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Stereospecific Ring Contraction of Bromocycloheptenes through Dyotropic Rearrangements via Nonclassical Carbocation–Anion Pairs

Shermin S. Goh, Pier Alexandre Champagne, Sureshbabu Guduguntla, Takashi Kikuchi, Makoto Fujita, K. N. Houk, and Ben L. Feringa

†Stratingh Institute for Chemistry, University of Groningen, Nijenborgh 4, 9747 AG Groningen, The Netherlands
‡Department of Chemistry and Biochemistry, University of California—Los Angeles, 607 Charles E. Young Drive East, Box 951569, Los Angeles, California 90095-1569, United States
§Department of Applied Chemistry, University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8656, Japan
⊥Rigaku Corporation, 3-9-12 Matsubara-cho, Akishima-shi, Tokyo 196-8628, Japan

Supporting Information

ABSTRACT: Experimental and theoretical evidence is reported for a rare type I dyotropic rearrangement involving a [1,2]-alkene shift, leading to the regio- and stereospecific ring contraction of bromocycloheptenes. This reaction occurs under mild conditions, with or without a Lewis acid catalyst. DFT calculations show that the reaction proceeds through a nonclassical carbocation–anion pair, which is crucial for the low activation barrier and enantiospecificity. The chiral cyclopropylcarbinylation may be a transition state or an intermediate, depending on the reaction conditions.

In the course of our investigation of the desymmetrization of meso-3,7-dibromocycloheptene 1, we discovered that the initially formed enantioomerically enriched homoallylic bromides 2 were spontaneously isomerized with retention of configuration to form chiral substituted cyclohexenes 3 (Scheme 1). This reaction could be accelerated by Lewis acids such as silica or ZnBr₂, with no change in stereoselectivity. We have studied this reaction by a combination of experiments and computations, and now report that this involves a rare dyotropic rearrangement involving nonclassical cyclopropylcarbinylenium cations on the reaction paths as either transition states or intermediates, depending on the conditions.

The copper-catalyzed desymmetrisation of 1 by asymmetric allylic substitution (AAS) with organolithium reagents initially afforded the expected products 2a–e (>99:1 dr), as observed by NMR spectroscopy of the crude reaction mixtures [see Supporting Information (SI)]. The reaction also proceeded with high enantioselectivity, as determined by chiral GC. However, upon exposure to silica, the bromocycloheptenes 2a–e isomerized to afford six-membered cyclic homoallylic bromides 3a–e. The ring contraction reaction proceeded with complete regioselectivity and enantiospecificity, as determined by chiral GC [see SI, part 1 and SI, part 2].

In fact, the rearrangement reaction was so facile that the transformation from cycloheptenes 2a–e to cyclohexenes 3a–e occurred even on neutral alumina, or when left standing in chloroform-d (t₁/₂ ≈ 6 days). The major enantiomer of 3d, obtained as a colorless oil, was determined to be (R,R) by X-ray crystallography using only 5 μg of compound and the crystalline sponge method developed by the Fujita group (Figure 1). A similar attempt was made to study the absolute configuration of its precursor 2d; however, the rearrangement occurred while soaking in crystalline sponge, and only 3d was detected when the X-ray analysis was performed.

The ring contraction reaction from 2a–e to 3a–e, interconverting the two isomeric homoallylic bromides, involves the 1,2-positional exchange of the allenyl and bromo groups; thus it is formally a [2,2]-dyotropic rearrangement. These were first described in 1972 by M. T. Reetz as a class of pericyclic valence isomerizations involving the simultaneous

Figure 1. Ball-and-stick representation of the X-ray structure of 3d determined by the crystalline sponge method.
intramolecular migration of two \(\sigma\)-bonds.\(^6,7\) Type I dyotropic rearrangements occur when the two migrating groups exchange their positions (e.g., the classic rearrangement of anti vicinal dibromides, Scheme 2a),\(^8\) while in type II rearrangements the groups migrate to entirely different positions. Dyotropic reactions have become more common recently in organic and organometallic chemistry\(^9\) and have even been applied to total syntheses.\(^9,10\) The concerted migration of carbon chains through a \([2,2]\)-shift on a static \(\text{C}−\text{C}\) scaffold is uncommon.\(^1\)

[\(\sigma\)2s + \(\sigma\)2s] processes are thermally forbidden by the Woodward−Hoffmann rules,\(^11,12\) but the reaction becomes allowed if one migrating group has a lone pair and migrates with inversion. Nevertheless, such reactions are still rare because the activation barriers are usually quite high.\(^13\)

Until recently, the only experimental examples of such reactions involved highly strained lactones reacting under strenuous conditions. Examples of alkyl group migration are the ring expansion of \(\beta\)-lactones to butyro lactones promoted by stoichiometric magnesium bromide,\(^14−16\) or the rearrangement of cage \(\delta\)-lactones to \(\gamma\)-lactones at 350 °C on a quartz column.\(^17\) Acyl group migration involving a \(\beta\)-lactone ring expansion promoted by stoichiometric Lewis acid is also known.\(^18\) In recent years, milder dyotropic rearrangements have been discovered. Gutta and Tantillo proposed a 1,2-positional exchange of an alkyl group and a hydrogen atom in their computed biosynthetic pathway for formation of pentalenene in 2006.\(^19\) More recently, Faza, Lopez, and co-workers reported the type I dyotropic ring expansion of hydrindane to decalin occurring at −78 °C upon mesylation (Scheme 2b).\(^20\) To the best of our knowledge, a concerted and uncatalyzed type I dyotropic migration of a \(\text{C}−\text{C}\) π system is still unknown.

The mechanism of this rearrangement was investigated by NMR spectroscopy. Time-dependent aliquot studies with silica as reagent (500% w/w) for the rearrangement of bromocycloheptene 2d showed that bromocyclohexene 3d (>99% es) was the only product generated. This was observed in both polar aprotic (chloroform-\(d\)) and apolar (benzene-\(d_6\)) solvents, although the rate of reaction was slower in benzene-\(d_6\) (Figure 2b,c); the lack of solvent dependence for selectivity indicates that the reaction does not proceed through a discrete carbocation. The use of Lewis acids (e.g., ZnBr\(_2\) and TMSOTf) led to poorer selectivity in the rearrangement reaction, with ca. 5−10% of a different diastereoisomer 4d observed (Figure 2d,e);\(^21\) its formation may be explained by the ionization of product 3d by the stronger Lewis acids [see SI]. There was, fortunately, no erosion in ee of the expected product. These reactions with Lewis acids could be monitored in situ by NMR time course experiments in either chloroform-\(d\) (Figure 2a) or benzene-\(d_6\), with no difference in product ratio or enantiospecificity, although the reaction was always slower in the apolar solvent [see SI]. The reaction could also be performed with Bronsted acids [see SI], or with catalytic amounts of Lewis acids (Figure 2e), albeit at a much reduced rate. When conducted in the presence of radical scavenger BHT (1.0 equiv), the reaction profile did not change [see SI], indicating that a radical pathway was not involved.

To further understand the mechanism and specificity of the rearrangement, we performed DFT calculations on compound

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**Scheme 2. Uncatalyzed Concerted Type I Dyotropic Rearrangements Occurring on a Static C−C Scaffold**

(a) Vicinal dibromide dyotropic rearrangement (Ref 8)

(b) Alkyl-mesyate dyotropic rearrangement (Ref 20)

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**Figure 2.** Left: (a) \(^1\)H NMR spectroscopic profiles of bromocycloheptene 2d with ZnBr\(_2\) (1 equiv) in chloroform-\(d\) with increasing time; reaction scheme is shown at top. Right: Reaction progress of 2d with silica (500% w/w) monitored by timed aliquots in (b) chloroform-\(d\) and (c) benzene-\(d_6\). Reaction progress of 2d monitored by in situ NMR spectroscopy with (d) ZnBr\(_2\) (1 equiv) in chloroform-\(d\) and (e) TMSOTf (0.5 equiv) in chloroform-\(d\).
CHCl₃ was used throughout. Computed structures were approach the geometry of a bromo groups from In contrast, the dyotropic rearrangement of the methyl and Δ acid (Figure 4). Formation of a dyotropic rearrangement involves the experimentally observed 1,2-shift of both the alkenyl and bromo groups to form 3a. The barrier for this transformation is only 25.2 kcal/mol (Figure 3), and the reaction is exergonic by 5.0 kcal/mol.

Figure 3. Calculated free energy profile for the concerted dyotropic rearrangements from the pseudoaxial (left part) or pseudoequatorial (right part) conformations of 2a.

In contrast, the dyotropic rearrangement of the methyl and bromo groups from 2a-ax, forming 5a, has a significantly higher barrier of 40.1 kcal/mol. The calculated ΔG‡ for TS-eq is consistent with our observations of a step uncatalyzed transformation of 2a-e to 3a-e at room temperature in chloroform (t½ ≈ 6 days).

Both TS-eq and TS-ax are highly polarized, with two long C–Br bonds (>3.0 Å) and two short C–C bonds, and as such can be described as tight ion-pairs of a carbocation and bromide anion. Indeed, the bromine atom in these two TSs bears an almost full negative charge (~0.95 to ~0.97 au, see SI). This is in stark contrast to classical type I dyotropic rearrangements of vicinal dibromides, where the C–Br bonds were calculated to be around 2.5–2.8 Å. It is known that delocalization of the formed π bond in the TSs of dyotropic rearrangements provides key stabilization. In the case of TS-eq, the large polarization causes the carbon backbone of the substrate to approach the geometry of a π-delocalized bisected cyclopropylcarbinyl (nonclassical) cation (vide infra). This greatly stabilizes the π bond of the TS (in blue, Figure 3) and explains why TS-eq has such a low barrier compared to TS-ax, for which the carbon backbone has the geometry of a less-stabilized corner-protonated cyclopropane.

Having established that the enantiomeric uncatalyzed reaction is very likely to operate through a concerted dyotropic rearrangement, we investigated the role of an external Lewis acid (Figure 4). Formation of 2a·ZnBr₃ from the isolated reactants is favorable by 8.9 kcal/mol [see SI]. From this coordinated species, no concerted dyotropic transition states could be located; instead a stepwise mechanism is found.

Figure 4. Calculated free energy profile for the stepwise transformation of 2a to 3a, catalyzed by ZnBr₂. For the structure of 6a·ZnBr₃, the ZnBr₃⁻ is hidden for clarity.

Ionization of the C–Br bond of complex 2a·ZnBr₃ through TS 1 has a low barrier of 14.6 kcal/mol and leads to a contact ion-pair consisting of nonclassical cyclopropylcarbinyl cation 6a and ZnBr₃⁻. From this intermediate, only 7.8 kcal/mol is required to reach TS 2, where the C–Br bond of 3a is formed. These calculations are consistent with the much faster reaction observed when ZnBr₂ is used as Lewis acid, since the activation barrier is predicted to be almost 10 kcal/mol lower than in the uncatalyzed case (14.6 vs 25.2 kcal/mol). While some stepwise ionic dyotropic rearrangements are known, these were limited to intramolecular examples (e.g., dyotropic rearrangement of Hamberg cycloducts via a zwitterion). The present mechanism is an unprecedented case of a stepwise formal dyotropic rearrangement proceeding through an ion-pair. Ionization of the C–Br bond in TS 1 happens with simultaneous backside attack of the alkynyl group, analogous to an S_N2 mechanism. Similarly, bromide attack in TS 2 occurs with release of the alkynyl group; therefore the C–Br bonds are broken and formed from the same face of 6a, the structure of which is determined by the stereochemistry of 2a. Thus 6a is a chiral carbocation; however, even in the presence of Lewis acids such as ZnBr₂, the reaction of 2d to 3d was shown to be perfectly enantiomERIC. We performed additional calculations to investigate the possible mechanism of racemization of 6a. It is now well established that cyclopropylcarbinyl cations ²⁶,²⁷ are in equilibrium with the related bicyclobutonium cations, with the latter being more stable for the parent C₅H₅⁺.²³,²⁴ For the bicyclic cyclopropylcarbinyl cation 6a, the profile is much more complex. The lowest-energy path for the racemization of 6a is through the meso-bicyclobutonium 7a, which is a TS (instead of a minimum) on the potential energy surface of cation 6a (Figure 5).³³ Once chiral cation 6a is formed from the C–Br bond cleavage of 2a, it requires an additional 10.9 kcal/mol of free energy to racemize through 7a·ZnBr₃, a bicyclobutonium ion-pair. In contrast, it only needs 7.8 kcal/mol to recombine with the ZnBr₃⁻ counterion to form the stable product 3a through TS 2. Moreover, the latter reaction is not reversible, as 3a·ZnBr₃ is 5.4 kcal/mol more stable than the starting complex. As such, there is a kinetic barrier to racemization in this system, allowing a stepwise enantiomERIC rearrangement to occur.
In summary, we have discovered an unanticipated ring contraction of bromocycloheptenes under mild conditions with remarkable regio- and stereochemistry. The ring contraction occurs via a double 1,2-migration of an alkene group and a bromide. DFT calculations show that the reaction proceeds through a nonclassical carbocation−anion pair; the πσ-delocalized bisected cyclopropylcarbinyl cation is crucial for the low activation barrier and enantiospecificity of the rearrangement. The reaction is concerted when uncatalyzed, presenting a rare type I dyotropic rearrangement of an alkene on a C−C stationary scaffold. In contrast, the reaction follows a stepwise mechanism under Lewis acid catalysis, and can be described as a formal dyotropic rearrangement. Our study also highlights how cations derived from chiral homoallylic halides may be productive intermediates in other enantiospecific reactions.

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