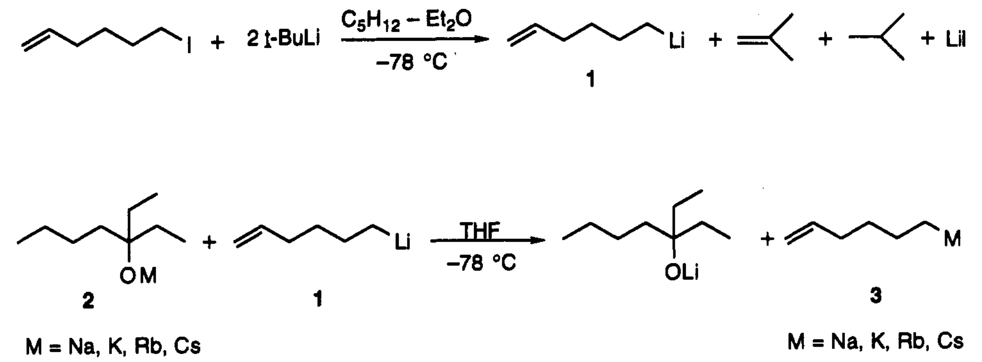
Scheme 1



quantitative lithium–heavier-alkali-metal exchange[6,9] (eq 1).

$$\text{R-Li} + \text{R'OM} \rightarrow \text{R-M} + \text{R'OLi} \qquad (1)$$

Be that as it may, it seemed worthwhile to investigate the behavior of "super bases" (depicted for the sake of pictorial clarity as organoalkalis) prepared, as illustrated in Scheme 1, by reaction of 5-hexenyllithium (**1**) with the alkali-metal alkoxides of 3-ethyl-3-heptanol (**2**, M = Na, K, Rb, Cs). Despite initial concern as to the viability of this approach for the generation of discrete 5-hexenylalkalis, it was felt that comparison of the behavior of the species prepared in this way (eq 1) with that reported by Garst's group[3] for 5-hexenylsodium and 5-hexenylcesium would serve to validate the approach (vide infra).

Solutions of 5-hexenyllithium (**1**) were prepared under argon at –78 °C, as illustrated in Scheme 1, by addition of 2 molar equiv of *t*-BuLi in pentane to 0.1 M solutions of 6-iodo-1-hexene in *n*-pentane–diethyl ether (3:2 by volume) following our general protocol for lithium–iodine exchange.[10] A small, accurately weighed quantity of dry *n*-octane was added to each solution of **1** to facilitate quantitation of reaction products by GC analysis, and the "super bases" (**3**, M = Na, K, Rb, Cs) were generated at –78 °C by addition of an excess (typically 20 molar equiv) of the appropriate 3-ethyl-3-heptoxide (**2**, M = Na, K, Rb, Cs) dissolved in dry THF (Scheme 1). As a control, lithium 3-ethyl-3-heptoxide (**2**, M = Li) was added in a separate series of experiments to solutions of **1**. It is to be noted that, although alkali alkoxides are normally used in stoichiometric amounts for the preparation of "super bases",[6-9] a large excess of **2** was employed in the present case to ensure complete conversion to **1** to **3** since the lithium iodide liberated in the preparation of **1** (Scheme 1) serves to regenerate **1** to **3** via the well-studied exchange illustrated in eq 2.[11] In this connnection, it is significant

(2)

that virtually identical results were obtained from experiments involving addition of either 10 or 20 equiv of alkoxide (Table 1; compare entries 4 and 5, 8 and 9).

Reaction mixtures containing the "super bases" (**3**, M = Li, Na, K, Rb, Cs) were transferred to a thermostated bath maintained at –52 ± 1 °C and stirred at this temperature under an atmosphere of argon for 1 h prior to quench with deoxygenated MeOD. Analysis of the resulting solutions by capillary GC–MS gave the results summarized in Table 1.

Cursory inspection of the data presented in Table 1 reveals that the 5-hexenyllithium species is unique among the 5-hexenyl "super bases". Thus, whereas cyclization is the exclusive mode of isomerization of the lithium species (Table 1, entry 1),[12] the sodium species is essentially inert (Table 1, entry 3), and the heavier-alkali-metal "super bases" rearrange via 1,4-proton transfer (Table 1, entries 4–8) with little, if any, evidence of ring-closure. Moreover, when warmed and allowed to stand at room temperature for 1 h, the 5-hexenyllithium system rearranges quantitatively to (cyclopentylmethyl)lithium (Table 1, entry 2), while there is virtually no change in the product distribution from the heavier-alkali-metal "super bases" (the results for the Rb species (Table 1, entries 6 and 7) are representative).[13] It should be noted that the small and variable amounts of methylcyclopentane (1–5%) detected in several of the product mixtures from experiments involving Na, K, and Cs "super bases" may well be an artifact of the exothermic lithium–halogen exchange used to prepare **1**. Indeed, such inadvertent cyclization of **1** to (cyclopentylmethyl)lithium, due to local heating during the addition of *t*-BuLi to the iodide at –78 °C, has been observed in a number of previous studies.[1].

Table 1. Rearrangement of 5–Hexenylalkalis[a]

		products, % yield (% d)[b]			
entry	M	1-hexene	(*E*)-2-hexene	(*Z*)-2-hexene	MCP[c]
1	Li	83 (94)	0	0	17 (93)
2	Li[d]	3	0	0	97 (80)
3	Na	96 (64)	<1	<1	3
4	K	58 (17)	6 (96)	25 (98)	5
5	K[e]	70 (7)	5 (83)	22 (82)	1
6	Rb	54 (14)	8 (75)	29 (89)	1
7	Rb[d]	65 (1)	11 (5)	16 (4)	1
8	Cs	53 (16)	10 (85)	33 (94)	3
9	Cs[e]	50 (14)	9 (85)	31 (84)	1

[a] Solutions of the 5-hexenylalkalis in THF, generated by addition of 20 equiv of the appropriate alkali 3-ethyl-3-heptoxide to solutions of 5-hexenyllithium unless otherwise noted, were held at –52 °C for 1 h prior to quench with MeOD. Yields were determined by GC analysis. [b] Percent deuterium incorporation upon quench with MeOD. [c] Methylcyclopentane. [d] The reaction mixture was allowed to warm and stand at room temperature (*ca.* +22 °C) for 1 h prior to quench with MeOD. [e] Ten equivalents of alkoxide was used to generate the 5–hexenylalkali.

Although there was some concern at the outset of this study that "super bases" derived from the heavier alkalis would be rapidly consumed by proton abstraction from the THF solvent prior to rearrangement, this was not a serious problem for mixtures held

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(9) The structures of a variety of pure organoalkalis that were prepared by lithium–heavier-alkali-metal exchange (eq 1) have been reported; see: Weiss, E. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1501 and references therein.

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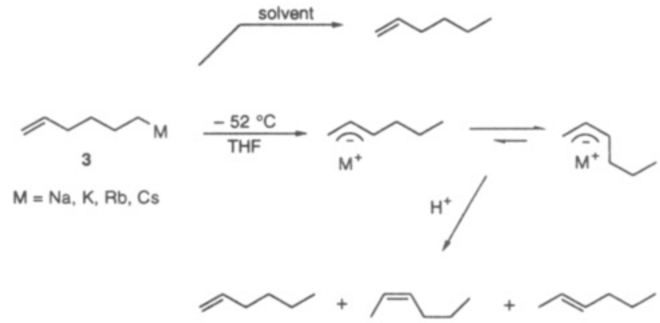
(12) The substantial proportion of (cyclopentylmethyl)lithium generated from a mixture of **1** and lithium 3-ethyl-3-heptoxide on standing for 1 h at –52 °C in THF solution (Table 1, entry 1) deserves comment. Ongoing kinetic studies of the effect of Lewis base additives on the rate of cyclization of **1**, which indicate that the ring-closure is significantly acclerated in the presence of THF, are consistent with the 17% yield of methylcyclopentane observed in this experiment.

(13) The Na, K, Rb, and Cs "super bases" are rapidly consumed by proton abstraction from the THF solvent when mixtures are allowed to warm to temperatures higher than *ca.* –50 °C.[14] The dramatic reduction in the extent of deuterium incorporation in product mixtures derived from the Rb species (**3**, M = Rb) when such mixtures are warmed to room temperature illustrates the general trend (Table 1, *cf.* entries 6 and 7).

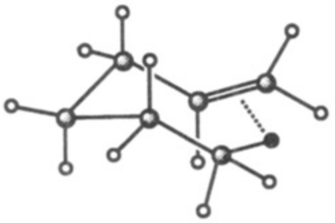
Scheme 2



at tempeatures below −50 °C.[13,14] The high level of deuterium incorporation in the (*E*)- and (*Z*)-2-hexenes produced upon isomerization of **3** (M = K, Rb, Cs) is consistent with the generation of persistent 1-propylallyl organometallics by 1,4-proton transer (Scheme 2), as suggested by Garst.[3] The *cis*-rich isomeric composition of the 2-hexenes (Table 1, entries 4–9) is undoubtedly a reflection of the well-established preference for allylic anions to adopt the *Z*-geometry.[15] The much lower deuterium incorporation observed in the 1-hexene fractions is also consonant with this scenario (Scheme 2) since 1-hexene results from inadvertent quench of the "super base" by proton abstraction from THF as well as from deuteration of the 1-propylallyl intermediate.[16]

Several additional features of the data presented in Table 1 are worthy of note. It is significant that the clean cyclization of 5-hexenyllithium (**1**) is unaffected by the presence of a large excess of lithium 3-ethyl-3-heptoxide (Table 1, entries 1 and 2).[12] This suggests that the isomerizations observed for the "super bases" derived from **1** and an excess of the heavier-alkali alkoxides (Table 1, entries 3–9) may well be indicative of behavior of discrete 5-hexenylalkalis. Comparison of the results presented in Table 1 for the Na and Cs species (Table 1, entries 3, 8, and 9) with those reported by Garst and co-workers for reactions of THF solutions of 6-chloro-1-hexene with Na and Cs mirrors[3] reveals that the Na and Cs "super bases" (**3**, M = Na and Cs) mimic the behavior of 5-hexenylsodium and 5-hexenylcesium prepared from the chloride: 2-hexene is the major product of the isomerization regardless of the method used for the preparation of the organometallics. The fact that little cyclization and no dimer formation is observed when 5-hexenylalkalis are generated by lithium–heavier-alkali-metal exchange (eq 1) indicates that such products, when observed,[3] are a consequence of the method used to prepare the organometallics rather than an intrinsic characteristic of their chemistry.

The fact that 5-hexenyllithium (**1**) is the only 5-hexenylalkali that undergoes facile cyclization is most likely a consequence of favorable intramolecular coordination of the small, electron-deficient lithium atom with the π-system. Ab initio molecular orbital calculations at the 3-21G level indicate that **1** adopts a ground-state geometry, depicted below, which resembles a chair-cyclohexane.[18] The stabilizing Li–π interaction serves to establish the geometry of the 5-hexenyl system prior to the activation step leading to (cyclopentylmethyl)lithium. It would seem that the larger alkali metals in the Na, K, Rb, and Cs 5-hexenylalkalis, which are presumably further from C(1) than the lithium atom in **1**, do not interact as strongly with the C(5)–C(6) π-bond as does Li.



In summary, 5-hexenyllithium is unique among the 5-hexenylalkalis in its ability to undergo facile cyclization. The heavier-alkali-metal derivatives of the 5-hexenyl system readily rearrange by 1,4-proton transfer (Scheme 2) to give the isomeric 1-propylallyl species.

Experimental Section

General Procedures. General spectroscopic and chromatographic procedures have been previously described.[18] All operations were performed under an atmosphere of dry, oxygen-free argon using standard syringe/cannula techniques, and all reagents and solvents used for the preparation of organometallics and metal alkoxides were freshly distilled under argon immediately prior to use. Diethyl ether and THF were freshly distilled from dark-purple solutions of sodium/benzophenone. The concentration of commercial solutions of alkyllithium reagents were determined immediately prior to use by the method of Watson and Eastham.[17] Analytical gas–liquid chromatography (GC) was accomplished using a Hewlett-Packard model HP5890A chromatograph equipped with a flame–ionization detector and a 19-m × 0.25-mm methyl phenyl (20%) silicone fused–silica capillary column using temperature programming (10 °C for 10 min, 15 °C/min to 200 °C). Area ratios were determined using a Hewlett-Packard model HP3396A recording integrator. GC–MS analyses were done on a Hewlett-Packard 5870B GC/MSD system with Chemstation software and fitted with a 25-m × 0.20-mm cross-linked methyl silicone fused-silica capillary column using temperature programming (10 °C for 15 min, 15 °C/min to 200 °C). Control of reaction temperatures (±1 °C) was accomplished using a Frigomix 1495 constant temperature bath equipped with a Thermomix 1460 temperature controller.

Literature procedures were followed for the preparation of 6-iodo-1-hexene[18] and 3-ethyl-3-heptanol.[19] Authentic samples of methylcyclopentane, 1-hexene, and (*E*)- and (*Z*)-2-hexene were obtained from the Aldrich Chemical Co.

Preparation of THF Solutions of Alkali 3-Ethyl-3-heptoxides. Approximately 1.0 M solutions of **2** (M = Li, Na, K, Rb, Cs) in dry THF were prepared as described below. In each instance, the solutions were cooled to room temperature, filtered under argon, and then transferred via cannula to dry, argon-flushed, septum–capped bottles and used within 1 day of preparation. The lithium alkoxide (**2**, M = Li) solution was prepared by cautious addition of 22.8 mL of a 1.33 M solution of "halide-free" methyllithium (0.05 M halide) in diethyl ether (30.3 mmol) to a solution of 4.368 g (30.28 mmol) 3-ethyl-3-heptanol in 30.0 mL of THF at room temperature. A solution of sodium 3-ethyl-3-heptoxide (**2**, M = Na) was prepared by heating at gentle reflux for 24 h a mixture of 3.715 g (25.75 mmol) of 3-ethyl-3-hepanol and 0.8752 g (36.50 mmol) of oil-free NaH in 25.0 mL of THF. The potassium alkoxide (**2**, M = K) solution was prepared analogously from 3.658 g (25.36 mmol) of 3-ethyl-3-heptanol and 1.544 g (38.49 mmol) of oil-free KH in 25.0 mL of THF. A mixture of 5.56 g (65.1 mmol) of rubidium metal and 8.50 g (58.9 mmol) of 3-ethyl-3-heptanol in 60 mL of THF was heated at reflux with stirring for a period of 24 h to generate a solution of rubidium 3-ethyl-3-heptoxide (**2**, M = Rb). The cesium 3-ethyl-3-heptoxide (**2**, M = Cs) solution was prepared in the same manner from a mixture of 5.552 g (41.78 mmol) of cesium metal and 5.570 g (38.61 mmol) of 3-ethyl-3-heptanol in 39.0 mL of the THF.

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(16) The 1-hexene derived from quench of the 1-propylallyl organometallic with MeOD would be deuterated at C(3), while any persistent 5-hexenylalkali would be deuterated at C(6). Although the relative proportions of these isomers are of interest in connection with the effect of the metal ion on both the rate of proton abstraction from solvent and the regioselectivity of the deuteration of 1-propylallylalkalis, it has not proved possible to unambiguously extract this information from the EI mass spectra due to uncertainty as to the structure of the ions generated upon fragmentation and rearrangement of 1-hexene.

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Preparation and Rearrangements of 5-Hexenylalkalis. In a series of separate experiments, solutions of 5-hexenyllithium (**1**) were prepared under argon at −78 °C by addition of 2.2 equiv of *t*-BuLi in *n*-pentane to approximately 0.1 M solutions of 6-iodo-1-hexene (typically 0.5–1.0 mmol) in *n*-pentane–diethyl ether (3:2 by vol) following the general protocol for lithium–iodine exchange.[10] Solutions of **1** were maintained under argon at −78 °C, and an accurately weighed quantity of pure *n*-octane was added to each solution as an internal standard. The 5-hexenylalkalis (**3**, M = Na, K, Rb, Cs) were generated at −78 °C by slow addition of a precooled (−78 °C) volume of a THF solution of the appropriate alkali 3-ethyl-3-heptoxide (**2**, M = Na, K, Rb, Cs) corresponding to 20 equiv of the alkoxide. Each mixture was stirred at −78 °C for 5 min; the reaction flask was then transferred into a constant-temperature bath thermostated at −52 ± 1 °C and allowed to stand at this temperature for 1 h prior to rapid quench with ~1.5 mL of dry, deoxygenated MeOD. Product mixtures were washed with water, dried ($MgSO_4$), and analyzed by GC and GC–MS using the columns and conditions described in the General Procedures to effect base-line separatiom of each component. Reaction products were identified by comparison of their GC retention times and mass spectra with those of authentic samples, and all yields (Table 1) were corrected for detector response under the conditions of the analysis using accurately weighed samples of pure product and standard.

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