Tetrahedron Letters, Vol. 34, No. 5, pp. 765-768, 1993
Printed in Great Britain

0040-4039/93 $6.00 + .00
Pergamon Press Ltd

Regioselectivity in Gas-Phase Elimination Reactions: 1,2 vs 1,4 and Allenic Ion vs Dienide Formation

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Key Words: gas-phase; eliminations; regiochemistry; flowing afterglow; methyl ethers

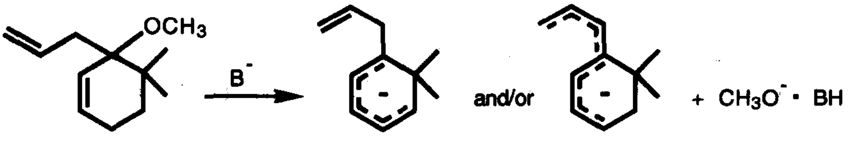
Abstract: *Gas-phase elimination reactions of deuterium labeled 1-allyl-1-methoxy-6,6-dimethyl-2-cyclohexene (1), 1-methoxy-4,4-dimethyl-1-vinyl-2-cyclohexene (2) and 3-methoxy-3-methyl-1-butene (3) have been investigated. 1,2-Elimination is the favored pathway when 1 reacts with hydroxide (3.5:1) and methoxide (2.6:1), but 1,4-elimination is preferred with fluoride by 2:1. Abstraction of a vinyl proton in the elimination reactions of 2 and 3 is dominant when amide and/or dimethylamide are used, whereas the loss of an alkyl proton is heavily favored with hydroxide.*

We have recently reported that the competition between 1,2- and 1,4-elimination in 3-methoxycyclohexene is dependent upon base strength.[1] 1,4-Elimination is heavily favored when strong bases such as hydroxide and amide are used, whereas the 1,2-pathway becomes more competitive when weaker bases such as methoxide are employed. A shift in mechanism from E1cB to E2 was proposed to account for this change in selectivity. The preference for the 1,4-channel may be a reflection of the enhanced acidity at the allylic position relative to the alkyl site. In solution, relatively few reports have focused on the competition between 1,2- and 1,4-eliminations, but the available data indicates that the selectivity is dependent upon the nature of the substrate and the reaction conditions.[2] Our gas-phase studies have now been extended to include 1-allyl-1-methoxy-6,6-dimethyl-2-cyclohexene (**1**) because in this substrate the two elimination channels are effectively "equal" since they both involve the removal of an allylic proton. Furthermore, we have discovered high regioselectivity in the elimination reactions of 1-methoxy-4,4-dimethyl-1-vinyl-2-cyclohexene (**2**) and 3-methoxy-3-methyl-1-butene (**3**). Both substrates show a strong preference for reaction at the vinyl C-H bond with amide and/or dimethylamide, whereas attack at the alkyl site dominates when hydroxide is used.

In our flowing afterglow apparatus,[3] **1** reacts with a variety of bases (B^-) to afford a cyclohexatrienide (**4**) and $MeO^- \cdot BH$ (**5**, Scheme I). Both of these ions can arise from a 1,2- or a 1,4- elimination, but the two pathways can be distinguished with an appropriately labeled substrate. 2,4,4-d$_3$-1-Allyl-1-methoxy-6,6-dimethyl-2-cyclohexene (**1a**) was used in this regard and was readily prepared from 6,6-dimethyl-2-cyclohexen-1-one. Deuterium was introduced into the enone via H/D exchange (OD^-/D_2O) to afford 2,4,4-d$_3$-6,6-dimethyl-2-cyclohexen-1-one. Addition of allyl Grignard and subsequent methylation (NaH/MeI) of the resulting alcohol afforded the desired deuterium labeled derivative (**1a**).

The results of the reaction of **1a** with several bases are shown in Scheme II. The deuterium content of the $MeO^- \cdot BH(D)$ cluster is indicative of the regioselectivity. Unfortunately, the cyclohexatrienide is of no value in

Scheme I: The reaction products of 1-allyl-1-methoxy-6,6-dimethyl-2-cyclohexene with a series of bases

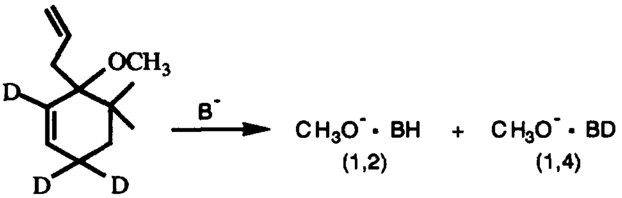


1 4 5

	4	5
NH_2^-	95%	5%
OH^-	58%	42%
MeO^-	45%	55%
t-BuO$^-$	37%	63%
F^{-a}	11%	76%

a. Adduct = 13%

Scheme II: Regioselectivity in the base-induced eliminations of 2,4,4-d_3-1-allyl-1-methoxy-6,6-dimethyl-2-cyclohexene[a]



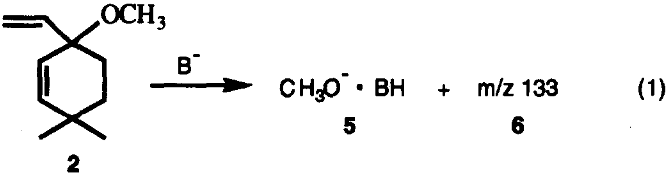
1a

	(1,2)	(1,4)
OH^-	78%	22%
MeO^-	72%	28%
t-BuO$^-$	42%	58%
F^-	34%	66%

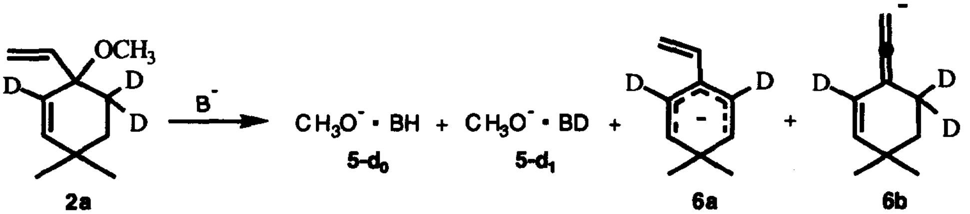
a. MS: 99% d_3

this case since 1,2- and 1,4-eliminations both lead to d_2-ions. Nonetheless, the data reveals that the selectivity is sensitive to the base strength. Hydroxide and methoxide react predominately via the 1,2-pathway, 3.5:1 and 2.6:1 respectively, whereas 1,4-elimination is favored with the weakest bases used in this study (t-BuO$^-$ and F^-). This is in sharp contrast to our results with 3-methoxycyclohexene, the 1,4-pathway is essentially the exclusive reaction channel with hydroxide,[1] indicating that allylic activation is important in governing the selectivity in these systems. It is worth adding that our rate measurements on 3-methoxycyclohexene indicate that the primary kinetic isotope effect is small ($k_H/k_D \leq 1.5$), consequently, we expect that it will have only a slight effect on the product ratios of **1a**. An obvious trend in Scheme II is the gradual shift toward 1,4-elimination as the base strength decreases. Our results on 3-methoxycyclohexene as well as some recent calculations[4] indicate that strong bases (NH_2^- and OH^-) react via an E1cB-like mechanism whereas weaker bases (F^-) proceed by an E2-type process. Therefore, our results with **1a**, a substrate in which both elimination channels have activated (allylic) hydrogens, suggest that an E1cB process favors 1,2-elimination and an E2 reaction proceeds preferentially via 1,4-elimination.

Compound **2** reacts with several bases to afford **5** and an ion with m/z 133 (eq 1). The latter species could be a cyclohexadienide or an allenic ion (**6a** and **6b**, respectively) depending upon whether a vinyl or an alkyl proton is abstracted in the elimination reaction.[5,6] These two mechanistic possibilities can be distinguished with the trideuterio labeled substrate **2a**. In particular, a d_1-cluster and a d_2-cyclohexadienide will be formed when the elimination involves the alkyl deuteron whereas a d_0-cluster and a d_3-allenic ion will arise from attack at the vinyl site. Our results are given in Scheme III and reveal that both amide and dimethylamide have a strong preference for the more acidic (vinyl) hydrogen. Dimethylamide appears to be more selective than amide



Scheme III: The reaction products of 2,6,6-d_3-1-methoxy-4,4-dimethyl-1-vinyl-2-cyclohexene with several bases.[a]



Products	Bases			Reactive Site
	NH_2^-	Me_2N^-	OH^-	
5-d_0	-	-	3.6%	Vinyl
5-d_1	-	-	80.7%	Alkyl
5-d_2	-	-	15.7%	Alkyl
6-d_1	-	-	18.3%	Alkyl
6-d_2	18.4%	8.1%	80.4%	Alkyl
6-d_3	81.6%	91.9%	1.3%	Vinyl

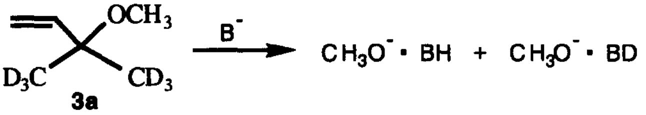
a. MS: 98% d_3

(11.3:1 vs 4.4:1), but this is misleading because the deuteron at the vinyl carbon in **2a** undergoes H/D exchange with amide.[7] The 4.4:1 ratio, consequently, is a lower limit and the two bases probably are not very different. We do observe, however, a remarkable change in selectivity with hydroxide. Both the cluster ion (**5**) and the cyclohexadienide (**6a**) indicate that the reaction proceeds predominately (> 96%), if not exclusively, at the alkyl center.[8]

The dramatic change in the regioselectivity of **2a** was unanticipated. Therefore, we decided to examine an acyclic analog in order to probe the generality of this competition. 3-Methoxy-3-methyl-1-butene (**3**) was found to be a suitable substrate and an appropriately labeled derivative (**3a**) was readily prepared from d_6-acetone. The reaction of **3a** with hydroxide mirrors the selectivity observed for **2a** with a 97:3 preference for attack at the alkyl center (Scheme IV). The results with amide and dimethylamide, however, are not as conclusive. Both bases were generated by electron ionization of their corresponding amines and the excess neutral reagent was found to wash out the isotopic label in the product ion i.e. **3a** reacts with amide to afford $MeO^- \cdot NH_3$ whereas ND_2^- (generated from ND_3) leads exclusively to the formation of $MeO^- \cdot ND_3$. Unfortunately, this problem could not be circumvented with amide, but by decreasing the amount of dimethylamine which was used the d_0/d_1 product ratio became independent of the amine concentration. In accord with **2a**, the reaction was found to proceed predominately (≥ 2:1) by abstraction of the vinyl proton. It is apparent that **2** and **3** react similarly and that the observed selectivity may be quite general in gas-phase elimination reactions.

We are currently extending this work to investigate the stereoselectivity of 1,2-eliminations in the appropriately deuterium labeled methoxycyclohexenes. These efforts will be reported in due course.

Scheme IV: Selectivity in the base-induced eliminations of 4-d_3-3-methoxy-3-d_3-methyl-1-butene[a]



3a

	$CH_3O^- \cdot BH$	$CH_3O^- \cdot BD$
Me_2N^-	~65%	35%
OH^-	3%	97%

a. MS: 99% d_6

Acknowledgment: Support from the National Science Foundation and the donors of the Petroleum Research Foundation, administered by the American Chemical Society, are gratefully acknowledged.

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5. An allenic ion is formed because the allenic position is the most acidic one in the conjugate acid of **6b**.
6. For a listing of gas-phase acidities see: Lias, S. G.; Bartmess, J. E.; Liebman, J. F.; Holmes, J. L.; Levin, R. D.; Mallard, W. G. *J. Phys. Chem. Ref. Data* **1988**, *17*, Suppl. 1.
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8. The vinyl deuteron in **2a** undergoes some exchange with hydroxide and this accounts for the formation of **5**-d_2 and **6**-d_1. Given the small amount of **5**-d_0 and **6**-d_3, however, H/D exchange will have little, if any, effect on the stereoselectivity.

(Received in USA 26 October 1992)