Generation and NMR studies of stable cations derived from monothia[3.2]- and dithia[3.3]metacyclophanes †

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Received (in Cambridge, UK) 5th January 2001, Accepted 27th March 2001
First published as an Advance Article on the web 20th April 2001

Monothia[3.2]- and dithia[3.3]metacyclophanes **1–5** are *S*-protonated in $FSO_3H{\cdot}SbF_5$ (4 : 1)–SO_2 (or SO_2ClF) superacids to give their corresponding acidic mono- and bis(sulfonium) cations. A detailed NMR study of the resulting cations and their precursors is provided; conformational aspects are also addressed *via* NOE measurements. PM3 calculations are used in selected cases as a guiding tool to identify preferred conformations. A remarkable deactivation of the aryl rings occurs upon *S*-protonation, whereby further ring protonation to form disulfoniomonoarenium trications does not occur, even though positive charge delocalization into the phenyl rings is limited.

Introduction

Over the years, thiacyclophanes have played an important role as synthetic intermediates in cyclophane chemistry.[1,2] They have also received considerable attention for their conformational behavior and NMR properties as a function of intra-annular substitution and other structural variations.[3–9] The dithia[3.3]-phane route has become a standard protocol for the synthesis of [2.2]cyclophanes and cyclophane-dienes *via* the Stevens rearrangement–Hoffmann elimination sequence, in which the bis(sulfonium) salts are the key intermediates.[8] Monothia[3.2]-cyclophanes are intermediates in the synthesis of [2.2]meta-cyclophane-monoenes whose chemistry is just beginning to be unravelled.[10]

Despite their importance, there have been very few direct studies of thiacyclophane onium ions.[11] In the context of our interest in cyclophane arenium ions and transannular interactions in charged cyclophanes,[12] in a previous study we generated examples of acidic bis(sulfonium) dications of fluorinated and non-fluorinated dithia[3.3]paracyclophanes and [3.3]meta-paracyclophanes by protonation in superacids and examined their NMR characteristics.[13] It was found that *S*-protonation causes severe deactivation of the arene π-decks towards further electrophilic attack to the extent that even in the strongest superacids a persistent disulfoniomonoarenium trication could not be observed.

The present study focuses on the superacid protonation behavior of monothia[3.2]- and dithia[3.3]metacyclophanes **1–5** with and without intra-annular methyl groups and on the NMR studies (at 500 MHz) of their mono- and bis(sulfonium) cations. PM3 was used as guiding tool for comparison with experiment. It becomes apparent that severe π-deactivation *via* *S*-protonation (or *S*-alkylation) also applies to [3.2]- and [3.3]metacyclophanes.

Results and discussion

NMR assignments

Detailed NMR assignments at 500 MHz for the neutral cyclophane precursors and their mono- and bis(sulfonium) cations are based on ^1H, ^{13}C, H/H COSY, HMBC, HMQC and NOED spectra.

Stable ion studies

Initial studies with $FSO_3H{\cdot}SbF_5$ (4 : 1)–SO_2ClF and with $FSO_3H{\cdot}SbF_5$ (1 : 1)–SO_2ClF showed that the resulting cations were not fully soluble. When SO_2ClF was replaced by SO_2, homogeneous cation solutions were obtained. Whereas the bulk of the study employed SO_2, in some cases solubility was adequate for the NMR analysis of $FSO_3H{\cdot}SbF_5$ (4 : 1)–SO_2ClF samples for comparison. In selected cases, the $FSO_3H{\cdot}SbF_5$ (4 : 1)–SO_2ClF samples were stored and subsequently quenched. This led to the formation of the [3.3]bis(sulfoxide) derivatives, in some cases, by oxidation in the superacid.

Protonation studies on monothia[3.2]cyclophanes 1, 2 with intra-annular methyls

The monothiacyclophanes **1** and **2** exist in the *anti*-conformation.[10] This is clearly judged from the highly shielded internal methyls which appear at δ 0.87 and 0.83, respectively, in the proton NMR (Fig. 1). The pseudo-axial methylene protons (on the ethano-bridge and on the thia-bridge) exhibit an NOE with the internal methyls, whereas the equatorial ones show an NOE with their corresponding ring protons in the case of **1** and with the methyl groups in **2**. The pseudo-axial/pseudo-equatorial pairs are quite distinct and those on the thia-bridge are noticeably more deshielded.

Low temperature reaction of **1** (Scheme 1) with $FSO_3H{\cdot}SbF_5$ (4 : 1)–SO_2 gave a pale-yellow solution which exhibited nicely resolved NMR spectra with narrow resonances at −50 °C. The data are consistent with the formation of monosulfonium cation $\mathbf{1H}^+$; there is no NMR evidence for additional ring protonation. The SH^+ signal appears as a multiplet at δ 6.71. The change in the chemical shift of the internal methyls is minimal (still highly shielded), suggesting that the *anti*-conformation is preserved. Methylene protons (and carbons) of the thia-bridge are deshielded, as are the ring protons. However, there is little charge delocalization into the benzene rings. Interestingly, the ring carbons attached to the thia-bridge become shielded upon *S*-protonation. This is probably caused by a change in the conformation at the thia-bridge.

For the *syn*-conformation, the thia-bridge "wobble" process generates two conformations (S-up/S-down), each with two

† Electronic supplementary information (ESI) available: selected ^1H, ^{13}C and H/H COSY data for the sulfonium cations. See http://www.rsc.org/suppdata/p2/b1/b1002651/

DOI: 10.1039/b1002651

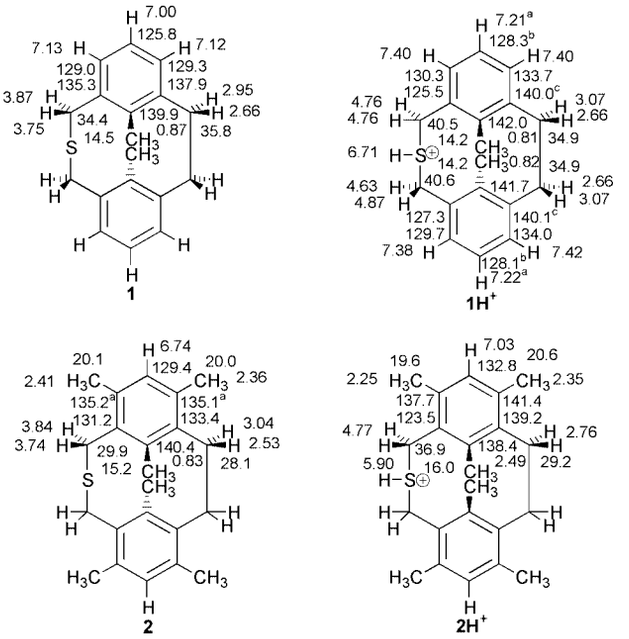
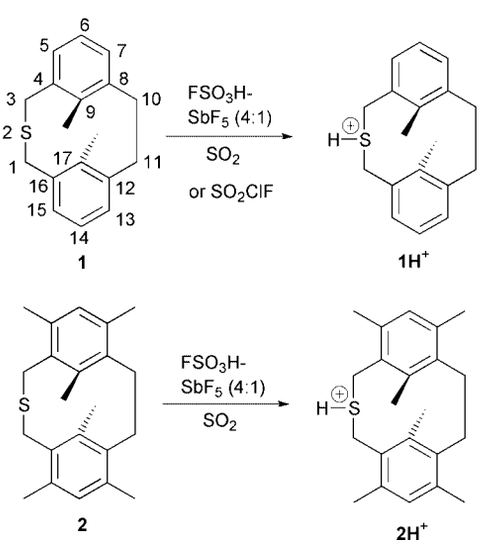


Fig. 1 NMR data for the monosulfonium cations $\mathbf{1H}^+$ and $\mathbf{2H}^+$ and their precursors; a, b, and c denote interchangeable assignments.



Scheme 1 Protonation studies on monothia[3.2]metacyclophanes **1** and **2**.

possible SH^+ pseudo-axial or pseudo-equatorial conformations. PM3 computes the difference in energy between SH^+ pseudo-axial and pseudo-equatorial in the S-down conformation to be about 3.8 kcal mol^{-1} in favor of pseudo-axial, which is the conformer with the smaller calculated dipole moment. For the *anti*-conformation, where the S-up/S-down forms are identical, only the pseudo-axial SH^+ is a minimum (the pseudo-equatorial form converged to pseudo-axial on PM3 minimization).

Similar protonation of the tetramethyl derivative **2** with $FSO_3H{\cdot}SbF_5$ (4 : 1)–SO_2 gave a pale-yellow solution of the monosulfonium cation $\mathbf{2H}^+$ with its S*H*$^+$ resonance appearing as a broad singlet at δ 5.90. Optimal spectra were obtained at −30 °C. Interestingly, the internal methyls move to δ 2.49 suggesting that the *anti*-conformation changed upon *S*-protonation. Other features, namely limited delocalization into the phenyl rings, the upfield shift of the ring carbons attached to the thia-bridge and noticeable deshielding of the C*H*$_2$ protons at the thia-bridge were similar to those of $\mathbf{1H}^+$. An NOE was detected for both the methylene bridge and the thia-bridge protons with the internal and the lateral methyls.

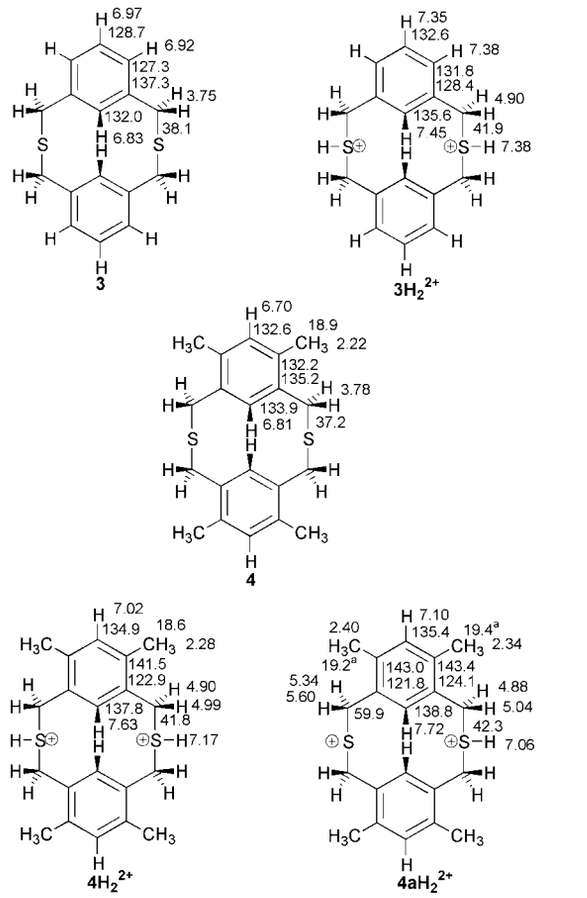


Fig. 2 NMR data for cyclophanes **3** and **4** and their sulfonium derivatives; a denotes interchangeable assignments.

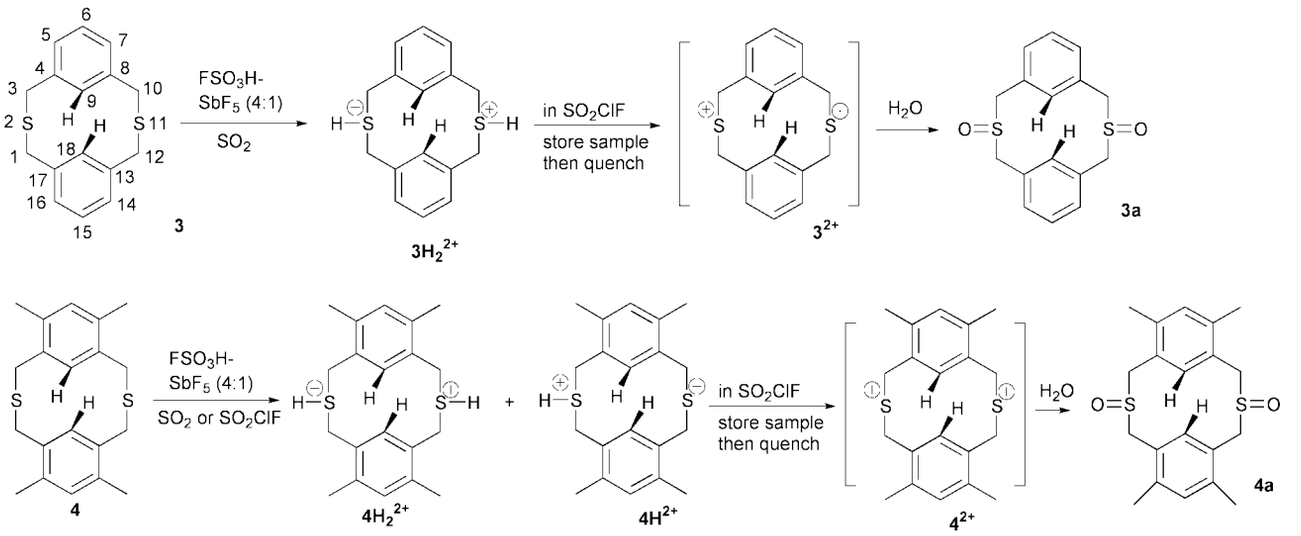
Protonation studies on dithia[3.3]cyclophanes 3, 4 without intra-annular methyls

The parent molecules **3** and **4** both exist in the *syn*-conformation.[4,5] Their internal protons do not experience transannular shielding and appear in the normal range (δ 6.83, 6.81, respectively) (Fig. 2). The thia-bridge protons are chemical shift equivalent and exhibit an NOE with both the internal-H's and the lateral H's (or methyls).

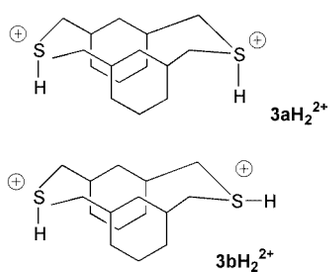
Low temperature reaction of **3** (Scheme 2) with $FSO_3H{\cdot}SbF_5$ (4 : 1)–SO_2 gave the bis(sulfonium) dication $\mathbf{3H_2}^{2+}$ as a yellow solution. Initial ^{1}H spectra collected at −70 °C were broad, and raising the temperature to −30 °C sharpened most resonances except the S*H*$^+$ (at δ 7.38). This resonance gives an NOE with the thia-bridge methylenes which also show an NOE with their corresponding *ortho* ring protons. The internal protons move from δ 6.83 to 7.45 in $\mathbf{3H_2}^{2+}$, whereas other ring protons become shielded in the dication. As in previous cases, the *ipso* carbons are shielded in the bis(sulfonium) dication. Judging from the magnitude of $\Delta\delta^{13}$C, there is limited charge delocalization into the phenyl rings. Dication $\mathbf{3H_2}^{2+}$ was the major constituent of a sample prepared in $FSO_3H{\cdot}SbF_5$ (4 : 1)–SO_2ClF, but an insoluble yellow precipitate was also present. Quenching after 2 weeks' storage at −70 °C did not return **3** but rather the bis(sulfoxide) **3a** as a single isomer, whose ^{1}H NMR data agree with the reported values.[7]‡ It is presumably formed *via* the oxidation dication $\mathbf{3}^{2+}$ in line with the work of Furukawa and co-workers in H_2SO_4.[14]

PM3 was used as guide to locate the most favorable conformations for $\mathbf{3H_2}^{2+}$ produced from **3**-*syn*. Among these $\mathbf{3aH_2}^{2+}$ and $\mathbf{3bH_2}^{2+}$ were most plausible with the former being 1.7 kcal mol^{-1} lower in energy.

‡ In ref. 7 the "*cis*" and "*trans*" isomers of the bis(sulfoxides) could not be differentiated.



Scheme 2 Protonation studies on dithia[3.3]metacyclophanes **3** and **4**.



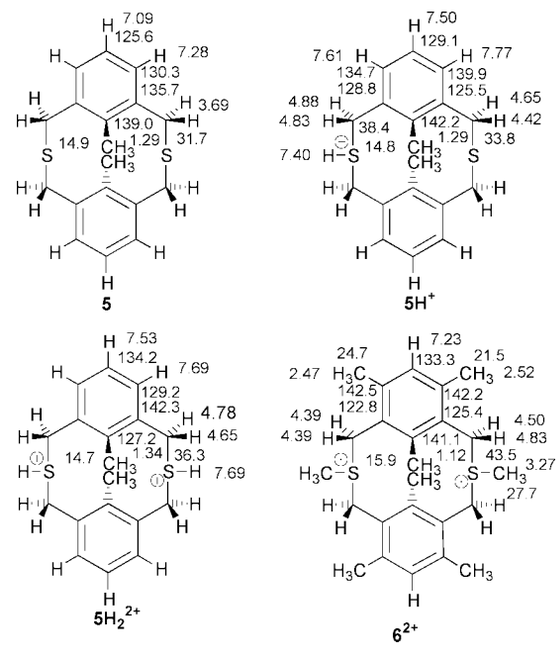


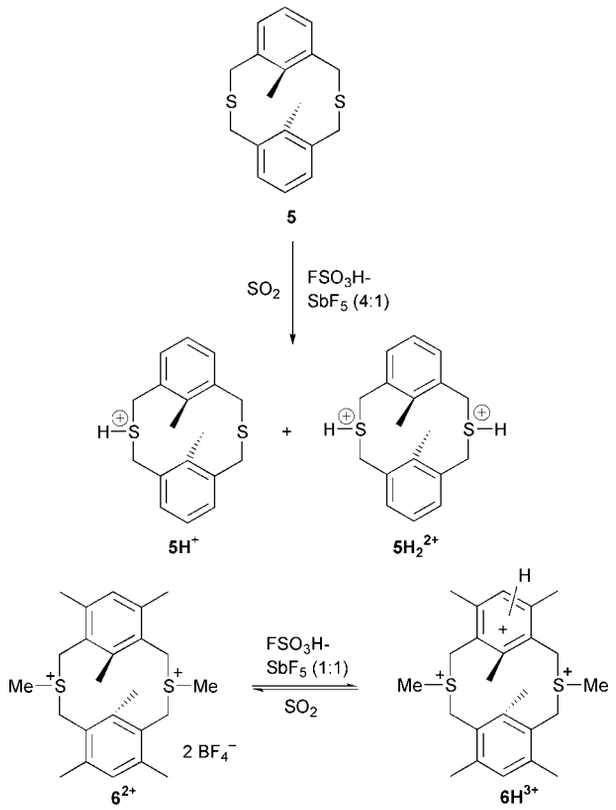
Fig. 3 NMR data for compounds **5**, $\mathbf{5H}^+$, $\mathbf{5H_2}^{2+}$ and $\mathbf{6}^{2+}$.

Low temperature reaction of the ring-methylated derivative **4** with $FSO_3H{\cdot}SbF_5$ (4 : 1)–SO_2 cleanly generated the bis(sulfonium) dication $\mathbf{4H_2}^{2+}$ (a clear pale-yellow solution) for which SH^+ appears at δ 7.17 as a multiplet. Although it is coupled to both pseudo-axial and pseudo-equatorial bridge-methylenes, it gave an NOE only with H_{ax}. The more deshielded H_{ax} has an NOE with the internal hydrogens, whereas H_{eq} exhibits an NOE with the *ortho* methyls. Shielding of the *ipso* carbon is observed. The methyl groups enhance charge localization into the phenyl rings.

Low temperature reaction of **4** with $FSO_3H{\cdot}SbF_5$ (4 : 1)–SO_2ClF gave a pale-red solution (with some red precipitation). Its NMR spectra showed two species in a 2 : 1 ratio. Whereas the major one was $\mathbf{4H_2}^{2+}$, the minor species exhibited two types of thia-bridge methylenes; one side distinctly more deshielded and the other side very close to those in $\mathbf{4H_2}^{2+}$. It possessed seemingly only one SH^+ and exhibited increased charge delocalization into the phenyl rings. The data are best interpreted in terms of the *S*-protonated/*S*-oxidized dication $\mathbf{4H}^{2+}$. Quenching gave the bis(sulfoxide) derivative **4a** plus some polymeric material. Since attempted purification of **4a** failed, confirmation of its identity relied on ^{1}H NMR (in a mixture) and ES-MS. Based on the work of Furukawa and co-workers in sulfuric acid,[14] it is conceivable that **4a** is generated *via* $\mathbf{4}^{2+}$, which is formed on exothermic quenching.

Protonation of dithia[3.3]cyclophane 5 with intra-annular methyls

The *anti*-conformation in [3.3]dithiacyclophane **5** is evident from the anisotropically shielded internal methyls which are at δ 1.29 (Fig. 3). Reaction of **5** with $FSO_3H{\cdot}SbF_5$ (4 : 1)–SO_2 at dry ice–acetone temperature (Scheme 3) gave a colorless solution whose NMR spectra recorded at −70 °C are consistent with monoprotonation to give $\mathbf{5H}^+$ for which SH^+ occurs at δ 7.40. The chemical shifts of the internal methyls are almost unchanged, suggesting retention of conformation. Whereas the thia-bridge methylene protons are deshielded at both bridges, deshielding at the protonated bridge is larger. An NOE is observed between the pseudo-axial CH_2's and the internal methyls on both sides, whereas the pseudo-equatorial CH_2's give an NOE with the outer ring protons. Moreover, SH^+ is coupled only to H_{eq} (COSY). There is limited charge delocalization into the phenyl rings and the *ipso* carbons are shielded on both sides. Increasing the temperature to −50 °C caused dramatic line-broadening in the ^{1}H NMR accompanied by broadening of the CH_2's and the *ipso* ring carbons. Further increase to −30 °C led to the formation of the bis(sulfonium) dication $\mathbf{5H_2}^{2+}$. This caused only slight deshielding of the internal methyls suggesting no major conformational change on diprotonation. Although charge localization into phenyls continued to be small, shielding of the *ipso* carbons observed in $\mathbf{3H_2}^{2+}$ was no longer detected. The NOE trends between $\mathbf{5H}^+$ and $\mathbf{5H_2}^{2+}$ are similar, *i.e.* H_{ax} with internal methyls and H_{eq} with the *ortho* ring proton. Quenching of the superacid solution returned the intact **5**. PM3 predicts that for the *anti*-conformation, among various possible conformations with bridge-up/bridge-down and pseudo-axial/pseudo-equatorial SH^+, the bridge-up/down (H_{ax}/H_{ax}) conformer is most favored,



Scheme 3 Protonation studies on dithia[3.3]metacyclophanes **5** and **6**.

whereas other conformations derived from bridge-down/down have very similar energies.

Reaction of the *anti*-bis(sulfonium) tetrafluoroborate salt 6^{2+} with superacids

Although the bis-*S*-methylated salt $\mathbf{6}^{2+}$ is a key precursor for Stevens rearrangement *en route* to [2.2]metacyclophanediene, its detailed NMR assignments were not previously reported.[8] In the context of the present study we wondered if $\mathbf{6}^{2+}$ could be further charged in superacid media by ring protonation. The onium salt was dissolved in $FSO_3H{\cdot}SbF_5$ (4 : 1)–SO_2 at dry ice–acetone temperature to give a clear pale-yellow solution (Scheme 3). The NMR spectral data provided no evidence for ring protonation. The S*Me*$^+$ signal is observed at δ 3.27; it exhibits an NOE with the pseudo-equatorial bridge methylenes. An NOE is also detected between H_{ax} and the outer methyls and between H_{eq} and the internal methyls. It is noteworthy that the internal methyls in the more crowded $\mathbf{6}^{2+}$ are slightly more shielded than in $\mathbf{5H_2}^{2+}$. Reaction of $\mathbf{6}^{2+}$ with $FSO_3H{\cdot}SbF_5$ (1 : 1)–SO_2ClF provided some evidence for ring protonation in equilibrium. The proton resonances were broadened and the aromatic singlet moved downfield by about 1 ppm, but a frozen trication could not be generated.

In summary, protonation studies are reported on several monothia[3.2]- and dithia[3.3]metacyclophanes with and without interannular methyl groups and detailed NMR analyses of the resulting mono- and bis(sulfonium) cations have been presented. The bis-*S*-methylated dication $\mathbf{6}^{2+}$ has also been analyzed. In the majority of cases formation of the bis-(sulfonium) ions does not alter the conformational preference in the [3.3]metacyclophanes. In line with previous examples of dithia[3.3]paracyclophanes and dithia[3.3]metaparacyclophanes it is clear that *S*-protonation and alkylation induce a rather remarkable deactivation of the phenyl rings towards electrophilic attack to the extent that a trication could not be generated even in $FSO_3H{\cdot}SbF_5$ (1 : 1). Whereas proton deshieldings in the phenyl decks upon sulfonium ion formation are pronounced, the magnitude of the $\Delta\delta^{13}C$ values implies limited charge delocalization. It is conceivable that the observed deactivation is a transannular phenomenon induced by the sulfonium bridge.

Experimental

The monothia[3.2]- and dithia[3.3]metacyclophanes **1–5** and the tetrafluoroborate salt $\mathbf{6}^{2+}$ were available from previous studies (in R.H.M. laboratory).

FSO_3H (Allied and Aldrich) and SbF_5 (Aldrich and Fluorochem) were distilled in an all-glass distillation apparatus under a dry nitrogen atmosphere and stored under nitrogen in Nalgene bottles with teflon seals. The superacids were prepared by addition of the required amount of FSO_3H to pre-weighed SbF_5 in Nalgene bottles under nitrogen.

SO_2ClF was synthesized from SO_2Cl_2, NH_4F and TFAH according to a modified procedure of Prakash and co-workers.[15]

NMR spectra were recorded on a 500 MHz Varian-INOVA instrument. Complete assignments for the precursors and the resulting cations were achieved by a combination of ^1H, ^{13}C, H/H COSY, C/H HETCOR, HMQC and HMBC, aided by NOED spectra.

PM3 calculations were carried out using the standard methods implemented in the Hyperchem Package version 5.11 (Hypercube, Inc) or Insight II Release 97.0 (MSI, 1999).

General procedure for stable ion generation

SO_2 or SO_2ClF (*ca.* 0.4 mL) was distilled into a 5 mm NMR tube containing the substrate (10 mg) and cooled to dry ice–acetone temperature. To the resulting suspension pre-cooled superacid was added (2 drops) and the mixture was mixed (vortex) until homogeneous. Then 2 drops of cold CD_2Cl_2 were added on top of the solution and the mixture was thoroughly mixed (vortex).

In quenching experiments, the NMR tube was carefully poured into ice–bicarbonate and the resulting mixture was extracted with CH_2Cl_2, washed (10% NaCl) and dried ($MgSO_4$). The solvent was removed under reduced pressure and the residue was analyzed by NMR.

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