Chemistry of Ethanediyl *S,S*-Acetals 6[¶] - An Example of Vicarious Nucleophilic Substitution of Hydrogen in 1,4-Benzodithians

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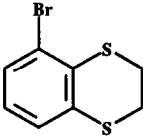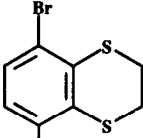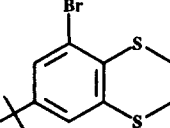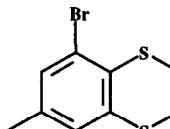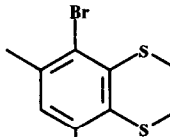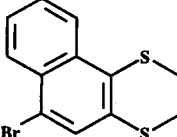*(Received in UK 17 September 1993)*

Abstract: 1,4-Benzodithians, when treated with bromine in anhydrous chloroform, undergo very fast monobromination at the aromatic ring. By the use of quantum mechanical semiempirical calculations, the reaction is shown to proceed most likely *via* a vicarious nucleophilic substitution of hydrogen.

In a recent study[1,2] on the conversion of ethanediyl *S,S*-acetals (1,3-dithiolanes) of cyclohexanones into 1,4-benzodithians by reaction with molecular bromine, we observed that the latter undergo a ready bromination at the aromatic ring in the absence of any catalysts. As a matter of fact, they afford in satisfactory yields their corresponding monobromoderivatives (e.g., compounds **5a-e** and **6** in Table 1) by treatment with equimolar bromine amounts at room temperature in anhydrous chloroform (independently of carrying out the reaction in the light or dark).

Based on literature reports[3], the first step of the reaction between bromine and 1,4-benzodithians (as **1a**) could be confidently assumed to lead to the formation of dibromodisulfonium ions (as **2a**). Such species, indeed, would subsequently either act as electrophilic Br[+] donors, toward other molecules of 1,4-benzodithian as such or, alternatively, undergo nucleophilic attack by a bromide ion on their own aromatic ring. (The formation of the brominated 1,4-dithian **6** from its parent 1,4-naphthodithian makes the occurrence of a [1,3] sigmatropic rearrangement to be ruled out.)

The substitution of bromine on the aromatic ring is rigorously regioselective, the bromine atom being invariably at one of the ring positions *ortho* to the sulfur atoms.   Where   the *ortho* positions are not equivalent, one of them is exclusively preferred (see the bromoderivatives **5c** and **5d** in Table 1). In our experience, the only exception is represented by the brominated 1,4-naphtodithian **6** in which the bromine atom is at the C-6 position[4,5], thus *para* and *meta* respectively to the sulfur atoms. This appears quite peculiar provided that an analogous orientation, although possible in any of the other 1,4-benzodithians tested, had

Table 1 -   **Reaction Products of 1,4-Benzodithians (1a-e) and one 1,4-Naphtodithian with Bromine in CHCl₃**

Product	Yield (%)	^{1}H NMR (δ), J (Hz)
5a	85	3.18-3.30 (*m*, 4H, -CH₂CH₂-), 6.85 (*t*, 1H, H $J_{6,5}=J_{6,7}=8.04$), 7.09 (*dd*, 1H, H-5, $J_{5,6}=8.$($J_{5,7}=1.35$), 7.28 (*dd*, 1H, H-7, $J_{7,5}=1.35$; $J_{7,6}=8.04$)
5b	89	2.40 (*s*, 3H, Me), 3.20 (*s*, 4H, -CH₂CH₂-), 6. (*d*, 1H, H-6, $J_{6,7}=8.41$), 7.18 (*d*, 1H, H-7, $J_{7,6}=8.41$)
5c	97	1.25 (*s*, 9H, Buᵗ), 3.25 (*s*, 4H, -CH₂CH₂-), 7. (*d*, 1H, H-5, $J_{5,7}=2.19$), 7.30 (*d*, 1H, H-7, $J_{7,5}=2.19$)
5d	90	2.38 (*s*, 3H, Me), 3.24 (*s*, 4H, -CH₂CH₂-), 7. (*d*, 1H, H-5, $J_{5,7}=2.10$), 7.25 (*d*, 1H, H-7, $J_{7,5}=2.10$)
5e	85	2.31 (*s*, 3H, Me), 2.45 (*s*, 3H, Me), 3.21 (*s*, 4 -CH₂CH₂-), 6.96 (*s*, 1H, H-6)
6	95	3.21-3.42 (*m*, 4H, -CH₂CH₂-), 7.51-7.54 (*m*, 3 aromatic Hs), 8.12-8.16 (*m*, 2H, aromatic Hs)

never occurred in the other cases.

The exploitation of a chemical reactivity analysis based on the frontier orbital theory gave us the tools to account for these results. Indeed, we envisaged two distinct sceneries: namely, the attack by the aromatic ring of the 1,4-benzodithian molecule onto a positively charged bromine (likely coming from a species as **2a**) or, in alternative, the attack by a bromide ion to the positive charge sharing positions of a dibromodisulfonium ion (as **2a**). In order to evaluate the differences consisting with the energy profiles of the above mentioned interactions, for each of the aromatic carbons in the substrates under consideration we have calculated the coefficients of both the HOMO orbital in the starting 1,4-benzodithians (as **1a**) and the LUMO orbital in their corresponding dibromodisulfonium ions (as **2a**).

These calculations were performed using the AM1, a last generation quantum mechanical semiempirical method[6]. All the reactant structures were then optimized at this level by the MOPAC package[7] and the results are summarized in the Tables 2, 3, and 4.

The highest HOMO coefficients in the starting 1,4-benzodithians, as appears from Tables 2 and 4, belong invariably to the sulfur atoms, this being in agreement with the reported[3] formation of dibromodisulfonium ions (as **2a**). On the other hand, the HOMO coefficients of the carbon atoms in the aromatic ring are too low to account for an effective interaction by a Br^+ species, mainly if one considers the actual positions at which the bromine substitution occurs.

Table 2 - HOMO Coefficients in 1,4-Benzodithians (1a-e)

Position[4]	1a	1b	1c	1d	1e
C-5	+0.099	+0.095	+0.070	+0.061	+0.110
C-6	-0.229	-0.239	-0.249	-0.248	-0.242
C-7	-0.229	-0.228	-0.234	-0.234	-0.248
C-8	+0.099	+0.110	+0.114	+0.111	+0.070
S-1	-0.545	-0.550	-0.557	-0.558	-0.517
S-4	-0.545	-0.539	-0.518	-0.514	-0.554

On the contrary, the LUMO coefficients and the charge quantities calculated for the aromatic carbons in the dibromodisulfonium ions **2a-2e** and the parent dibromodisulfonium ion of **6** (cfr Tables 3 and 4) are in quite good agreement with the hypothesis of a nucleophilic attack onto these species by a bromide ion. Indeed, for the dibromodisulfonium ions **2a**, **2b**, and **2e** the coefficients of the LUMO orbitals are unequivocally higher at the ring positions where the substitution occurs. In the case of **2c** and **2d** the *ortho* position C-5 is not attacked, in spite of its higher LUMO coefficient value (cfr Table 3), and bromination occurs at the other *ortho* position, C-8, which anyhow displays the next highest LUMO coefficient value. This might be due to steric hindrance by the C-6 substituent although, in our opinion, the experimental evidences can be better rationalized considering

Table 3 - LUMO Coefficients and Net Atomic Charges (in |e⁻|) in Dibromodisulfonium Ions (2a-e)

Position[4]	2a	2b	2c	2d	2e
C-5	+0.186 (-0.012)	+0.182 (+0.087)	+0.208 (-0.023)	-0.205 (-0.033)	+0.171 (+0.0!
C-6	+0.134 (-0.035)	+0.147 (-0.055)	+0.135 (+0.067)	-0.134 (+0.062)	+0.137 (-0.0ٌ
C-7	-0.134 (-0.035)	-0.120 (-0.038)	-0.124 (-0.067)	+0.126 (-0.068)	-0.119 (+0.0ٌ
C-8	-0.186 (-0.012)	-0.206 (-0.007)	-0.183 (+0.003)	+0.175 (+0.002)	-0.219 (-0.0ٌ

Table 4 - HOMO Coefficients in the 1,4-Naphtodithian and LUMO Coefficients and Net Atomic Charges (in |e⁻|) in its Corresponding Dibromodisulfonium Ion

Position[4]	HOMO	LUMO	Charge
C-5	-0.012	-0.204	-0.072
C-6	-0.248	-0.156	+0.018
C-7	+0.152	+0.068	-0.075
C-8	+0.167	-0.079	-0.087
C-9	-0.077	-0.123	+0.022
C-10	-0.178	+0.008	-0.213
S-1	-0.513	-0.283	+1.103
S-4	-0.505	+0.468	+1.046

both the orbital overlap and the electrostatic attraction[8,9] that actually favour the C-8 position (cfr Tἀ This view is also consistent with the observed substitution at C-6, rather than C-5, in the dibromodisul ion that should lead to **6**. Confirmatory calculations were also made to ascertain the major stab. intermediates like **3c** and **3d** versus their corresponding C-6 brominated analogues.

Based on these considerations, the mechanism of the monobromination of 1,4-benzodithians confidently assumed to be that outlined in Scheme 1, thus representing an interesting example of the uncommon *vicarious nucleophilic substitution* of hydrogen (VNS reaction)[10].
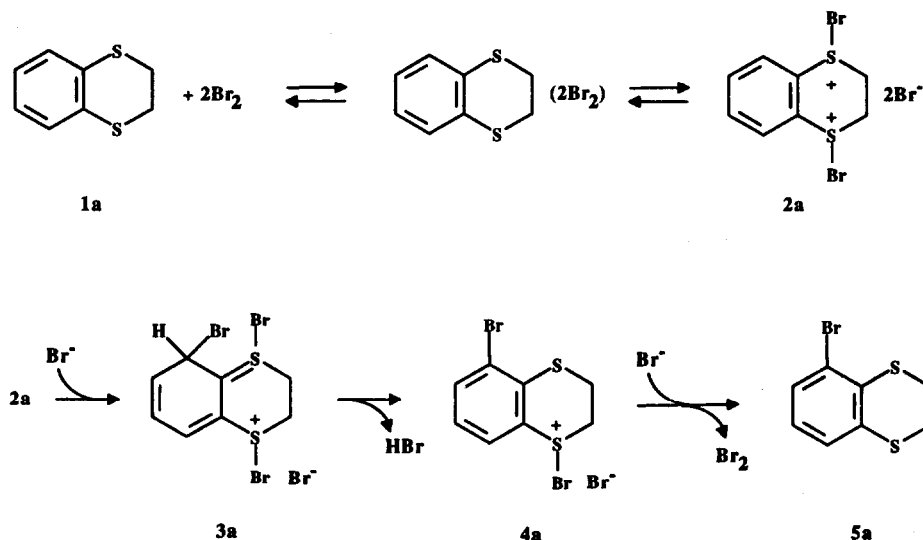
EXPERIMENTAL

Starting 1,4-benzodithians were prepared from their parent ethanediyl *S,S*-acetals according to rͼ procedures[1]. Silica gel for flash-cromatography was Merck 60 (400-230 mesh). ^{1}H NMR spectr

recorded on a Bruker WH (270 MHz) instrument in CDCl$_3$ solutions. Molecular orbital calculations were carried out with a MOPAC 6.0 program compiled for Digital VAXstation 3100.

Reaction of 1,4-Benzodithian (1a) with bromine - Typical procedure.

To a solution of the title 1,4-benzodithian (0.50 g; 3.0 mmol) in anhydrous chloroform (30 cm^3), dry bromine (0.53 g; 3.3 mmol) dissolved in the same solvent (10 cm^3) was added dropwise under magnetic stirring. After

Scheme 1 - Aromatic Bromination of 1,4-Benzodithians *via* Vicarious Nucleophilic Substitution of Hydrogen

60 min at room temperature the acidic chloroform solution was washed with saturated aq sodium hydrogen carbonate and water until neutral, then 5N aq sodium thiosulfate (2x5 cm^3), and water again. The evaporation *in vacuo* of the dried organic layer finally gave an oily residue that after flash-chromatography afforded 5-bromo-1,4-benzodithian (5a) (0.63 g; 2.5 mmol; 85% yield), oil, ^{1}H NMR see Table 1; m/e = 246, 248.

Under the same conditions:

5b: (89% yield), oil; ^{1}H NMR see Table 1; m/e = 260, 262

5c: (97% yield), oil; ^{1}H NMR see Table 1; m/e = 302, 304

5d: (90% yield), oil; ^{1}H NMR see Table 1; m/e = 260, 262; Found C, 41.16; H, 3.30; Calc. for C$_9$H$_9$BrS$_2$ C, 41.38; H, 3.47%.

5e: (85% yield), oil; ^{1}H NMR see Table 1; m/e = 274, 276.

6: (95% yield), m.p. 83.5-84.5 °C; ^{1}H NMR see Table 1; m/e = 296, 298.

Desulfurization of 6 and 5e.

A solution of **6** (0.89 g; 3.0 mmol) in glacial acetic acid (10 cm^3) was added in one portion to a suspension commercial (Fluka AG) Ni(Ra)-W2 (2.7 g) in the same solvent (5 cm^3) at room temperature and und magnetic stirring. The resulting suspension was heated at 40 °C and stirred for 50 min. After cooling in an i bath, the solid was filtered off and washed with glacial acetic acid (3 x 5 cm^3). The filtrate was then neutraliz with 5N aq NaOH and extracted with Et$_2$O. Careful distillation of the dried (Na$_2$SO$_4$) ethereal extract final afforded a crude residue that after chromatography on silica gel gave pure (^{1}H NMR; GCM! 1-bromonaphtalene (0.57 g; 2.7 mmol; 90% yield) identical with an authentic sample.

Under the same conditions, **5e** (0.28 g; 1 mmol), treated with Ni(Ra)-W2 (0.8 g), afforded pure (^{1}H NM! GCMS) 1-bromo-2,4-dimethylbenzene (0.16 g; 0.9 mmol; 90% yield) identical with an authentic sample.

ACKNOWLEDGMENT

REFERENCES AND NOTES

¶   For part 5 in the same series, see ref. 2.

1. Caputo, R; Ferreri, C.; Palumbo, G.; Russo, F. *Tetrahedron*, 1991, **47**, 4187.

2. Caputo, R; Ferreri, C.; Palumbo, G.; Pedatella, S.; Russo, F. *Heterocycles*, 1993, **36**, 281.

3. Mc Cullaugh, J.D.; Chao, G.Y.; Zuccaro, D.E. *Acta Cryst.*, 1959, **12**, 815.

4. An arbitrary clockwise numbering starting from the upright sulfur atom was utilized in order to avo ambiguous numbering differences between starting 1,4-benzodithians and their bromine carryii derivatives.

5. The substitution patterns in compounds **5e** and **6** were confirmed by comparison of the desulfuriz derivatives of the latter with authentic samples.

6. Dewar, M.J.S.; Zoebisch, E.G.; Healy, E.F.; Stewart, J.J.P. *J. Am. Chem. Soc.*, 1985, **107**, 3902.

7. Stewart, J.J.P., *MOPAC 6.0 Quantum Chemistry Program Exchange*. Program No 455.

8. Salem, L. *J. Am. Chem. Soc.*, 1968, **90**, 543.

9. Klopman, G. *J. Am. Chem. Soc.*, 1968, **90**, 223.

10. Mekosza, M. *Synthesis*, 1991, 103