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The Gas-Phase Elimination Reaction of 3-Methoxycyclohexene: Regiochemistry

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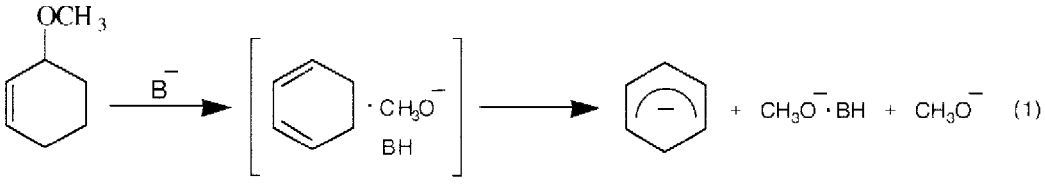
Abstract: *Gas-phase elimination reactions of deuterium labeled 3-methoxycyclohexenes have been investigated. 1,4-Elimination is heavily favored over 1,2-elimination when strong bases such as hydroxide and amide are used. The 1,2-pathway becomes more competitive when weaker bases such as methoxide are employed, and the mechanism shifts from E1cB to E2.*

Elimination reactions have been extensively studied in solution and have been the subject of many mechanistic investigations.[1] Numerous aspects of this reaction have been probed including isotope, leaving group, solvent, and structural effects, rates of reaction, regiochemistry, and stereochemistry among others. In contrast to 1,2-eliminations, 1,4-eliminations have received much less attention in the literature.[2] In particular, relatively few reports have focused on their stereochemistry or the competition between 1,2- and 1,4-pathways.[3] The available data, however, does indicate that the selectivity, *syn* vs *anti* and 1,2- vs 1,4-, is dependent on the nature of the substrate and the reaction conditions.

In the gas-phase, elimination reactions have also been studied extensively.[4] Both cyclic and acyclic substrates have been used in kinetic investigations, and to explore isotope effects, regioselectivity, and stereoselectivity. Despite these efforts many questions still remain. One reason for this is that eliminations are often difficult to distinguish from substitution reactions because they both can lead to the same ionic products. Two *direct* approaches for resolving this ambiguity and obtaining regio- and stereochemical information are identifying the neutral products of ion-molecule reactions,[5] and designing systems such that the essential information is retained in the detected ionic products. The former approach is proving successful in our laboratory,[6] but the latter method was chosen for exploring the competition between 1,2- and 1,4-eliminations (regioselectivity). We report herein the initial results of our work, and the first observation of a 1,4- elimination reaction in the gas-phase.

3-Methoxycyclohexene (**1**) reacts with NH_2^-, OH^-, and CH_3O^- (B^-) in our flowing afterglow apparatus[7] to afford cyclohexadienide (**2**) and MeO^- BH (**3**) as the major products (eq. 1). Neither ion can result from a substitution reaction, and consequently, they must be formed by an elimination. The resulting complex (**A**) can dissociate into cyclohexadienide (**2**), a MeO^-·BH cluster (**3**), or methoxide. The formation of **2**, the "bite-back" product, is a consequence of the fact that CH_3O^- is a strong enough base (ΔH_{acid} (CH_3OH) = 380.6 kcal mol^{-1}) to deprotonate the diene (ΔH_{acid} (1,3-cyclohexadiene) = 373.3 kcal mol^{-1}).[8] In any case, **2** and **3** can be used



1		A	2	3	
	NH_2^-		48%	5%	47%
	OH^-		33%	50%	17%
	CH_3O^-		18%	82%	–

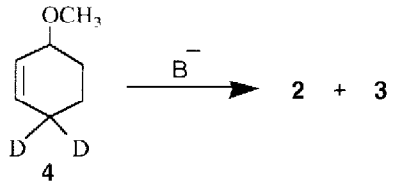
to establish the regioselectivity in this reaction with the appropriately labeled compounds.

Isotopically labeled 3-methoxycyclohexenes (**4** and **5**) were prepared from the corresponding alcohols which have been previously described.[9] The deuterium was introduced by H/D exchange, and as a result neither compound was isotopically pure. Integration of the fully resolved ^{1}H-NMR spectra (500 MHz) furnished the location of the label and the percent incorporation at each site. The deuterium content was verified by mass spectrometry, and the relative amounts of each isotopomer e. g. d_1, d_2, etc. was obtained. The location of the label in each isotopomer was readily calculated by assuming that the deuterium was statistically distributed at the exchangeable sites (C2, C4, and C6) during the synthesis of **4** and **5**. It is a simple matter, consequently, to predict what the isotope content in **2** and **3** would be after a 1,2- or 1,4-elimination. This model and the experimental results obtained using three different bases are summarized in tables I and II. The data for **4**, clearly indicates that a 1,4-elimination is heavily, if not exclusively, favored with OH^- and NH_2^-. This preference occurs despite the fact that a primary isotope effect would retard this pathway. Compound **5** must also be undergoing a 1,4-elimination, but it will not be disfavored by an isotope effect. The experimental and predicted results, however, do not agree to the same extent as with **4**. The deuterium content in **3** is consistent with a 1,4-elimination, but the distribution in **2** is anomalous. It does not fit either pathway or any combination of the two. This discrepancy can be resolved by postulating an isotope effect of 2 - 3 for the second step in the formation of **2**. In other words, CH_3O^- must abstract a proton more readily than a deuteron from cyclohexadiene in **A**. An isotope effect of this magnitude is quite reasonable.

When methoxide is used as a base, our data indicates that the course of the reaction changes. A 1,2-elimination takes place and begins to successfully compete with the more dominant 1,4-pathway. This is evident in both the cyclohexadienide (**2**) and CH_3O^-·CH_3OH(D) (**3**) product ratios. Moreover, this result makes intuitive sense in that the selectivity changes with base strength. 1,4-Eliminations result from the abstraction of a relatively acidic proton, whereas, the 1,2-pathway involves removing a nonacidic proton. Strong bases such as amide and hydroxide presumably react via an E1cB mechanism, and this leads to 1,4-selectivity. Weaker bases such as methoxide are not strong enough to remove an allylic proton, and an E2 elimination (which can afford both 1,2- and 1,4-products) becomes more favorable.[10]

Further evidence for the preference for 1,4-eliminations is found in the reactions of **6** and **7**. In the former, the 1,2-pathway is blocked by the geminal methyl groups, and NH_2^- and OH^- induce an elimination reaction analogous to the one illustrated in equation 1. Compound **7**, is prevented from undergoing a 1,4-elimination because of its geminal dimethyl group, and in this case the 1,2-pathway does not take place either. Instead, the major product is due to proton transfer.

Table I: Elimination of 6,6-d_2-3-methoxycyclohexene (**4**)[a]



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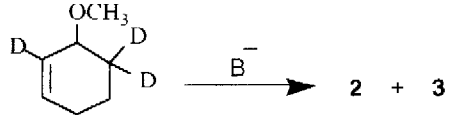
	Predicted (%)		Observed (%)		
Product	1,4	1,2	OH^-	NH_2^-	CH_3O^-
2-d_0	4.4	3.5	2.8	4.5	4.6
2-d_1	66.4	37.3	64.8	66 8	48.8
2-d_2	23.6	45.6	23.2	18.4	30.7
2-d_3	5 1	12 5	6 3	5.1	9.3
2-d_4	0.5	1.0	3 0	5.2	6.5
3-d_0	6.3	85.2	10.2	-	29.0
3-d_1	93.7	14 8	89.8	-	71.0

a. MS: 5 5%d_1, 63.2%d_2, 17.9%d_3, 4.1%d_4, 9.2%d_5; NMR, 15.0%d_1(C2), 30 0%d_2(C4), 87 0%d_2(C6).

Table II· Elimination of 2,4,4-d_3-3-methoxycyclohexene (**5**)[a]



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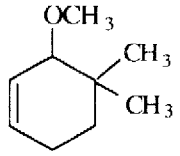
	Predicted (%)		Observed (%)		
Product	1,4[b]	1,2	OH^-	NH_2^-	CH_3O^-
2-d_0	0.3(0 2)	0 4	0.0	0.0	0.0
2-d_1	12.3(6.7)	23.3	5.9	5.8	5.9
2-d_2	48.7(36.0)	73.7	36.7	36.6	40.3
2-d_3	37 7(55 7)	2 0	56.7	52.6	53.1
2-d_4	0.9(1.4)	0.5	0.6	4 9	0.7
3-d_0	97.6	1.9	92.1	-	77.3
3-d_1	2.4	98.1	7.9	-	22.7

a MS: 0 8%d_1, 20 9%d_2, 63.2%d_3, 14.6%d_4, 0.5%d_5; NMR: 77 0%d_1(C2), ≥96%d_2(C4), 5 0%d_2(C6)

b. Values in parentheses are based on the assumption that k_H/k_D=3 for the deprotonation step in **A**.



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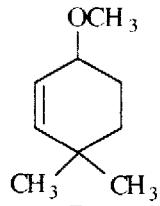

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An obvious extension of this work would be to synthesize, stereospecifically, deuterium labeled 3-methoxycyclohexenes in order to elucidate the stereochemistry in these elimination reactions. Efforts along these lines are underway, and will be reported in due course.

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10. This idea is also supported by our data on 3-butenyl ethyl ether. Strong bases lead only to the formation of EtO^-, and weaker bases are less selective.

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