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Planar Chirality Change in Dediazoniation Reactions of Paracyclophanes and Mechanistic Implication

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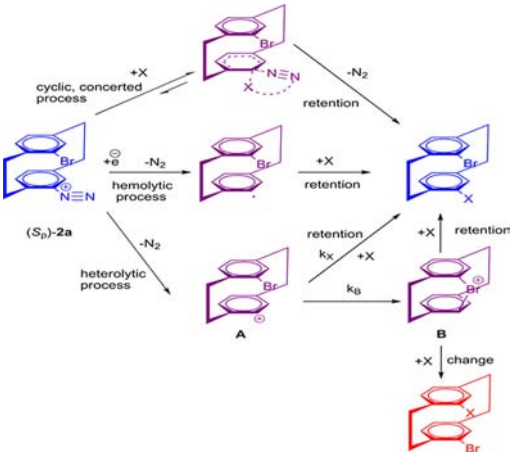
ABSTRACT



Dediazoniation reactions of (S_p)-4-bromo-13-[2.2]paracyclophanyldiazonium fluoborate 2a through a heterolytic cleavage process gave products with partial racemization. In contrast, dediazoniation reactions of (S_p)-2a undergoing a nonheterolytic cleavage process afforded products with retention of configuration. A key intermediate, the bromonium cation B, caused the racemization. The unexpected racemization allowed the mechanisms of the dediazoniation reaction to be probed.

[2.2]Paracyclophane, the singular framework, has derivatives with unique electronic and steric properties, making them excellent scaffolds for a range of applications.[1] Some chiral [2.2]paracyclophane derivatives have been successfully applied in hydrogenation reactions, enantioselective 1,2-addition, and 1,4-addition of organozinc reagents to aldehydes and imines, etc.[2] It is known that the chiral [2.2]paracyclophane backbone is chemically and configurationally stable under ambient conditions. Thermal racemization is possible only upon cleavage of the ethano-bridge at about 200 °C.[3] Because of this, enantiopure compounds with this backbone can be obtained by transformations of the starting optically pure [2.2]paracyclophane derivatives under typical conditions of fine organic synthesis.

In previous studies, our group has shown that 13-amino-4-bromo[2.2]paracyclophane is a versatile building block for the synthesis of planar chiral [2.2]paracyclophane-based ligands with substituents on both rings.[4] The two enantiomers of **1a** can be readily obtained by the resolution

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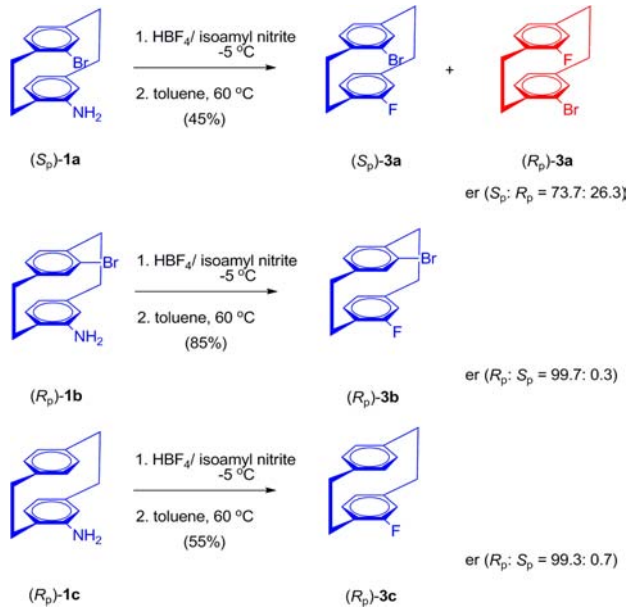
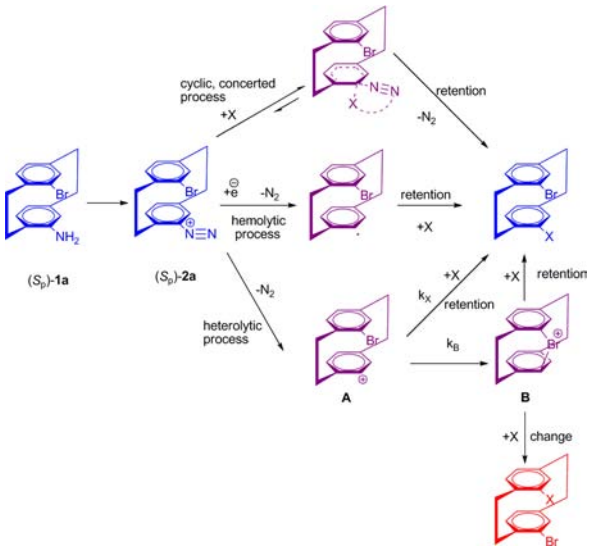
Scheme 1. Balz–Schiemann Reaction of Amino [2.2]Paracyclophanes **1a–c**



of racemic **1a** with (1*R*)-(−)-10-camphorsulfonyl chloride ((−)-CSC).[4a] To extend this work, we tried to synthesize (S_p)-4-bromo-13-fluoro[2.2]paracyclophane **3a** from optically pure (S_p)-**1a** by the Balz–Schiemann reaction at 60 °C (Scheme 1). To our surprise, the transformation of (S_p)-**1a** gave product **3a** with an er value of 73.7:26.3 by chiral HPLC analysis. However, when optically pure 12-amino-4-bromo[2.2]paracyclophane **1b** and 4-amino-[2.2]paracyclophane **1c** were subjected to the Balz–Schiemann reaction under the same reaction conditions, they afforded nearly enantiopure fluoro[2.2]paracyclophane derivatives (**3b** and **3c**). Thus, the observed racemization of **3a** under the same conditions as **3b** and **3c** clearly rules out all reaction mechanisms that involve the cleavage of the ethano-bridge of the [2.2]paracyclophane system. Ring rotation without methylene bond breakage is impossible in [2.2]paracyclophane, and an alternate mechanism without ring rotation needed to be sought.

The racemization is highly dependent on the structures of the substrates or the reaction intermediates. The above results suggested that racemization of **3a** during the Balz–Schiemann reaction might involve a key intermediate: the bromonium cation **B** (Scheme 2). The thermal decomposition of diazonium fluoborate (S_p)-**2a** was based on the well-established heterolytic pathway[5] and the key step was loss of N_2 to generate the singlet aryl

Scheme 2. Mechanistic Details of Dediazoniation and Racemization



cation **A**. Because of the proximity of the two rings in [2.2]paracyclophane,[6] it was easy for the lone-pair electron of bromine in the *pseudogem* position to attack the vacant orbital of the singlet aryl cation. The bromonium cation **B** carried a positive charge distributed over both rings, so it was more stable than the singlet aryl cation **A**. Since the bromonium cation **B** had a nonchiral structure, the product **3a** racemized when the bromonium salt reacted with the nuclephiles (Scheme 2). The diazonium salts derived from **1b** and **1c** were able to generate singlet aryl cations, but, unlike (S_p)-**2a**, were unable to form the nonchiral bromonium cations, and the corresponding products **3b** and **3c** thus obtained were not racemized remarkably (Scheme 1). These results can be explained by the theoretical calculation (see the Supporting Information). The bromine atom in the structure **A** is close to the cation in the 13-position (2.40 Å), but the distance between the bromine atom and the cation in the 12-position is much greater (4.11 Å).

We sought to determine whether similar partial racemization would take place when other compounds were used as the dediazoniation reagents. We were also interested in investigating whether an aryl radical or a cyclic concerted mechanism could also lead to the racemization. The results summarized in Table 1 (entries 1–6) give the details of our survey.

In both aqueous and nonaqueous solvents under acidic conditions, the nitrogen evolution followed first-order kinetics, and there was a great deal of evidence that heterolytic cleavage of the C–N bond was occurring.[7] The partial racemization of products **4–6** (Table 1, entries 1–3) strongly supports the involvement of a bromonium cation mechanism. The reduction of the diazonium ion (S_p)-**2a** to 4-bromo[2.2] paracyclophane **7** proceeded by a hemolytic cleavage process (Table 1, entry 4).[8] Dediazoniation with

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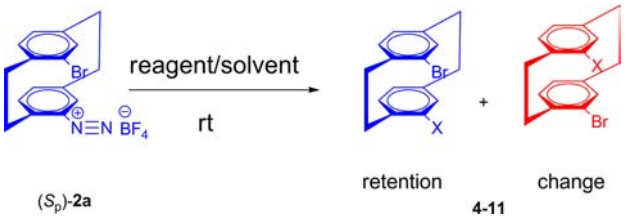
Table 1. Dediazoniation Reaction of **2a** with Different Reagents



entry	solvent	reagent	product X	er (retention/change)[a]	yield[b] (%)
1	MeOH		**4**, OMe	74.9:25.1[c]	80
2	DMSO	H_2O	**5**, OH	73.0:27.0	84
3	Ac_2O	AcOH	**6**, OAc	72.5:27.5	65
4	MeOH	AcONa	**7**, H	99.7:0.3	61
5	DMSO	PhSNa	**8**, SPh	99.2:0.8	53
6	DMSO	NaN_3	**9**, N_3	97.7:2.3[d]	76
7	CH_3CN	KI	**10**, I	98.6:1.4	87
8	CH_3CN	KI + I_2	**10**, I	91.5:8.5	85
9	H_2O	KI	**10**, I	81.9:8.1	71
10	H_2O	HI	**10**, I[e]	55.6:44.4	55
11	CH_3CN	KSCN	**11**, SCN	55.1:44.9	60
12	DMSO	KSCN+ CuSCN	**11**, SCN	93.2:6.8	52

[a] Enantiomeric ratio was determined by chiral HPLC analysis (Chiralpak IA column). [b] Isolated yield. [c] Compound **4** was transformed to **5** for HPLC analysis (see the Supporting Information). [d] Compound **9** was transformed to **1a** for HPLC analysis (see the Supporting Information). [e] The coproduct was **5** with an er value of 93.5:6.5 in 35% yield.

sodium benzenethiolate in DMSO, undergoing a free radical mechanism ($S_{RN}1$ reaction), afforded 13-benzenesulfenyl-4-bromo[2.2]paracyclophane **8** (Table 1, entry 5).[9] Entry 6 in Table 1 is the dediazoniation with sodium azide in DMSO which occurred through attack of the azide upon the diazonium ion with formation of aryl pentazole and its subsequent product **9**.[10] None of these products racemized remarkably (Table 1 entries 4–6). We can conclude that reactions that undergo C–N bond breakage through a heterolytic cleavage process give products with partial racemization, and reactions that occur by a hemolytic cleavage process or a cyclic concerted process give products with retention of configuration (Scheme 2).

It has been known for some time that the singlet aryl cation is a short-lived species which is unselectively captured by a nucleophile or a solvent molecule at a diffusion-controlled rate (its reaction rate constant $k_X \approx k_{diff} \approx 1 \times 10^{10}$ M^{-1} s^{-1}).[11] However, it is uncertain whether the excessive reactivity of this species allowed it to be considered an intermediate in thermal reactions.[12] Fortunately, the formation of the bromonium cation **B** from the singlet aryl cation **A** was fast enough to compete with the reaction between the **A** and a nucleophile (or solvent). Entry 1 in Table 1 describes the solvolysis reaction of diazonium ion in methanol.[13] Because bromonium cation **B** gave products with complete racemization and singlet aryl cation **A** gave products with retention of configuration, we conclude that, when methanol was in large excess, the relative rate could be evaluated as $r_B/r_X = k_B \times [A]/k_X \times [A] \times [MeOH] = k_B/k_X \times [MeOH] = [racemic]/[excess] = 2[change]/[retention - change] = 1.01$, where r_B is the rate of formation of bromonium cation **B** and r_X is the rate of reaction between singlet aryl cation **A** and methanol, while k_B and k_X are the corresponding rate constants. Thus, the relative rate constant could be evaluated as $k_B/k_X \approx k_B/k_{diff} = 1.01 \times [MeOH] = 24.8$ M at room temperature. Substitution of the value of k_{diff} gives the absolute rate constant k_B as 2.48×10^{11} s^{-1} at room temperature. The formation of the bromonium cation **B** is a unimolecular reaction, whose reaction rate (r_B) is almost the same as that of the reaction between singlet aryl cation **A** and methanol (r_X). So it displays high sensitivity to the singlet aryl cation **A**. Moreover, as the stability of bromonium cation **B** is much higher than that of singlet aryl cation **A**, it is expected that the former could selectively react with different nucleophiles while the latter could not. To summarize, the racemization caused by bromonium cation **B** could act as a mechanistic probe for the reaction leading to the singlet aryl cation.

In order to check the probe, we carried out another series of experiments (Table 1, entries 7–12). The iododediazoniation reaction has been exploited for a considerable length of time and a number of workers have proposed that the iododediazoniation reaction proceeds through a free radical mechanism.[14] However, our results showed that the mechanism of the iododediazoniation reaction was not a simple radical process but a complex blended process which was determined by the reaction conditions. For example, under the reaction conditions of entries 7 and 8 in Table 1, a radical process was the predominant mechanism. A small amount of optically pure (S_p)-**2a** underwent a heterolytic cleavage through bromonium cation **B** to give a racemic product. When (S_p)-**2a** was treated with an aqueous solution of KI (Table 1, entry 9), the product **10** was 36% racemized. This further confirms that the iododediazoniation reaction proceeds by two mechanisms including heterolytic and hemolytic cleavage processes. When (S_p)-**2a** was treated with hydroiodic acid (Table 1, entry 10), the degree of racemization was nearly 90%, that is, a heterolytic cleavage process was the predominant mechanism. Interestingly, the coproduct **5** obtained in high optical purity (er value of 93.5: 6.5 in 35% yield) indicated that the singlet aryl cation combined mainly with water instead of hydroiodic acid. On the other hand, the results also showed that the bromonium cation **B** could selectively react with the stronger nucleophile (HI) rather than the solvent molecule (H_2O).

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Aryl thiocyanates are of interest as compounds with high biological activity and convenient sources of thioaromatic compounds.[15] (S_p)-**2a** reacted with potassium thiocyanate in acetonitrile to afford the thiocyanato[2.2]paracyclophane **11** in 60% yield 10% ee (Table 1, entry 11), that is to say, this reaction mainly underwent a bromonium cation process. In most cases, the reaction between SCN^- and aryldiazonium fluoroborates would occur without a catalyst in extremely low yield.[16] **1c** was also tested under the same reaction conditions, and only a trace amount of product could be found (< 5%). This suggested again that the bromonium cation **B** intermediate resulted in nearly racemic products **11**. When cuprous thiocyanate and potassium thiocyanate were used together as dediazoniation reagents as in Sandmeyer-type reactions in nitrile synthesis (Table 1, entry 12),[17] the products were only slightly racemized in moderate yield. Obviously, the Sandmeyer reaction in the presence of a cuprous salt was mainly a radical process.[18]

It is noted that *N*-aromatic secondary amides can be transformed into *O*-aromatic esters in high yield via *N*-nitrosamide intermediates, which would thermally rearrange to acyloxyazoaromatics and decompose to give *O*-aromatic esters and nitrogen.[19] As this reaction had similar intermediates as the dediazoniation reaction, its mechanism could also be investigated by our probe. The results showed that this reaction underwent a heterolytic cleavage process (Scheme 3) rather than the radical mechanism presented by Glatzhofer.[19b]

Scheme 3. Conversion of *N*-Aromatic Amides to *O*-Aromatic Esters

In conclusion, we discovered a novel type of partial racemization of [2.2]paracyclophane derivatives, which is caused by the bromonium cation **B** in the dediazoniation reaction. The experimental results strongly indicate that the partial racemization is closely related to the cleavage of the C−N bond, that is, only heterolytic cleavage process can lead to the partial racemization. The formation of [2.2]paracyclophanylbromonium cation **B** provides an intriguing probe for future mechanistic and kinetic studies.

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Supporting Information Available. Full experimental details and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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