Kinetics and Stereochemistry of $LiNR_2$-Induced 1,2-Elimination of Homoallylic Ethers[1]

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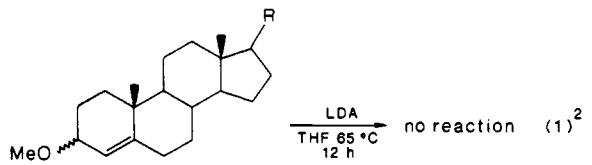
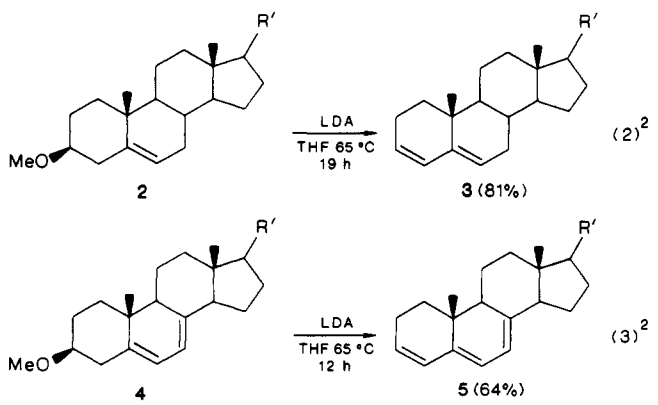
The cis and trans isomers of 2-ethenyl-1-methoxycyclohexane were prepared and treated with $LiNR_2$ in the solvents ether, tetrahydrofuran, and hexane. The diene 1-ethenylcyclohexene was formed in high yield from both substrates. In the ethereal solvents, syn elimination is favored over anti, although both pathways are viable and the k_{syn}/k_{anti} ratio is only 3–5. In contrast, anti elimination is favored when lithium diisopropylamide is employed in hexane solvent. This inversion in selectivity is associated with depression of k_{syn} rather than enhancement of k_{anti}, relative to reactions in ether and THF. Syn elimination is favored in all three solvents for reactions of lithium tetramethylpiperidide, again by modest factors (3–5). Rates were measured under excess base conditions and, with few exceptions, first-order losses of the homoallylic ether substrates were observed. The $LiNR_2$ concentration was varied to examine the effect on rate. The calculated second-order rate constants drifted downward with increasing concentration in ethereal solvents, suggesting a net kinetic order in base between $^1/_2$ and 1. The k_{syn}/k_{anti} ratios were only moderately sensitive to base concentration. A novel method for the preparation of cis-enriched homoallylic ether is described. Treatment of cyclohexene in methanol with *N*-bromosuccinimide gives *trans*-1-bromo-2-methoxycyclohexane, which, when subjected to vinylmagnesium bromide/CuI catalyst, affords 2-ethenyl-1-methoxycyclohexane in good yield, as a mixture of stereoisomers containing ca. 85% of the cis product.

Previous work in this laboratory has established the notable generality of the $LiNR_2$-induced 1,4-elimination of allylic and benzylic ethers, which allows ready access to various simple cyclic and acyclic 1,3-dienes at one end of a product reactivity spectrum, through isobenzofurans and on to *o*-xylylenes at the other. One of the few instances in which an allylic ether failed to undergo 1,4-elimination was observed by Svedberg;[2] the progesteryl derivative **1** was unchanged even by the rather harsh treatment with excess lithium diisopropylamide (LDA) shown in eq 1.



1
(ca. 35% α, 65% β)

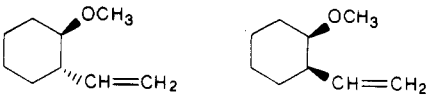
Svedberg found that the homoallylic ethers **2** and **4** derived from cholesterol and ergosterol, respectively, gave the corresponding diene **3** and triene **5**, showing that 1,2-elimination was not similarly inhibited. These and related observations suggested that mechanistic examination of this potentially general reaction of homoallylic ethers would be of interest. In this paper, the kinetics and stereochemistry of $LiNR_2$-induced 1,2-elimination of model cyclohexyl homoallylic ether stereoisomers are described.



2 **3** (81%)

4 **5** (64%)

Preparation of Substrates. The trans and cis isomers of 2-ethenyl-1-methoxycyclohexane (**6** and **7**) were chosen



6 **7**

as model substrates for stereochemical examination, because prospective immediate precursors had already been characterized and it was thought that the conformational features of the cyclohexane ring might dictate the course of elimination. Three stereospecific routes to the trans alcohol **6a** are described in the literature.[3] Of these, the simplest involves the opening of cyclohexene oxide with vinyllithium, as reported by Crandall and co-workers.[3a] Because vinyllithium is expensive and often difficult to obtain, we decided to explore the use of Cu(I) catalysts and commercial vinylmagnesium bromide with cyclohexene oxide. The Grignard reagent alone was known to be unsuitable for the desired reaction; the major product, depending upon the conditions used, is either the bromohydrin[4] or 1-cyclopentyl-2-propen-1-ol,[5] which arises from

(1) Portions of this work were presented at the 194th National Meeting of the American Chemical Society, New Orleans, Sept 2, 1987 (Orgn 160).

(2) Svedberg, D. P. Ph.D. Dissertation, UCSB, 1979. Compound **1** was formed by $LiAlH_4$ reduction of progesterone, followed by conversion to the bis methoxy ether; it contained ca. 65% β isomer.

(3) (a) Crandall, J. K.; Arrington, J. P.; Hen, J. *J. Am. Chem. Soc.* **1967**, *89*, 6208. (b) Marvell, E. N.; Rusay, R. *J. Org. Chem.* **1977**, *42*, 3336. Compound **6a** was obtained in modest overall yield by a three-step procedure starting with cyclohexene and ethyl diazoacetate (carbenoid cyclopropane formation, reduction, and acid-catalyzed rearrangement). The cis alcohol **7a** (ca. 95% isomeric purity) was obtained by Collins oxidation of **6a** followed by L-Selectride reduction, with preparative GC used to obtain pure material. (c) Carlson, R. G.; Huber, J. H.; Henton, D. E. *J. Chem. Soc., Chem. Commun.* **1973**, 223. Lithium acetylide opening of cyclohexene oxide was followed by Na/NH_3 reduction to form **6a**. The authors noted that this procedure failed with cyclooctene oxide, as did efforts to open the latter epoxide with vinyllithium or lithium divinylcopper.

(4) Henin, F.; Muzart, J. *Synth. Commun.* **1984**, 1355.

(5) Wiberg, K. B.; Pfeiffer, J. G. *J. Am. Chem. Soc.* **1970**, *92*, 553. The trans alcohol **6a** was also formed as a minor (26%) product from the treatment of cyclohexene oxide with vinylMgBr in THF.

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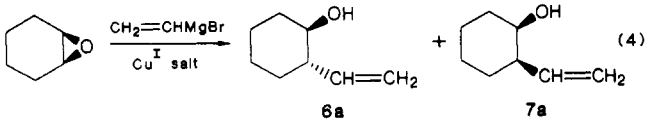
Table I. Reaction of Cyclohexene Oxide with Vinylmagnesium Bromide and Divinylmagnesium in THF Solvent[a]

CuX	T, °C	time, h	6a (%)[b]	7a (%)[b]	cyclohexanol (%)[b]	6a/7a[c]
vinylMgBr						
CuI[d]	−20	8	38	51	11	43/58[e]
CuI[d]	−20	9	84	15	1	85/15
CuI[d]	−20	9.5	78	17	5	82/18
CuI[d,f]	−20	8	73	15	12	82/18
CuI[d]	25	8	40	45	15	47/53
CuI[d]	−70	8		no reaction		
CuI[d]	−70 to 25	14	64	4	32	94/6
CuI[g]	0	2.5	49	40	11	55/45
CuI[g]	−30	1.5	91	9		91/9
CuI[h]	−30	1.5	82	11	7	88/12
CuCN	0	12	93	6.5	0[i]	93/7
CuCN	−30 to 20	4.5	97	2.5	0[i]	97/3
CuBr·SMe$_2$[j]	0	2	62.5	2.5	35	97/3
CuBr·SMe$_2$[j]	−20	10	100	0	0	>99.9/0.1[k]
divinylMg						
no CuX	35	17	74	2	2[l]	97/3
CuI[g]	0	2.5	63	37	0[i]	63/37
CuI[h]	0	2	75	14	9	84/16
CuCN	0	24	70	0.2	30	>99.5/0.5

[a] Two equivalents of Aldrich 1.0 M vinylmagnesium bromide in THF (two different bottles) was used. The solvent in entries 1–8 was ether/THF = ca. 30/70; 0.1 equiv of catalyst was used, except for entries 1–8 (0.3 equiv). [b] Crude material balances were high in all runs. The percentages refer to uncorrected GC peak areas. [c] This is the ratio of trans to cis alcohol normalized in 100%. [d] Aldrich 98% CuI (0.3 equiv) was used. [e] Distillation gave a yield of 72%. [f] In this run, the vinylmagnesium bromide was added to a mixture of cyclohexene oxide and CuI. [g] Aldrich analytical grade (99.999%) CuI was used. [h] Aldrich 98% CuI was recrystallized: Kauffman, G. B.; Teter, L. A. *Inorg. Synth.* **1963**, *7*, 10. [i] A trace of cyclohexanol was observed. [j] The procedure of Wuts was used to purify CuBr·SMe$_2$: Wuts, P. G. M. *Synth. Commun.* **1981**, *11*, 139. [k] The solvent in this especially clean reaction was ether/THF = 25/75. [l] The remainder of the material was the starting epoxide.

addition of the Grignard reagent to cyclopentanecarboxaldehyde, the ring contraction product of the bromohydrin.

Ring opening is indeed enhanced by catalytic amounts of Cu(I) salts, but unlike most[6] reactions of RMgX/Cu(I) with epoxides, the process is not stereospecific under many of the conditions examined. The expected trans product (**6a**) was accompanied by varying amounts of cis isomer (**7a**) (eq 4). The results of several runs are displayed in Table I.



(4)

6a **7a**

Cyclohexanol, which probably arises by a one-electron reduction, was also formed in these reactions, but there was no obvious correlation between the amount of this product and the ratio of stereoisomers. Consistently high purity and good yields of **6a** were obtained when CuBr·SMe$_2$ was used, and for overall convenience this is the method of choice. Divinylmagnesium in the absence of copper salts also gave essentially pure **6a**, in a rather slow reaction. It is interesting to note that the high level of stereoselectivity observed with this reagent is lost when CuI is added, although largely retained with CuCN.

Formation of the ether **6** was accomplished by addition of *n*-butyllithium to a solution of the alcohol **6a** in ether/hexamethylphosphoric triamide (HMPA), followed by treatment with excess methyl iodide. This variant of the Williamson ether synthesis gives complete reaction in a short time. Samples of pure **6**, free of **7**, were obtained by preparative GLC.

At about the time this work was initiated, two groups[4,7] reported similar observations from reactions of epoxides with vinylMgBr/Cu(I). Henin and Muzart[4] also used cyclohexene oxide, and our results approximately parallel theirs, except that we have been unable to duplicate their finding that high purity CuI affords only trans alcohol product.[9] These authors suggested that trace amounts of Lewis acids were responsible for the loss of trans specificity, but they argued that $MgBr_2$ was not the responsible agent. The contrary view was advanced by Brockway et al.,[7] who found that aged Grignard reagent from which $MgBr_2$ had precipitated gave higher trans selectivity in reaction with a substituted pyran epoxide. These authors suggested that the salt of the trans bromohydrin is an intermediate on the pathway leading to cis product and further noted that the unusually facile displacement of a secondary bromide implied an activating role for the adjacent OMgBr group.

We prepared the trans bromohydrin of cyclohexene and briefly examined reactions with vinylMgBr. Negligible reaction was observed in the absence of catalyst, but in the presence of CuI a mixture of homoallylic alcohols (**6a**/**7a** = 46/54) was formed, establishing that the bromohydrin (salt) is indeed a viable intermediate for the formation of both stereoisomers.

The literature procedures[3a,b] for formation of the cis alcohol **7a** give material contaminated with **6a**, and preparative GC is needed to obtain pure material. Thus a method such as the reaction of the bromohydrin, which leads to cis-enriched product, could be competitive with

(6) Several citations from the literature are given by Brockway et al.[7] Other recent examples are found in the work of Tius and Fauq,[8] who described the regioselective (and apparently anti stereospecific) opening of some β-hydroxy epoxides with Me, *n*-Bu, vinyl, and isopropenyl Grignard reagents in the presence of CuI. The level of sensitivity for detection of syn addition product is not clear from the brief description given in this communication. The only claim of syn addition product from a Grignard reagent other than vinylMgBr is a brief comment by Henin and Muzart[4] that the reaction of cyclohexene oxide and *n*-butylMgBr/CuI afforded some *cis*-2-butylcyclohexanol. The generality of stereochemical outcome remains open to question.

(7) Brockway, C.; Kocienski, P.; Pant, C. *J. Chem. Soc., Perkin Trans. 1* **1984**, 875. The rate-enhancing effect suggested in this paper may also be invoked to explain the regioselectivity observed in, e.g., the work of Tius and Fauq.[8]

(8) Tius, M. A.; Fauq, A. H. *J. Org. Chem.* **1983**, *48*, 4131.

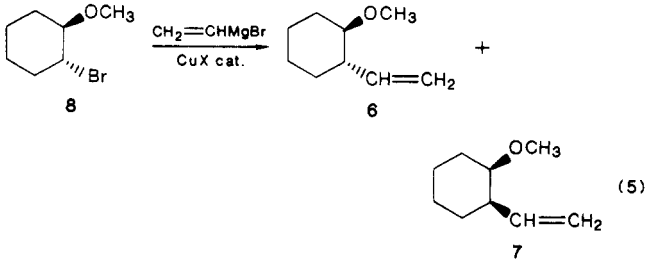
(9) Others have commented on the difficulty of removing traces of Cu(II) salts, and these may be responsible for the inability to duplicate work between laboratories; see: Hutchinson, D. K.; Fuchs, P. L. *J. Am. Chem. Soc.* **1987**, *109*, 4930.

Table II. Reaction of *trans*-2-Bromo-1-methoxycyclohexane (8) with Vinylmagnesium Bromide[a]

CuX	T, °C	time, h	6 (%)	7 (%)
CuI[b]	−25 to 25	5	16	84[c]
CuI[b,d]	−30 to 25	16	11	89[e]
CuI[f]	−30 to 0	2.5	13	87
CuCN	25	1.5	13	87
$CuBr{\cdot}SMe_2$	−40 to 15	10	18	82

[a] Two equivalents of Aldrich 1.0 M vinylmagnesium bromide was used. The solvent was ether/THF = 30/70, and 0.1 equiv of the catalyst was employed. [b] Aldrich 98% CuI was used. [c] Repetition of this run gave 6/7 = 23/77. [d] In this run the vinylMgBr solution had been cooled to −20 °C; a copious precipitate was observed, and the supernatant liquid was used. [e] Two repetitions of this run both gave 6/7 = 14/86. [f] Recrystallized CuI was employed in this run.

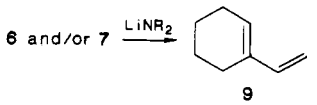
existing multistep approaches. It also appeared that if substituents other than OMgBr were effective in enhancing the rate of secondary bromide displacement, a variant might be developed for direct formation of the homoallylic ether **7**. To this end, *trans*-2-bromo-1-methoxycyclohexane (**8**) was prepared, by treating cyclohexene in methanol with *N*-bromosuccinimide. Treatment of **8** with vinylMgBr/Cu(I) caused facile displacement of bromide by a vinyl group. Under the same conditions, bromocyclohexane is essentially unreactive (3% vinylcyclohexane is formed). Although the reaction shown in eq 5 leads to a mixture of stereoisomers (see Table II), the desired cis isomer **7** is dominant. The trans isomer **6** may arise from bromide–bromide displacement with inversion prior to the desired coupling or by formation of a radical intermediate that is attacked preferentially from the cis face.



8 6 7 (5)

This sequence is especially convenient for the preparation of **7**, with pure material isolated by preparative GC. Although the level of cis selectivity is somewhat lower than found in the L-Selectride reduction of 2-ethenylcyclohexanone,[3b] the need to prepare (by oxidation of **6a**[3a,b] or other methods[10]) this rearrangement-sensitive[10a] ketone is avoided. The apparent activating influence of the adjacent methoxy group appears to be restricted in scope, since attempts to use MeMgBr or PhMgBr (with CuI catalyst) in place of vinylMgBr gave no product; **8** was recovered unchanged.

Kinetics and Stereochemistry of Elimination. Both **6** and **7**, under all of the strong base conditions examined in this study, undergo elimination and afford exclusively 1-ethenylcyclohexene (**9**) in quantitative yield as measured by GLC (eq 6). This product is stable to the times/conditions needed for kinetic runs except in THF, where slow partial conversion of **9** to a slightly longer retention time



9 (6)

(presumably isomeric) material was observed. The structure of **9** was confirmed by comparison of its ^1H NMR spectrum with a published description.[11] Since both syn and anti elimination pathways are accessible, detection of any stereochemical preference required kinetic analysis. No interconversion of **6** and **7** takes place under the conditions employed, as shown by GLC analysis of several reaction mixtures starting with pure isomers. Thus, if a carbanion intermediate is involved for either syn or anti elimination, any reprotonation must rigorously maintain the stereointegrity of the individual substrates.

The rates of elimination were first determined for the individual pure isomers **6** and **7**, in order to establish the absence of interconversion. Subsequent kinetic runs utilized 1:1 mixtures of the two, which has the advantage of giving rate data for both under identical conditions. The rate constants listed in Table III were obtained from such mixtures.

The rates were studied under pseudo-first-order conditions, with a large excess (typically ≥ 10-fold) of the base. The bases LDA and LTMP (lithium tetramethylpiperidide) were used in the solvents ether, THF, and hexane. Good first-order plots of ln [**6**] (or **7**) vs time were obtained, with one exception. The most rapid reaction examined involved LTMP in THF, where the rate of loss of homoallylic ether diminished as the reaction progressed, perhaps because of decomposition of the base by reaction with solvent.[12] This precluded the determination of meaningful rate constants under these conditions, although it was established that syn elimination was preferred (k_{syn}/k_{anti} = ca. 5).

The concentration of base was systematically altered to test the effect of this variable on rate. The significant conclusions derived from the data in Table III are as follows. (a) For both LDA and LTMP, the effect of solvent on rate is THF > ether > hexane. (b) In the ethereal solvents, LTMP is more reactive than LDA. (c) Both **6** and **7** undergo elimination under all conditions examined. With one important exception (LDA in hexane), syn elimination (of **6**) is more rapid than anti elimination (of **7**), although the level of syn/anti selectivity is modest. (d) In the ethereal solvents, calculated second-order rate constants (displayed in Table III) for both LDA and LTMP decrease with increasing base concentration. The effect appears to be somewhat greater on syn than on anti elimination, resulting in a small downward drift of k_{syn}/k_{anti} with increasing concentration. (e) The syn/anti rate ratio is inverted, compared to all other base/solvent combinations, *for LDA in hexane*. This effect is associated with depression of k_{syn}, since k_{anti} is more nearly solvent independent (compare the rate constants for identical [LDA] in ether, THF, and hexane at 24 °C). (f) The rate data for LTMP in ether were obtained with solutions of the base which had been "aged" for 1.5 h prior to the addition of substrate. When the substrate was added immediately after generation of the base, the initial rate was signifi-

(10) (a) Chang, T. C. T.; Rosenblum, M.; Samuels, S. B. *J. Am. Chem. Soc.* **1980**, *102*, 5930. (b) Hudrlik, P. F.; Kulkarni, A. K. *Ibid.* **1981**, *103*, 6251.

(11) Hanack, M.; Schneider, H.-J.; Schneider-Bernlohr, H. *Tetrahedron* **1967**, *23*, 2195.

(12) It is clear that LTMP reacts readily with THF on warming, to give the enolate of acetaldehyde plus ethylene.[13] However, the change in rate in the present study was greater than anticipated on the basis of the $t_{1/2}$ (30 h at 25 °C) for 1 M LTMP in THF that has been reported by Martin and co-workers.[14] Concentration effects or catalysis by products may be responsible for this difference. Rathke et al.[15] found a half-life of LTMP in THF containing TMEDA at 24 °C of 12 h.

(13) Fleming, I.; Mah, T. *J. Chem. Soc., Perkin Trans. 1* **1975**, 964.

(14) Taylor, S. L.; Lee, D. Y.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4156; see footnote 21 in this paper.

(15) Kopka, I. E.; Fataftah, Z. A.; Rathke, M. W. *J. Org. Chem.* **1987**, *52*, 448.

Table III. Kinetics of Elimination of 6 and 7[a]

base	solvent	[B][c]	[6 + 7][d]	10^5k (s^{-1})		10^5k (M^{-1} s^{-1})[b]		
				k_6	k_7	k_6	k_7	k_{syn}/k_{anti}
LDA	Et_2O	0.25	0.025	5.59	1.72	22.4	6.88	3.26
		0.50	0.050	8.78	2.56	17.6	5.12	3.44
		0.75	0.038	11.2	3.37	14.9	4.49	3.32
		1.00	0.050	13.1	3.95	13.1	3.95	3.32
		1.50	0.050	18.0	5.97	12.0	3.98	3.02
		2.00	0.067	20.0	7.17	10.0	3.58	2.79
	THF	0.25	0.025	8.94	1.82	35.8	7.28	4.92
		0.50	0.050	12.9	2.87	25.8	5.74	4.49
		0.75	0.038	15.6	3.81	20.8	5.08	4.09
		1.00	0.050	16.5	4.08	16.5	4.08	4.04
	hexane (24 °C)	0.50	0.050	0.23	2.14	0.46	4.28	0.11
	hexane (68 °C)	0.25	0.025	0.86	7.53	3.46	30.1	0.12
		0.50	0.050	1.76	19.7	3.52	39.4	0.09
		0.75	0.038	1.58	26.0	2.11	34.7	0.06
		1.00	0.050	3.03	45.3	3.03	45.3	0.07
LTMP	Et_2O	0.25	0.025	11.7	2.76	46.8	11.0	4.25
		0.50	0.050	17.9	3.96	35.8	7.92	4.52
		0.75	0.038	24.1	5.54	32.1	7.39	4.34
		1.00	0.050	28.1	6.57	28.1	6.57	4.28
	hexane (24 °C)	0.50	0.050	2.07	0.63	4.14	1.27	3.26
	hexane (68 °C)	0.25	0.025	4.57	1.85	18.3	7.40	2.47
		0.50	0.050	9.58	4.38	19.2	8.76	2.19

[a] These rates were determined by using 1:1 mixtures of 6 and 7. Except where otherwise noted, the reactions were carried out at room temperature (24 ± 1 °C). [b] Calculated by dividing the measured first-order rate constants by the base concentration. [c] Initial concentration of the designated base. [d] Initial concentration of the 1:1 mixture of 6 + 7.

cantly faster (estimated 5×) and then leveled off to the linear first-order slope obtained with aged solutions. Neither excess MeLi nor added LiOMe affected this behavior. A recent NMR study by Podraza and Bassfield[16] supports the view that base formation is quite rapid under our experimental conditions in both hexane and THF and presumably in ether as well. The unusual kinetic behavior of LTMP in ether may be caused by previously unrecognized slow aggregation.

Discussion

Ethers have received far less attention than activated derivatives of alcohols (e.g. tosylates) as 1,2-elimination substrates, and few studies of stereoselectivity have appeared. Letsinger and Bobko[17] several years ago found that $k_{syn} > k_{anti}$ for the reaction of butyllithium with the cis and trans isomers of 2-phenyl-1-methoxycyclohexane in both pentane (slower reaction; degree of selectivity not determined) and pentane/ether (faster reaction; k_{syn}/k_{anti} = ca. 8 based on yield of olefin and recovered starting material). These authors suggested a cyclic transition-state mechanism featuring lithium coordination to the methoxy oxygen to explain the preference for syn elimination. Cation sensitivity was clearly demonstrated in the work of Hunter et al.,[18] who found a positive correlation between coordinating ability and syn selectivity for the elimination of 1-methoxyacenaphthene in *tert*-butyl alcohol. High syn selectivity has been demonstrated for the reactions of $LiNEt_2$ with substituted cyclohexene oxides,[19] for which a similar explanation may be offered. In these and the present study, lithium coordination avoids the intuitively unreasonable alternative of generating a "naked" oxyanion in poor solvating media. On the other hand, cation-free base-induced elimination reactions of ethers in the gas phase are well documented,[20] and competing syn and anti pathways have been proposed for the reactions of diethyl ether and the methyl ethers of *cis*- and *trans*-4-*tert*-butylcyclohexanol with hydroxide ion in the gas phase. Also, one might expect that the effects of lithium coordination with an ethereal substrate would be more significant in hydrocarbon than in ethereal solvent and that such coordination would favor syn elimination even if a cyclic transition state were not involved (e.g., ion pair reaction). These expectations are not borne out by the present results.

The kinetic order in stoichiometric base concentration can be influenced by several factors, including the major aggregation states and their equilibrium constants, the rate of dissociation, the existence of one or more kinetically competent species, and the details of the transition-state structure. We have no way of distinguishing these possibilities with the information at hand, but some features deserve comment. In ethereal solvents, no difference in kinetic order in base for syn vs anti elimination is discernible. The previously noted inverse relationship between concentration and calculated overall second-order rate constant indicates that the apparent order in base is less than unity. Conversely, calculation based on an assumption of half-order in base gives values that increase with concentration (in ether for both LDA or LTMP, by about 30% over the concentration range examined). Thus the apparent order in base lies between half and first order. While several complex mechanisms could be envisaged to accommodate this feature, dissociation of a dimer or higher aggregate to a more kinetically active species is probably involved. Whatever the nature of the reactive species, it does not offer a major kinetic advantage to syn elimination. This fact along with the apparently similar kinetic order for anti elimination casts doubt on a simple cyclic transition state for this process in ethereal solvents.

The reactions of LDA and LTMP in hexane diverge, with the former favoring anti elimination while the latter retains the modest preference for syn elimination found

(16) Podraza, K. F.; Bassfield, R. L. *J. Org. Chem.* **1988**, *53*, 2643.
(17) Letsinger, R. L.; Bobko, E. *J. Am. Chem. Soc.* **1953**, *75*, 2649. See also: Letsinger, R. L.; Pollart, D. F. *Ibid.* **1956**, *78*, 6079.
(18) Hunter, D. H.; Lin, Y.-T. *J. Am. Chem. Soc.* **1968**, *90*, 5921. Hunter, D. H.; Sheering, D. J. *Ibid.* **1971**, *93*, 2348.
(19) Thummel, R. P.; Rickborn, B. *J. Am. Chem. Soc.* **1970**, *92*, 2064; *J. Org. Chem.* **1972**, *37*, 3919.
(20) de Koning, L. J.; Nibbering, N. M. M. *J. Am. Chem. Soc.* **1987**, *109*, 1715 and references therein.

in ethereal solvents. The approximately 10-fold preference for anti elimination with LDA in hexane is associated with a sharp decrease in the syn elimination rate, relative to reactions in ethereal solvents, suggesting that some structural feature of LDA in hexane disfavors the syn mechanism. Recent studies[21] of lithium dialkylamide structures, while not providing direct answers for these particular base–solvent pairs, offer some interesting insights. LTMP crystallizes as a cyclic tetramer[21a] from hydrocarbon solvent, whereas the solvated dimer[21b] (in equilibrium with monomer) appears to be favored for this base, as well as for other LiNR$_2$ species, in THF solvent.[21b,c] The crystal structure of unsolvated LDA has apparently not been determined, but lithium hexamethyldisilazide[21d] and lithium dibenzylamide[21e] both form cyclic trimers, and these may be better analogues of LDA. Differences in behavior between LDA and LTMP in hexane solvent may be due to the presence of different aggregate types (e.g. trimer vs tetramer), although alternative explanations are also possible.

Comparison of the present results with those from an earlier study[22] of 1,4-elimination shows that such differences can either be masked or may not be applicable in all instances. Syn 1,4-elimination was favored for both LDA and LTMP, as well as other bases, in various solvents including THF, ether, and hexane. The degree of syn stereoselectivity was greatest (within measurement error, 100%) in hexane solvent for both LDA and LTMP, and no distinction between the two could be made. The 1,4-elimination reaction gave naphthalene very rapidly, precluding determination of relative rates or kinetic order, which might have pointed up differences. The present work shows that LDA and LTMP in hexane may have more fundamentally divergent properties than anticipated from the generally similar behavior that has been observed when the two bases are compared.

The cyclohexyl model system used in this work is biased toward anti elimination, from the standpoint of the rotational energy needed to attain syn-coplanar vs anti-coplanar arrays. In this respect the model is atypical. Based on analogy with earlier studies of epoxide β-eliminations,[19] one might expect much higher syn elimination preference for other cyclic and acyclic homoallylic ethers.

Experimental Section

All reactions were carried out under an argon atmosphere. Ether and THF were distilled from $LiAlH_4$ and sodium–benzophenone ketyl, respectively, immediately before use. Hexane, diisopropylamine, and 2,2,6,6-tetramethylpiperidine were distilled from CaH_2 and stored under N_2. The sources and modifications of Cu(I) salts are indicated in the footnotes of Table I. Preparative GLC was done on a Varian Aerograph 200 instrument, with a 25 ft × $^1/_4$ in. 20% Carbowax 6M/Chromosorb W 60/80 column, at oven temperatures near 100 °C. ^{1}H NMR spectra were recorded on Nicolet NT-300, Varian NT-20, or Varian EM-360A instruments, in $CDCl_3$ solvent. Combustion analyses were performed by MicAnal (Desert Analytics), Tucson, AZ.

***trans*-2-Ethenylcyclohexanol (6a).** To a magnetically stirred 200-mL flask equipped with an addition funnel were added 1.0 g (5.0 mmol) of CuBr·SMe$_2$ and 20 mL of dry ether. This slurry was cooled to −40 °C and 5.05 mL (50 mmol) of cyclohexene oxide was added. Vinylmagnesium bromide (60 mL, 100 mmol) was added dropwise over a period of 1 h to the cold solution, and the mixture was subsequently stirred for 10 h with the temperature held below −20 °C. The dark solution was poured into saturated NH_4Cl solution that had been brought to pH 8 with ammonia. The layers were separated, and the aqueous phase was extracted with ether (3 × 50 mL). The combined organic phase was washed with saturated NaCl solution, dried over K_2CO_3, and rotary evaporated to give 5.5 g (87%) of a yellow oil, which was mainly **6a** by GLC analysis (no **7a** was detected). A sample of pure **6a** was obtained by preparative GLC. Its NMR spectrum was identical with that described by Marvell and Rusay.[3b] The remainder of the crude product was converted to **6** as described below.

For GLC identification purposes, a sample of the pure cis isomer **7a** was obtained by preparative GLC of mixed cis/trans product obtained from a similar reaction using CuI catalyst (see Table I). The NMR spectrum was also identical with that described in the literature.[3b]

***trans*-2-Ethenyl-1-methoxycyclohexane (6).** To a 500-mL flask were added 100 mL of hexamethylphosphoric triamide (HMPA) and 5.5 g (44 mmol) of crude **6a**. The solution was cooled in an ice bath, and 41 mL (65 mmol) of *n*-BuLi (1.6 M in hexane) was added. The dark red solution was treated with excess MeI (20 mL), stirred for 2 h, and then taken up in 200 mL of water. The desired product was extracted into pentane (3 × 50 mL), and the organic phase was washed repeatedly with water and saturated NaCl, before drying over K_2CO_3. Rotary evaporation afforded 5.2 g of yellow oil, which upon short-path distillation, bp 32–35 °C (2 Torr), gave 2.8 g (45%) of colorless oil; GLC analysis showed this to be 98% **6** and 2% unknown material, with <0.1% of the cis isomer (**7**).

Samples of pure **6** were obtained by preparative GLC. ^{1}H NMR: δ 1.10–1.30 (m, 4 H), 1.62–1.82 (m, 3 H), 1.97–2.15 (m, 2 H), 2.84–2.93 (m, 1 H), 3.34 (s, 3 H), 4.98–5.10 (m, 2 H), and 5.87 ppm (ddd, 1 H, J = 18, 10, and 7 Hz). Anal. Calcd for $C_9H_{16}O$: C, 77.09; H, 11.50. Found: C, 77.38; H, 11.60.

***trans*-2-Bromo-1-methoxycyclohexane (8).** To a 500-mL flask equipped with a magnetic stirrer and a reflux condenser were added 20.5 g (0.25 mol) of cyclohexene and 100 mL of methanol. *N*-Bromosuccinimide (44.5 g, 0.25 mol) was then added in portions (exotherm) over a period of 0.5 h. The mixture was stirred overnight and then most of the solvent was removed by heating on a steam bath. The remaining material was taken up in water and hexane; following the usual separation, extraction, washing, and drying (Na_2SO_4), rotary evaporation gave 48.1 g of crude oily product, which was vacuum distilled to give 41.8 g (87%) of pure **8**;[23] bp 80–84 °C (1 Torr). ^{1}H NMR δ 1.23–1.40 (m, 2 H), 1.60–1.90 (m, 4 H), 2.13–2.23 (m, 1 H), 2.27–2.37 (m, 1 H), 3.20–3.28 (m, 1 H), 3.43 (s, 3 H), and 3.94–4.02 ppm (m, 1 H).

***cis*-2-Ethenyl-1-methoxycyclohexane (7).** A mixture of 1.0 g (5.3 mmol) of CuI (98%) and 40 mL of ether was cooled to −40 °C, and a −20 °C solution of vinylmagnesium bromide (200 mL, 0.34 mol) was added. To the cold solution was added **8** (14.7 mL, 0.104 mol), and the mixture was then allowed to warm to room temperature. The usual workup and rotary evaporation gave 13.6 g (94%) of crude oil, which was mainly a mixture of **6**/**7** in a ratio of 14/86. Short-path distillation gave 6.6 g (45%) of colorless oil, bp 40–43 °C (5 Torr), with essentially no isomer fractionation (**6**/**7** = 12/88). Pure **7** was obtained by preparative GLC. ^{1}H NMR: δ 1.25–1.90 (m, 8 H), 2.28–2.38 (m, 1 H), 3.25–3.40 (m, 1 H), 3.32 (s, 3 H), 5.01–5.10 (m, 2 H), and 5.98 ppm (ddd, 1 H, J = 18, 10, and 7 Hz). Anal. Found: C, 77.16; H, 11.58.

1-Ethenylcyclohexene (9). A sample of this diene was isolated by preparative GLC of the crude product from LDA treatment of a mixture of **6** + **7**. The NMR spectrum of **9** coincided with that described by Hanack et al.[11]

Kinetics. The base solutions were prepared by addition of either MeLi (in ether) or *n*-BuLi (in hexane) to the amine in the appropriate solvent, in flasks surrounded by an ambient temperature (24 °C) water bath. The unusual LTMP/ether initial rapid reaction was not caused by the exotherm that accompanies base formation, since base prepared in an ice bath and then placed

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in the room temperature bath exhibited the same behavior. Control experiments with excess RLi or amine showed that these did not materially affect the rates. Aliquots were removed periodically, quenched with 5% HCl, diluted with hexanes for handling, dried over K_2CO_3, and analyzed by capillary GC. Known samples of **6**, **7**, and **9** vs undecane showed that no peak area correction factors were needed to convert the GC areas to molar ratios. Most analyses involved 6–10 points, covering 1–3 half-lives.

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Reactions of 4,4-Diphenylcarbena-2,5-cyclohexadiene and Related Systems in Dimethyl Sulfoxide

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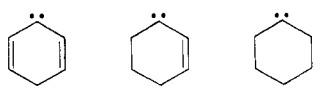
Thermal decomposition of the lithium salt of the tosylhydrazone of 4,4-diphenyl-2,5-cyclohexadienone (**10**) in dimethyl sulfoxide produces 4,4-diphenyl-2,5-cyclohexadienone, *p*-benzylbiphenyl, 3,4-diphenyltoluene, 6,6-diphenyl-1-methylene-2,4-cyclohexadiene, and *o*-terphenyl, while similar treatment of the lithium salt of the tosylhydrazone of 4,4-diphenylcyclohexenone (**26**) generates 4,4-diphenylcyclohexenone, 5,5-diphenyl-1,3-cyclohexadiene, 4,4-diphenyl-1-methylene-2-cyclohexene, and 6,6-diphenyl-1-methylene-2-cyclohexene. Thermolysis of the lithium salt of the tosylhydrazone of 4,4-diphenylcyclohexanone (**32**) in dimethyl sulfoxide yields 4,4-diphenylcyclohexene, 4,4-diphenylcyclohexanone, and 4,4-diphenyl-1-methylcyclohexanol. The kinetics of the thermal decomposition of tosylhydrazone lithium salts **10**, **26**, and **32** in dimethyl sulfoxide in the temperature range 90–125 °C were analyzed by evaluating the rate constants for the two consecutive first-order steps. The second step, for parent salts **10**, **26**, and **32**, decomposition of diazo compound to carbene, exhibited values for k_2 (110 °C) of 8.22, 197, and 363 h^{-1}, $\Delta G^{\ddagger}$s of 27.2 ± 3.1, 24.8 ± 3.1, and 24.2 ± 0.9 kcal mol^{-1}, and $\Delta S^{\ddagger}$s of −10.7 ± 5.7, −6.3 ± 5.8, and −8.1 ± 1.7 eu. The activation parameters for decomposition of the diazo compounds are interpreted in terms of an increasing dipole moment in the transition state relative to ground state. Product formation from carbene intermediate is viewed in terms of a competition of a singlet oxygen abstraction reaction with intersystem crossing to triplet.

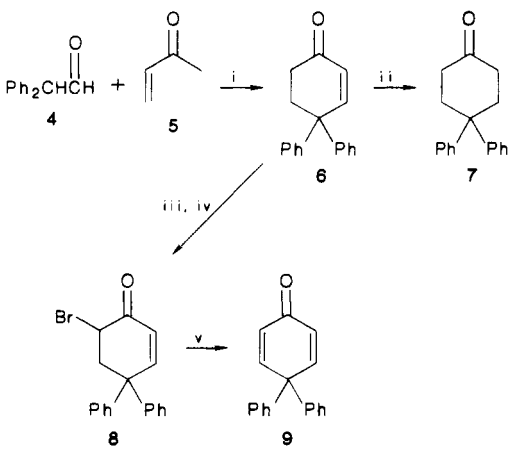
Although there have been a number of interesting studies on the nature of vinylcarbenes,[1] there remain questions concerning the effects of conjugation on the stability and reactivity of vinylcarbene intermediates. An interesting series to illustrate the nature of conjugated carbenes, we thought, might well be the series carbena-2,5-cyclohexadiene (**1**), carbena-2-cyclohexene (**2**), and carbenacyclohexane (**3**), the cyclic framework serving the useful purpose of preventing the intramolecular insertion into the double bond to produce a cyclopropene moiety due to strain considerations. A priori, one might expect on the basis of simple qualitative MO theory that the electrophilicity of the carbene center in the singlet would increase as the delocalization of the π system is decreased from a four electron five orbital system to a two electron three orbital system to a completely localized system (**1** to **3**).



1 **2** **3**

If one considers the present state of knowledge of the nature of carbocation intermediates in organic chemistry, it is clear that measurement of rates of solvolytic reactions and characterization of reaction pathways through identification of products have been preeminent as investigative modes of analysis.[2] Use of both modes of analysis in carbene studies has been rare due to the lack of a generally useful method for analysis of the rate of carbene formation that would play the same role as tosylate solvolysis has in carbocation chemistry. It appeared to us that the decomposition of the lithium salts of tosylhydrazones

Scheme I[a]



[a] i = 3 M KOH/ether; ii = H_2, Pd/C; iii = $CH_3CO_2C(CH_3)$=CH_2, *p*-TsOH; iv = Br_2/CCl_4; v = Li_2CO_3, LiBr, DMF.

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