Stereoselectivity in 1,2-Elimination Reactions. The Gas-Phase Reactivity of Deuterium-Labeled 1-Methoxy-1-*tert*-butyl-4,4-dimethyl-2-cyclohexene and 1-Methoxy-3-*tert*-butyl-6,6-dimethyl-3-cyclohexene

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Received November 18, 1993

The stereochemistry of 1,2-elimination reactions has been exhaustively studied in solution.[2] A wide variety of substrates have been examined under a myriad of reaction conditions in order to probe the effects of solvent, counterion, base strength, and leaving group. Given the large number of variables, it is not surprising that the whole range of the syn/anti dichotomy has been observed. It is well-known, however, that anti 1,2-eliminations are generally favored. The situation in the gas phase is not so clear-cut. In fact, no convincing stereochemical evidence has been reported to date.[3] We have previously shown that appropriately labeled methoxycyclohexenes can be used to elucidate the competition between 1,2- and 1,4-eliminations as well as the stereoselectivity for the latter process.[4] In this report we now provide the first direct experimental evidence on the stereochemistry of 1,2-eliminations using deuterium-labeled 1-methoxy-1-*tert*-butyl-4,4-dimethyl-2-cyclohexene (**1**) and 1-methoxy-3-*tert*-butyl-6,6-dimethyl-3-cyclohexene (**2**). A wide variety of bases are relatively nonselective with the former compound, whereas the latter derivative displays high syn selectivity with weak bases and moderate anti selectivity with strong bases.

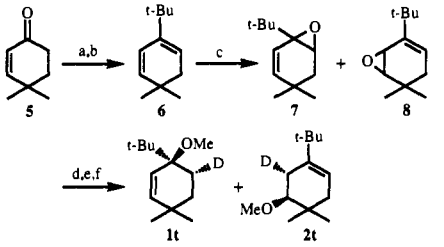
1-Methoxy-1-*tert*-butyl-4,4-dimethyl-2-cyclohexene (**1**)[5] reacts readily with a number of bases in our flowing afterglow device[6] to afford two ionic products: a cluster between the protonated base and methoxide (**3**), and a cyclohexadienide ion (**4**, eq 1 and Table 1).[7] These species must arise from a 1,2-elimination reaction since the 1,4-pathway is precluded by the *gem*-dimethyl group. In order to examine the stereospecificity of this reaction, both *cis* and *trans* deuterium-labeled derivatives at C6 were synthesized. The route for the *trans* compound is illustrated in Scheme 1.

Table 1. Initial Product Distributions for the Reactions of **1** with a Series of Bases[a]

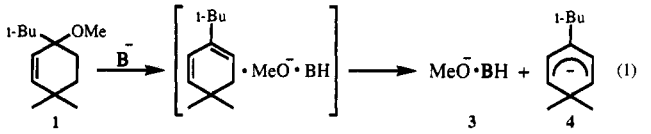
base	products, % 3	4
NH_2^- [b]	5 (–26.5)	90 (–22.1)
Me_2N^-	10 (–27.3)	90 (–23.5)
OH^-	54 (–22.6)	46 (–9.2)
MeO^-	75 (–17.3)	25 (1.1)
t-BuO^- [c]	70 (–7.5)	23 (6.8)
F^- [d]	83 (–18.0)	4 (10.6)

[a] Parenthetical values correspond to the reaction enthalpy (in kcal mol^{-1}) for the formation of the identified product. [b] 5% MeO^- (–11.5). [c] 7% adduct. [d] Reaction carried out at 120 °C; 13% adduct.

Scheme 1



[a] Key: (a) *t*-BuLi, $LiClO_4$, THF, –78 °C; (b) I_2, Δ; (c) *m*-CPBA, CH_2Cl_2, 0 °C, 1 h; (d) $LiEt_3BD$, THF, 65 °C, 48 h; (e) separation (column chrom. on neutral alumina); (f) NaH, MeI, THF, 50 °C, 4 h.



(1)

To afford the *trans* compound, 4,4-dimethyl-2-cyclohexen-1-one (**5**)[8] was converted to diene **6** in a one-pot procedure by the Lewis acid catalyzed 1,2-addition of *tert*-butyllithium and distillation of the resulting mixture over iodine. Omission of the Lewis acid or the use of *t*-BuMgBr or *t*-$BuCeCl_2$ leads to less favorable 1,2:1,4 ratios; i.e., the ratio decreases from 4:1 to no better than 1:1. Epoxidation of **6** afforded nearly equal amounts of **7** and **8** (1:1.3), both of which could be selectively reduced with Super-Deuteride. Separation of the resulting alcohols followed by methylation afforded gram quantities of **1t** and **2t**. The *cis* derivatives, **1c** and **2c**, were prepared via the same sequence except that deuterium was introduced into the starting enone (**5**) by base-catalyzed exchange and the deuterated epoxides were reduced with Super-Hydride. Both sets of transformations afforded ethers with >96% deuterium incorporation and stereospecificity.[9]

The reactions of **1t** and **1c** afford very similar product distributions to the unlabeled substrate, and incorporation (or lack thereof) of deuterium into the ionic products *directly* reveals the stereoselectivity. For example, **1t** reacts by an anti elimination to give a d_1-cluster and a d_0-cyclohexadienide whereas the syn pathway leads to a d_0-cluster and a d_1-cyclohexadienide (eq 2). By measuring the initial product distribution, the stereochemical preference was obtained for a series of bases (Table 2). The overall selectivity is quite modest, ~3:2 anti/syn, and does not appear to vary substantially with base strength.

Both **3** and **4** arise from syn and anti eliminations, contrary to a previous suggestion.[3f] From a mechanistic standpoint, it seems reasonable to conclude that strong bases react via an $E1_{cb}$

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(1) Taken in part from the Ph.D. Thesis of John J. Rabasco (University of Minnesota, 1993).

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(3) For early work on 1,2-eliminations in the gas phase, see: (a) Ridge, D. P.; Beauchamp, J. L. *J. Am. Chem. Soc.* **1974**, *96*, 637, 3595. (b) Sullivan, S. A.; Beauchamp, J. L. *J. Am. Chem. Soc.* **1976**, *98*, 1160. (c) Sullivan, S. A.; Beauchamp, J. L. *J. Am. Chem. Soc.* **1977**, *99*, 5017. (d) DePuy, C. H.; Bierbaum, V. M. *J. Am. Chem. Soc.* **1981**, *103*, 5034. (e) DePuy, C. H.; Beedle, E. C.; Bierbaum, V. M. *J. Am. Chem. Soc.* **1982**, *104*, 6483. (f) de Koning, L. J.; Nibbering, N. M. M. *J. Am. Chem. Soc.* **1987**, *109*, 1715. (g) van Berkel, W. W.; de Koning, L. J.; Nibbering, N. M. M. *J. Am. Chem. Soc.* **1987**, *109*, 7602. (h) de Koning, L. J.; Nibbering, N. M. M. *J. Am. Chem. Soc.* **1988**, *110*, 2066.

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(7) The proton affinity of **4** was estimated to be 370 kcal mol^{-1}. All other thermochemical data comes from the following: (a) 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. (b) Benson, S. W. *Thermochemical Kinetics*, 2nd ed., John Wiley and Sons: New York, 1976.

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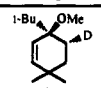
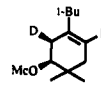
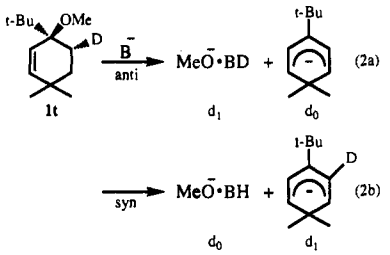
Table 2. Stereoselectivity in the 1,2-Elimination Reactions of **1** and **2**[a]

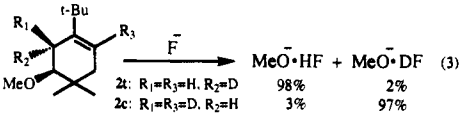
		product[c]					selectivity[d]			
		3		4			av		overall	
compd	base	syn	anti	syn	anti	k_H/k_D[c]	syn	anti	syn	anti
 1t	Me_2N^-			58	42	1.40 ± 0.08	58	42		
	OH^-	26	74	24	76	1.16 ± 0.10	25	75		
	MeO^-	61	39	66	34	2.48 ± 0.95	63	37		
	t-BuO^-	70	30	60	40	3.95 ± 0.83	68	32		
	F^-[e]	65	35			3.91[f]	65	35		
 1c	Me_2N^-			28	72	1.23 ± 0.14	28	72	43	57
	OH^-	22	78	25	75	1.13 ± 0.10	24	76	25	75
	MeO^-	11	89	44	56	1.86 ± 0.13	24	76	43	57
	t-BuO^-	15	85	35	65	2.43 ± 0.65	22	78	45	55
	F^-[e]	25	75			1.82[f]	25	75	45	55
 2t	Me_2N^-			23	77	1.14 ± 0.09	23	77		
	OH^-	43	57	28	72	1.00 ± 0.16	38	62		
	MeO^-	48	52	19	81	1.16 ± 0.15	46	54		
	t-BuO^-	55	45	15	85	1.36 ± 0.22	50	50		
	F^-[e]	98	2				98	2		
	$FCH_2CH_2O^-$[e]	92	8				92	8		
 2c	Me_2N^-			6	94	1.00[f]	6	94	14	86
	OH^-	21	79	17	83	0.95 ± 0.04	19	81	28	72
	MeO^-	30	70	13	87	1.16 ± 0.13	28	72	37	63
	t-BuO^-	29	71	7	93	1.69 ± 0.14	21	79	35	65
	F^-[e]	97	3				97	3	98	2
	$FCH_2CH_2O^-$[e]	87	13				87	13	90	10

[a] The normalized product distributions and isotope effects have not been corrected for the deuterium content and stereospecificity of the starting compounds or the occurrence of the competing (syn/anti) pathway. [b] Branching ratios were measured to obtain the initial product distributions. [c] Isotope effects are the average of those measured by monitoring the decrease in the reactant ion signal resulting from the addition of equal flows of the labeled and unlabeled material, and a 1:1 mixture of the labeled and unlabeled compound. The reported errors are the standard deviations in our measurements, but it is unlikely that the isotope effects are more reliable than ±20%. [d] The average selectivity is the weighted mean of the normalized selectivities for **3** and **4** (i.e., % syn = Σ(% syn products) and % anti = Σ(% anti products)). The overall selectivity is simply the mean of the average selectivities for **1t**/**1c** and **2t**/**2c**. A more thorough analysis accounting for the deuterium content and stereospecificity of the substrate, as well as the kinetic isotope effects, has been carried out but gives very similar results.[1] [e] Reaction carried out at 120 °C. [f] Isotope effect based solely on the product distribution for the reaction of a 1:1 mixture of labeled and unlabeled compound.



pathway whereas weaker bases shift toward the E2 continuum.[3,10] In either case, proton transfer is involved in the rate-determining step since a normal primary isotope effect is observed; it is diminished by the occurrence of syn elimination from **1t** and anti elimination from **1c**. The lack of selectivity from the $E1_{cb}$ channel is not surprising since proton abstraction reactions usually are facile and somewhat indiscriminate.[11] One might expect the E2 pathway, however, to show a marked preference for anti elimination.[10] Molecular mechanics calculations using the MMX force field[12] reveal that the *tert*-butyl group is locked into a pseudoequatorial position in this conformationally restricted ring system. This prevents the leaving group and the β-hydrogen from achieving a periplanar arrangement, and dihedral angles of 31.5° and 146.7° result. Since the syn pathway is much less sensitive to the conformational dependence of the substrate,[10b] the intrinsic bias for the anti channel should be greatly diminished. Steric crowding appears to favor the syn pathway; the anti proton is blocked by the axial methyl at C4 and one of the *tert*-butyl methyl groups, and this may also contribute to making the two reaction avenues competitive with each other.

The stereoselectivity was found to change dramatically upon activating the β-hydrogen. Compound **2** affords the expected products (**3** and **4**), and the stereoselectivity is similar to that of **1** when strong bases are used (Table 2). Weak bases such as fluoride and fluoroethoxide, however, show a strong preference for the syn pathway (eq 3). The greater acidity of **2** and the lack



of a primary isotope effect with F^- and $FCH_2CH_2O^-$ suggest that the rate-determining step is expulsion of the leaving group. Since the only thermodynamically accessible product is $MeO^-{\cdot}BH$,[7] and the leaving group and protonated base can interact much more readily in a syn elimination, this pathway is highly favored. Ab initio computations seem to support this notion and should be of great value in unraveling the mechanistic complexities in this system.[13]

Acknowledgment. Support from the National Science Foundation, the Minnesota Supercomputer Institute, and the donors of the Petroleum Research Fund, as administered by the American Chemical Society, is gratefully acknowledged.

(9) **1t**: >97% d_1 and >97% trans; **2t**: >97% d_1 and >97% trans. **1c**: >96% d_2 and >96% trans. **2c**: >97% d_2 and >97% trans. The location of the label follows from the synthetic procedure, but was confirmed by ^1H NMR chemical shifts and 2D-NOESY experiments. It is worth adding that **1c** and **2c** have two deuteriums (one each at C2 and C6 in **1c** and one each at C2 and C4 in **2c**) because the base-catalyzed exchange of **5** leads to incorporation of deuterium at the α-vinyl position and the methylene group adjacent to the carbonyl.

(10) Such a conclusion is consistent with high level calculations and several literature reports. (a) Gronert, S. *J. Am. Chem. Soc.* **1991**, *113*, 6041. (b) Gronert, S. *J. Am. Chem. Soc.* **1992**, *114*, 2349. (c) Gronert, S. *J. Am. Chem. Soc.* **1993**, *115*, 652. (d) Bickelhaupt, F. M.; Baerends, E. J.; Nibbering, N. M. M.; Ziegler, T. *J. Am. Chem. Soc.* **1993**, *115*, 9160.

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(12) PCModel (4.50)^V, Serena Software, Box 3076, Bloomington, IN; 1993.

(13) Unpublished data, S. Gronert and S. Kass.