DAEHAN HWAHAK HWOEJEE
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소다아미드를 포함하는 복합염기에 의한 탈할로겐화수소 반응 (제 1 보). 트란스-1, 2-디할로시클로헥산의 탈할로겐화수소 반응의 메카니즘 연구

李鍾建 · 姜敬泰* · 李億石†
부산대학교 자연과학대학 화학과
*부산대학교 사범대학 화학교육과
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Dehydrohalogenation Reactions Induced by Sodamide Containing Complex Bases (I). Mechanistic Studies on Dehydrohalogenation from *trans*-1, 2-Dihalocyclohexanes

Jong Gun Lee, Kyung-Tae Kang* and **Euk-Suk Lee**
Department of Chemistry, Busan National University, Busan 607, Korea
**Department of Chemical Education, Busan National University, Busan 607, Korea*
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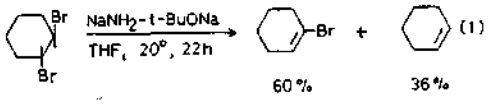
요 약. 소다아미드를 포함하는 복합염기에 의한 트란스-1, 2-디할로시클로헥산으로부터의 탈할로겐화 수소반응을 연구 검토한 결과 이성질화, 중수소 동위원소 효과 및 이탈기의 원소효과 등이 모두 E2 반응 매카니즘으로 반응이 진행됨을 강력히 시사하고 있다.

ABSTRACT. Sodamide-containing complex base induced dehydrohalogenations from *trans*-1, 2-dihalocyclohexanes were investigated. Isomerization, deuterium isotope effect along with element effect and others provided strong evidence in favor of E2 reaction mechanism.

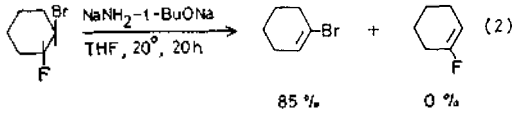
INTRODUCTION

Base-promoted β-elimination in which two atoms or groups are removed from adjacent atoms resulting in a formation of a multiple bond is one of the most frequently encountered type of organic reactions.[1a] These reactions can be induced by a variety of bases, among which alkali metal alkoxides have been most popular. Mechanism-wise, base-promoted β-eliminations exhibit a strong preference for anti elimination where a proton and a leaving group are removed from opposite sides of the incipient double bond[1b]. Much less favorable syn elimination stereochemistry has been observed in some occasions where anti elimination stereochemistry is unattainable or severely disturbed.[1c]

Recently, Caubere has reported that treatment of *trans*-1, 2-dibromocyclohexane with "complex base" $NaNH_2$-*t*-BuONa produces 60% of 1-bromocyclohexene and 36 % of cyclohexene.[2,3] Neither sodamide nor sodium *t*-butoxide alone yield measurable amounts of 1-bromocyclohexene or cyclohexene. Furthermore, mixture



bases of already-made sodamide and sodium *t*-butoxide were barely effective in this transformation.[4] Recently, it was also reported that



1-bromocyclohexene was the only 1-halocyclohexene detected from the reaction of complex base on *trans*-1-bromo-2-fluorocyclohexane.[5]

These reactions are rather striking for the following reasons. First of all, 1-bromocyclohexene can only result from less favorable *syn*-elimination. anti-Elimination is greatly preferred with ordinary bases. Secondly, 1-fluorocyclohexene is expected to be the only product from the reaction of complex base upon *trans*-1-bromo-2-fluorocyclohexane. Dehydrobromination is believed to be induced with far greater ease than dehydrofluorination.[1a]

The reasons for this remarkable efficiency of the complex bases in promoting syn-elimation, especially, involving poor halogen leaving group are pure speculation at the present time. Mechanistic study on these reactions was carried out in order to understand the factors responsible for this unusual behavior of the complex base-promoted dehydrohalogenations.

EXPERIMENTAL

1. Synthesis of Halocyclohexenes

1-Bromocyclohexene. *trans*-1, 2-Dibromocyclohexane (120g) was slowly added to complex base-solvent system prepared from 55g of *t*-butanol and 59g of sodamide in 1200m*l* of dry THF. After 24 hours at room temperature, the mixture was partitioned into water and ether. The ether extract was washed, dried ($MgSO_4$) and concentrated. The residue was distilled to give 47g(58%) of chromatographically pure 1-bromocyclohexene, bp 64~65°/22mm.

1-Chlorocyclohexene. Reaction of *trans*-1, 2-dichlorocyclohexane with complex base in THF following the procedure similar to the one above gave 1-chlorocyclohexene, bp 142~143°C, in 85% yield.

3-Bromocyclohexene. Cyclohexene (60g) was reacted with 22g of N-bromosuccinimide in reflexing carbon tetrachloride for 15 hours.[6] Cold reaction muxture was filtered and the filtrate was fractionated twice to yield 25g of 3-bromocyclohexene, bp 80°/30mm.

3-Chlorocyclohexene. *t*-Butyl hypochlorite (25g) was slowly added to 100 m*l* of cyclohexene containing 0.5g of azobisisobutyronitrile. After 3 hour reflux, the whole content was distilled into a -78° trap under high vacuum, and the distillate was fractionated three times to get 16g of 3-chlorocyclohexene, bp 51°/22mm.

2. Synthesis of *trans*-1, 2-Dihalocyclohexanes.

***trans*-1, 2-Dibromocyclohexane.** Snider and Book's procedure[8] was used without modification to get 360g of *trans*-1, 2-dibromocyclohexane from 210g of bromine and 150m*l* of cyclohexene.

1-Deuterio-*trans*-1, 2-dibromocyclohexane. 1-Deuteriocyclohexene was prepared by lithiation of 1-bromocyclohexene[9] and was brominatied by Snider and Brook's procedure.[8] Thus, 1 mole of *t*-butyllithium in pentane (2.03*M* solution from Aldrich) was diluted with 1.5 liter of dry THF was cooled in an ice bath and half of the content was distilled off under 2-3mm pressure. The remaining solution was again diluted to 2 liters with dry THF. At 0°C, the

solution was concentrated to 1.2 liter. The *t*-butyllithium solution was further cooled to −78 °C and 1-bromocyclohexene (80g) was slowly added. The solution was stirred for 6 hours at −78°C, before 20g of deuterium oxide in 100m*l* dry THF was slowly added. The mixture was allowed to warm up to room temperature. The mixture was diluted with enough water and extracted with pentane three times. The combined pentane extract was repeatedly washed with water to remove THF. The residual pentane solution was carefully concentrated and fractionated twice to yield 28 grams of 1-deuteriocyclohexene. GC-MS analysis [10] showed 97.2 % deuterium incorporation. A portion of cyclohexene-d_1 (5g) was brominated following the procedure in Organic Synthesis[8] to yield 9.8g of 1-deuterio-*trans*-1, 2-dibromocyclohexane, bp 68°C/2mm. The deuterium content of the dibromide was regarded the same as in cyclohexene-d_1.

***trans*-1, 2-Dichlorocyclohexane.** Cyclohexene was chlorinated with a slow stream of chlorine in the dark in a 30°C bath according to the procedure of Carroll *et al.* [11]

1-Deuterio-*trans*-1, 2-dichlorocyclohexane. 1-Deuteriocyclohexene (10.8g) was chlorinated in the same manner to give 5.9g of 1-derterio-*trans*-1, 2-dichlorocyclohexane, bp 43°/2mm. The deuterium content was regarded unchanged at 97%.

3. Elimination Procedures

Preparation of Complex Base. Tetrahydrofuran was always freshly distilled from sodium-benzophenone. The ratio of $NaNH_2$: NaO-*t*-Bu: substrate (3:3:2) was maintained same for all elimination reactions and the amount of tetrahydrofuran was adjusted such that total formal base concentration be 1.2 *M*. Under argon atmosphere, a proper amount of sodamide (Fisher) was weighed into a flask and quickly covered with dry THF. The flask was equipped with a condenser through the top of which argon was passed through. One half of the amide was destroyed by adding a proper amount of potassium dried *t*-butanol. The mixture was magnetically stirred for 1 hour before any halogeno substrate was added.

Isomerization Studies. Halocyclohexenes were added to the complex base solvent system maintained at 20°C in a constant temperature bath. After appropriate reaction period, the mixture was partitioned into water and pentane. The pentane solution was analyzed by gas chromatography.

Elimination Procedures. *trans*-1, 2-Dihalocyclohexanes were added to complex base in THF. The amount of the substrate was adjusted such that the concentration be 0.4*M*. The mixture was stirred for an appropriate reaction period under argon atmosphere. The content was partitioned into aquous ether and the ether layer was analyzed by gas chromatography.

4. Analytical Procedures.

Product Analysis. Products from the dehydrohalogenation reactions and isomerization studies were analyzed by gas chromatography using Shimadzu GC 6-A. A 1/8 inch×10 foot column of 20% SE-30 on Chromosorb P operating at 80~110° was used. Molar responses of 0.796 for cyclohexene, 1.032 for 1-bromocyclohexene and 0.986 for 1-chlorocyclohexene against toluene (an internal standard) were obtained by analyzing equimolar mixtures of these compounds using the same column. The yield and molar ratios of products were calculated based on peak areas and molar reponses.

RESULTS AND DISCUSSION

In order to understand the striking feature of the complex base in promoting syn elimination involving poorer halogen leaving group from

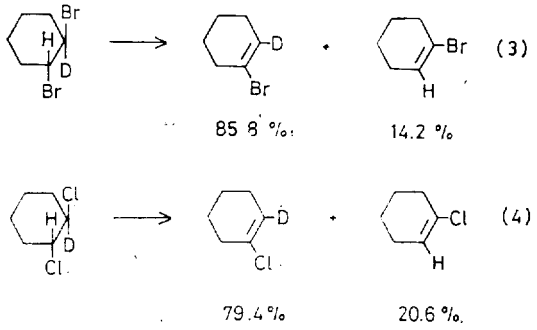
trans-1, 2-dihalocyclohexanes, the mechanism of the complex base induced dehydrohalogenation has to be investigated. A conceivable route for the formation of 1-halocyclohexenes which does not involve syn elimination is anti -elimination followed by isomerization of 3-halocyclohexenes to 1-halocyclohexenes. Anti Elimination-isomerization sequence was found responsible for the exclusive formation of 1-phenylcyclopentene from *trans*-2-phenyl-cyclopentyl tosylate when treated with complex base.[3]

Authentic samples of 3-bromocyclohexene and 3-chlorocyclohexene were subjected to complex base solvent system. At three to four hour time interval, the reaction mixture was analyzed by gas chromatography. It was found that 3-halocyclohexenes disappear rapidly, but no 1-halocyclohexenes could be detected. At the end of a 24 hour reaction period, neither 3-halocyclohexenes nor 1-halocyclohexenes were detected. However no further attempts were made to detect or identify the products. From these experiment, it can be safely concluded that 1-halocyclohexenes resulted from direct β-dehydrohalogenation from *trans*-1, 2-dihalocyclohexanes.

For many years, divergence from anti elimination was thought to be indicative of Elcb mechanism.[1b] Thus, this apparent syneliminination could be suggestive of prior formation of a carbanion to any other bond rupture. In order to measure the timing of carbon-hydrogen and carbon-halogen leaving group bond breakage, primary deuterium isotope effect has to be determined. In basepromoted dehydrohalogenation from *trans*-1, 2-dihalocyclohexanes, two identical direction of 1-halocyclohexene involving syn eliminations are feasible. If one of the proton can be replaced by a deuterium, the resulting 1-deuterio-*trans*-1, 2-dihalocyclohexanes seem to serve perfectly for internal compitition between dehydrohalogenation and dedeuterohalogenation (Equation 3 and 4).

1-Bromocyclohexene was lithiated through metal exchange reaction with *t*-butyllithium according to a known procedure.[9] 1-Lithiocyclohexene thus obtained was treated with deuterium oxide to give 1-deuteriocyclohexene. It can be assumed that the satisfactory deuterium content in 1-deuteriocyclohexene (97.2%) remains unchanged during the subsequent chlorination or bromination.

The deuterated *trans*-1, 2-dihalocyclohexanes were reacted with complex base in THF. These reactions were conducted at 20°C for 15 hours and the product 1-bromocyclohexene and 1-chlorocyclohexene were analyzed by GC-MS.[10]

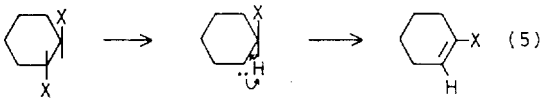


For the bromo-derivative, the deuterium content in the product 1-bromocyclohexene was found to be 85.8 %. For the chlorine analog, it was 79.4 %. These values were adjusted for less than unity deuterium incorporation in the starting 1-deuteriocyclohexene and the primary kinetic isotope effect was calculated to be 5.7 for dehydrobromination and 3.6 for dehydrochlorination.

These primary deuterium isotope effect values[12] are supposedly large enough to exclude the possible operation of Elcb mechanism. Fairly high primary kinetic deuterium isotope effect values were reported for Elcb elimina-

tions, but those reactions usually involve greatly acidified protons and very poor leaving groups. It was also reported that a syn E2 elimination reaction show smaller primary deuterium isotope effect than the corresponding *anti* elimination from the same substrates[12,13]. On the ground of these findings, Elcb mechanism is not a reasonable pathway for complex base-promted dehydrohalogenation from *trans*-1, 2-dihalocyclohexanes.

Another possible reaction between haloalkanes and a very strong base is a formation of carbenes. 2-Halocyclohexyl carbenic specis could produce 1-halocyclohexenes as shown the equation 5.

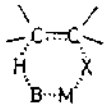

(5)

No carbene addition product, however, could be detected from the reaction mixture. 1-Halocyclohexene and cyclohexene were the only products. They were produced in greater than 60 and 36% yield respectively from *trans*-1, 2-dibromocyclohexane. It was 89% and 9% for the chlorine anlog.

It is usually true, however, that the rate determining step for carbene formation is not the proton removal and the large enough deuterium isotope effect make this alternative look inferior. Besides, detection of only 1-bromocyclohexene from complex baseinduced dehydrohalogenation of *trans*-1-bromo-2-fluorocyclohexane[5] cannot justify the fact that hydrogen on halogen-bonded carbon atoms are more acidified by bromo-than fluoro-substituent.[14]

Having ruled out two conceivable mechanistic possibilities which involve carbanionic species, the E2 mechanism appears very reasonable. Significant magnitude of the primary deuterium isotope effect serves as a strong evidence for an E2 pathway.

The striking feature of the complex base in promoting synelimination has been suggested to result from the highly aggregated nature of the complex base.[7] syn E2 transition state is known to be greatly stabilized by the simultaneous coordination of a metal counter ion of the base with the leaving group as well as the base[15,16]. This implies that the halogen leaving group of *trans*-1, 2-dihalocyclohexanes and sodium ion in highy aggregated complex base must be very strongly coordinated in the transition state of these dehydrohalogenation reactions.


(6)

A couple of reports on the nature of complex base-induced dehydrohalogenation are worthmentioning. By changing the alcoholic activator of the complex base, Caubere[3] found the effectiveness of the base in dehydrohalogenation is not at all affected by the strength of the base but the geometry of it. More recently, the reversed order halogen leaving group ability in complex base-induced dehydrohalogenation from trans-1-bromo-2-chlorocyclohexane was almost completely restored when 15-crown-5, a sodium ion complexing agent, was added.[17] Isomerization and deuterium isotope effect studies in this report coupled with these findings by orthers strongly suggest that E2 cyclic transition state depicted in 6 is operating in dehydrohalogenation reactions of *trans*-1, 2-dihalocyclohexanes poomoted by sodamide containg complex base.

CONCLUSION

Absence of an *anti* elimination-isomerization sequence, high magnitude of deuterium isotope

effect, and findings by Caubere[3], and others[5] strongly indicate the operation of an E2 reaction mechanism in complex base promoted syn-dehydrohalognation of *trans*-1, 2-dihalocyclohexanes. The transition state appears to be greatly stabilized by the metal-leaving group coordination (Equation 6) which is extremely strong with highly aggregated complex base.

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