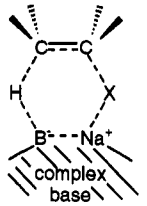
Comparison of β-Chloro-Activated, Syn and Anti Dehydrochlorinations Induced by Complex Base

Alan P. Croft[1] and Richard A. Bartsch*

Department of Chemistry and Biochemistry, Texas Tech University, Lubbock, Texas 79409-1061

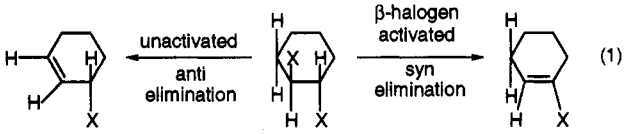
Received November 23, 1993

Heterogeneous mixtures of sodium amide and sodium alkoxide in THF exhibit unusual propensity for formation of 1-halocycloalkenes from *trans*-1,2-dihalocycloalkanes.[2-8] Thus for such "complex bases", the product of β-halo-activated syn elimination, but not unactivated anti elimination, is observed (eq 1). Such favoring of the syn-



1

elimination pathway has been rationalized in terms of a cyclic, six-centered transition state 1 in which the leaving group, as well as the β-hydrogen, interacts with the complex base surface.[2-6,8] Subsequently, it has been established that the sodium alkoxide serves to activate the sodium amide surface which is the functional base species.[6,7]



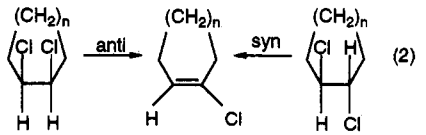
(1)

Comparisons of base-promoted, β-halogen activated anti and syn dehydrohalogenations from conformationally mobile substrates are rare due to an overwhelming preponderance for the anti-elimination process. Cristol and co-workers[9] in their classic study of base-promoted dehydrochlorination of benzene hexachloride isomers (1,2,3,4,5,6-hexachlorocyclohexanes) observed a very strong preference for anti-elimination stereochemistry. Thus the isomer with all of the chlorines trans to each other around the ring which is only capable of syn elimination reacted with base 7000–24000 times slower than did the other isomeric hexachlorides for which anti dehydrochlorination was possible.

Facilitation of β-halogen-activated syn eliminations by complex base might make the anti and syn elimination rates more comparable. We now report results for competitive β-chloro-activated anti and syn dehydrochlorinations from 1,2-dichlorocycloalkanes induced by $NaNH_2$–NaO-*t*-Bu in THF.

Results and Discussion

To assess the relative propensities for β-halogen-activated anti and syn eliminations promoted by $NaNH_2$–NaO-*t*-Bu in THF at 20 °C, competitive dehydrochlorinations from medium ring *cis*- and *trans*-1,2-dichlorocycloalkanes, **2** and **3**, respectively, to give 1-chlorocycloalkenes (**4**) were conducted (eq 2). Periodic sampling of the



(2)

2	n	4	3
a	1	a	a
b	2	b	b
c	3	c	c
d	4	d	d

heterogeneous reaction mixture followed by gas chromatographic (GC) analysis allowed the concentrations of the product **4** and the unconsumed reactants **2** and **3** to be determined as a function of time. From this data, the ratio of rate constants for the β-halogen-activated anti- and syn-elimination pathways (k_{anti}/k_{syn}) was calculated.[10]

Results for competitive dehydrohalogenations from 1,2-dichlorocyclopentanes, -hexanes, -heptanes, and -octanes are present in Table 1. The k_{anti}/k_{syn} ratios of 9–36 which are observed for eliminations from these medium-ring 1,2-dichlorocycloalkanes induced by complex base are very much smaller than the ratios of 7000–24000 reported by Cristol and co-workers[9] for reactions of 1,2,3,4,5,6-hexachlorocyclohexanes with NaOH in aqueous ethanol at 30 °C. This marked diminution of the k_{anti}/k_{syn} ratio provides further support for the proposed six-centered transition state **1** in which syn elimination is facilitated by strong interactions of both the β-hydrogen and the leaving group with the sodium amide surface. For steric reasons such simultaneous interactions of the β-hydrogen and leaving group with the base species are not possible in the transition state for anti elimination.

A limited effect of ring size upon the relative propensities for complex base-promoted eliminations from the *cis*- and *trans*-1,2-dichlorocycloalkanes is apparent from the ratios presented in Table 1. As the ring size is increased from cyclopentane to cyclohexane, there is a perceptible decrease in the relative rate of β-chloro-activated anti elimination. The k_{anti}/k_{syn} ratios for the cyclohexane and cycloheptane derivatives are the same within experimental error, but the ratio increases appreciably for the 1,2-dichlorocyclooctanes. It is proposed that this enhancement results from a disfavoring of the syn-elimination transition state due to the interactions of the cyclooctane ring with the sodium amide surface. Modified behavior of *trans*-1-bromo-2-chlorocyclooctane in complex base-promoted eliminations relative to the cyclopentane, cyclohexane, and cycloheptane, analogues has been reported previously.[6]

(1) Present address: The Dow Chemical Co., Freeport, TX 77541.
(2) Caubere, P. *Acc. Chem. Res.* **1974**, *7*, 301 and references cited therein.
(3) Lee, J. G.; Bartsch, R. A. *J. Am. Chem. Soc.* **1979**, *101*, 228.
(4) Ndebeka, G.; Raynal, S.; Caubere, P.; Bartsch, R. A. *J. Org. Chem.* **1980**, *45*, 5394.
(5) Croft, A. P.; Bartsch, R. A. *Tetrahedron Lett.* **1983**, *24*, 2737.
(6) Croft, A. P.; Bartsch, R. A. *J. Org. Chem.* **1983**, *48*, 876.
(7) Hudlicky, M. *J. Fluorine Chem.* **1986**, *32*, 441.
(8) Bartsch, R. A.; Cho, B. R.; Pugia, M. J. *J. Org. Chem.* **1987**, *52*, 5494.
(9) Cristol, S. J.; Hause, N. L.; Meek, J. S. *J. Am. Chem. Soc.* **1951**, *73*, 674.

(10) Derivation of the kinetic equations for calculating the relative rate constants for the competitive anti- and syn-elimination processes is provided in the supplementary material.

0022-3263/94/1959-1930$04.50/0

Table 1. Competitive β-Halogen-Activated Anti and Syn Dehydrochlorinations from 2 and 3 Induced by $NaNH_2$–NaO-*t*-Bu in THF at 20 °C

cis-1,2-dichlorocycloalkane	*trans*-1,2-dichlorocycloalkane	$k_{anti}{}^a/k_{syn}$
2a	3a	15.0 ± 1.6[b]
2b	3b	10.2 ± 0.9
2c	3c	8.8 ± 2.1
2d	3d	36.5 ± 45

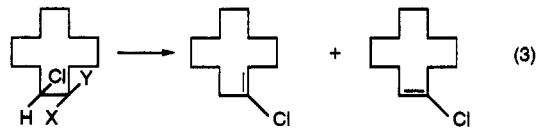
[a] Ratio of rate constants obtained from four analyses each of 2–5 reaction mixtures. [b] Standard deviations from analysis of 8–20 reaction samples.

Table 2. Competitive Anti and Syn Dehydrochlorination from *cis*- or *trans*-1,2-Dichlorocyclododecane Induced by $NaNH_2$–NaO-*t*-Bu in THF at 20 °C or *t*-BuOK–*t*-BuOH at 50 °C

substrate	base/solvent	$k_{anti}{}^a/k_{syn}$
5	$NaNH_2$–NaO-*t*-Bu	25
6	$NaNH_2$–NaO-*t*-Bu	18
5	*t*-BuOK–*t*-BuOH	38

[a] Estimated uncertainty is ±10‰ of the stated value.

A limited examination of base-induced eliminations from the much more flexible *trans*- and *cis*-1,2-dichlorocyclododecanes (**5** and **6**, respectively) was also undertaken. For these larger ring systems, conformational flexibility allows the formation of both β-chloro-activated anti- and syn-elimination products from a single substrate. Thus from *trans*-1,2-dichlorocyclodocecane (**5**), anti elimination gives (*Z*)-1-chlorocyclododecene (**7**), and syn elimination yields (*E*)-1-chlorocyclododecene (**8**). Alternatively from



(Z) (E)

	X	Y		
5	Cl	H	7	8
6	H	Cl		

cis-1,2-dichlorocyclododecane (**6**), the products of β-chloro-activated anti and syn dehydrochlorination are **8** and **7**, respectively. Results for complex base-promoted eliminations from **5** and **6** at 20 °C and for elimination from **5** induced by the less-reactive base–solvent system of *t*-BuOK–*t*-BuOH at 50 °C are recorded in Table 2. The k_{anti}/k_{syn} ratios for complex base-promoted eliminations from both **5** and **6** are about 20. In comparison, the k_{anti}/k_{syn} ratio for reaction of **5** with *t*-BuOK–*t*-BuOH is approximately twice as large. This agrees with the results of previous work in which it was demonstrated that the favoring of β-halogen-activated syn elimination is greater with complex base than with the associated base species in *t*-BuOK–*t*-BuOH.[5]

Experimental Section

Materials. Tetrahydrofuran (MCB) was distilled from lithium aluminum hydride under nitrogen immediately before use. Sodium amide powder (Fisher) was transferred and weighed in a nitrogen-flushed dry bag. *tert*-Butyl alcohol (Fisher) was distilled three times from potassium metal before use. Other reagent grade chemicals were used as received from commercial suppliers. The *trans*-1,2-dichlorocycloheptane (**3c**) and *trans*-1,2-dichlorocyclododecene (**5**) were obtained by the dark reaction of cycloheptene and *cis*-cyclododecene,[11] respectively, with molecular chlorine, in analogy to a reported procedure.[12] Compound **3c** had bp 44–48 °C/0.6 torr (lit.[13] bp 93–94 °C/11–12 torr). Compound **5** had bp 156–160 °C/1.5 torr. Anal. Calcd for $C_{12}H_{22}Cl_2$ (**5**): C, 60.76; H, 9.35. Found: C, 60.97; H, 9.37. (*Z*)-1-Chlorocyclododecene (**7**) was isolated by preparative GC from the products of the reaction of *trans*-1,2-dichlorocyclododecane (**5**) with 0.5 M *t*-BuOK–*t*-BuOH at 50 °C for 48 h. (*E*)-1-Chlorocyclododecene (**8**) was isolated by preparative GC from the products of reaction of *cis*-1,2-dichlorocyclododecane (**6**) with complex base. Compounds **7** and **8** were authenticated by employing a selective dehalogenation procedure[14,15] and analysis of the resulting cyclododecenes. Other compounds used as elimination substrates or as authentic samples of elimination products (for GC standards and molar response studies) were available from previous work (**2b**,[16] **3a**,[16] **3b**,[16] **3d**,[16] **4a–d**[5]), or were prepared by standard procedures (**2a**,[17] **2c**,[18] **2d**,[18] **6**[18]). Elemental analyses were preformed by Galbraith Laboratories of Knoxville, TN.

Gas Chromatography. GC analysis for reactions of **2** and **3** was conducted with a Varian Model 2400 FID gas chromatograph and a 10 ft × 1/8 in. column of 20% SE-30 on Chromosorb P operated at 72–115 °C. GC analysis for reactions **5** and **6** was conducted with a Varian Model 3700 capillary gas chromatograph with FID detector and a 0.20 mm × 25 m vitreous silica capillary SE-30 column (WCOT) operated with programmed temperature capability. Preparative GC, when required, was performed with an Antek Model 461 TCD gas chromatograph and a 10 ft × 1/4 in. column of 20% SE-30 on Chromosorb P operated at 250 °C. Molar response corrections were applied.

Competitive Complex Base Eliminations from 2 and 3. Under nitrogen, 9.80 mmol of $NaNH_2$ was weighed into a three-necked, 25-mL, round-bottomed flask fitted with a reflux condenser in the central neck. The side arms of the flask were fitted with rubber septa. To the top of the reflux condenser was attached a T-tube through which a slow flow of nitrogen was passed during the reaction. *tert*-Butyl alcohol (4.90 mmol) and 8.0 mL of dry THF were added to the flask, and the mixture was stirred magnetically for 1 h. After addition of 1.63 mmol each of **2** and **3** to the magnetically stirred heterogeneous reaction medium at 20.0 °C, 1.0-mL samples of the reaction mixture were removed from the reaction vessel at timed intervals and added to 4.0-mL portions of THF which contained a known amount of an internal standard in 5-mL volumetric flasks that were suspended in a dry ice–acetone bath. After four such aliquots were removed (within 10–30 min), the remainder of the reaction mixture was discarded. After a volumetric flask was shaken, the diluted sample of the reaction mixture was held at −78 °C until GC analysis for residual **2** and **3** which involved direct injection of the sample at dry ice–acetone temperature into the gas chromatograph.

Complex Base Elimination from 5 or 6. The complex base mixture was prepared as described above and 3.26 mmol of **5** or **6** was added to the magnetically stirred, heterogeneous reaction mixture at 20.0 °C. Periodically 2-μL aliquots were removed and analyzed directly for unreacted substrate by GC. When the elimination substrate had been consumed, the remaining reaction mixture was poured into 70-mL of ice–water in a 100-mL volumetric flask, and the reaction flask was rinsed with a small amount of diethyl ether. The rinsings and additional diethyl ether (total of 30 mL) were added to the ice–water mixture. An appropriate internal standard was added and, after being shaken, the flask was allowed to stand overnight in a refrigerator. The organic layer was then analyzed by GC for the elimination products.

(11) Nozaki, H.; Noyori, R. *J. Org. Chem.* **1965**, *30*, 1652.
(12) Carroll, B.; Kubler, D. G.; Davis, H. W.; Whaley, A. M. *J. Am. Chem. Soc.* **1951**, *73*, 5382.
(13) Henniger, P. W.; Wapenaar, E.; Havinga, E *Rec. Trav. Chim.* **1962**, *81*, 1053.
(14) Caubere, P.; Coudert, G. *Bull. Soc. Chim. Fr.* **1973**, 3067.
(15) Nozaki, H.; Nisikawa, Y.; Kawanisi, M.; Noyori, R. *Tetrahedron* **1967**, *23*, 2173.
(16) Lee, J. G. Doctoral Dissertation, Texas Tech University, 1978.
(17) Isaacs, N. S.; Kirkpatrick, D. *Tetrahedron Lett.* **1972**, 3869.
(18) Croft, A. P.; Bartsch, R. A. *J. Org. Chem.* **1983**, *48*, 3353.

Elimination from 5 by *t*-BuOK–*t*-BuOH. A 0.50 M solution of *t*-BuOK in *t*-BuOH was prepared from potassium metal and *tert*-butyl alcohol. The elimination substrate **5** (1.63 mmol) was weighed into a 5-mL volumetric flask, and freshly prepared *t*-BuOK–*t*-BuOH was added to the mark. The flask was shaken and suspended in a constant temperature bath at 50.0 °C. Periodic removal of 2-μL samples and GC analysis were used to measure the consumption of **5**. Following completion of the reaction, the mixture was poured into ice–water, worked up, and analyzed by GC by the same procedure which is given in the complex base elimination procedure for **5**. Following completion of the reaction, the mixture was poued into ice–water, worked up, and analyzed by GC by the same procedure which is given in the complex base elimination procedure for **5**.

Acknowledgment is made to the Donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this work.

Supplementary Material Available: Kinetic calculation method for competitive complex base-promoted elimination reactions (3 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.