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CONFORMATION AND BARRIER TO INVERSION OF A 12-MEMBERED HETEROCYCLE CONTAINING TWO DISULFIDE BONDS

ZEV LIDERT
Division of Organic Chemistry 1, Chemical Center, University of Lund, Lund, Sweden

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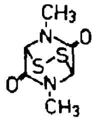
Abstract—Raman and ^1H NMR spectroscopic data obtained for a dimeric product **4c** formed on iodine oxidation of N-phenyl-N-thiomethyl-thioglycolic acid amide (**3c**) indicate that this product is 4,11-diphenyl-4,11-diaza-1,2,7,8-tetrathia-cyclododecane-5,10-dione. The barrier to interconversion between the conformers of **4c** has been determined by DNMR. The height of the barrier ($\Delta G^{\neq} = 17.3 \pm 0.1$ kcal/mol) is in agreement with the proposed structure. This investigation thus gives a support to the previously proposed mechanism of regiospecific dimeric oxidations of unsymmetrical dithiols of type **3c**.

The synthesis of 4-aza-1,2-dithiane-5-ones **2a** and **2b**, which are monocyclic analogues of the antiviral agent N,N'-dimethyl epidithiopiperazinedione **1**[1] has been described in a recent report.[2]



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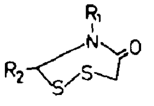

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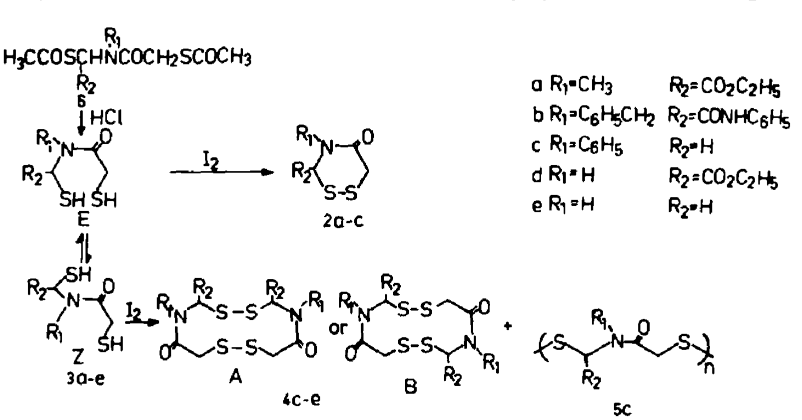
In the last step of the approach, dithiols **3a** and **3b** (Scheme 1) were oxidized by iodine to yield the desired products. However, when the same procedure was applied to **3c**,[3] together with the desired **2c** and polymeric (**5c**) products, a dimeric 12-membered heterocycle (**4c**) was also obtained. Only dimeric products **4d**[2] and **4e**[3] were obtained on oxidation of the corresponding dithiols **3d** and **3e** (Scheme 1). The formation of polymers **5** or dimers **4** rather than monomers **2** was attributed to the high *Z*/*E* ratio of amide conformers of **3c–e** compared to those of **3a** and **3b**.[2]

Interestingly, only one of the two possible isomeric dimers **A** and **B** (Scheme 1) was formed on each oxidation. This was suggested[2] to be a consequence of regiospecific, stepwise coupling, first of the more nucleophilic α-carbonyl thiols and then of the less nucleophilic N-thiomethyl thiols of two reacting molecules of **3c–e** (Scheme 2). This mechanism would lead to isomers containing two symmetrically substituted disulfide bonds, thus being of type **A**.

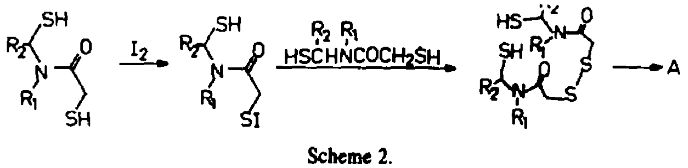
No evidence has yet been presented to support either of the proposed mechanism of oxidations or the structures of **4c–e**. However, the failure to prepare dimer **8** of type **B** from dithioacetal **7**[4] by the method of Kishi *et al.*[5] (Scheme 3) could be interpreted[3] as being due to the instability of such a structure and in consequence provide circumstantial evidence for structure **A** of **4c–e**. Indeed, in the light of the arguments (1)–(3) presented below, which were based on NMR and Raman spectral data, structure **B** of compound **4c** seems quite improbable.

Discussion of NMR and Raman spectral data of 4c

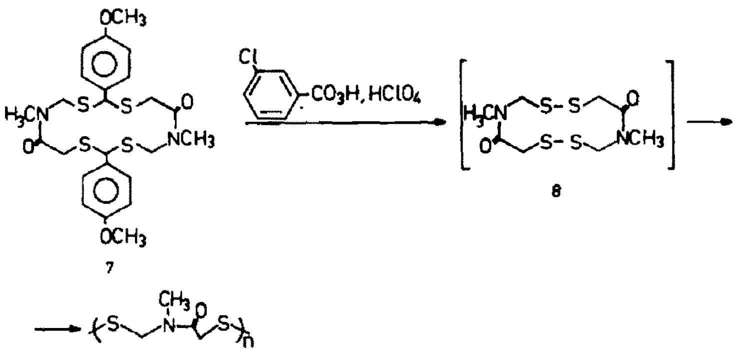
(1) The group of four N-methylene and that of four α-carbonyl protons of **4c** each give rise to one AB-



Scheme 1.



Scheme 2.



Scheme 3.

Table 1. ¹H NMR chemical shifts[a] (δ ppm) of 3c and 4c

Compound	H_{arom}	NCH_2	$COCH_2$
3c($CDCl_3$)	7.44-7.48(5H)	4.76(d,2H)	3.07(d,2H)
4c($CDBr_3$,rt)	7.40-7.68(10H)	6.12(d,2H) 4.34(d,2H)	3.74(d,2H) 3.15(d,2H)
		J_{AB} = 14.6 Hz	J_{AB} = 17.9 Hz
4c($CDBr_3$,122°C)		5.17(4H)	3.47(4H)

[a]all shifts except those for 4c at 122°C are from Ref. 3.

quartet (Table 1). This shows that within each group the protons are pairwise equivalent or enantiotopic and that the geminal protons have different environments.

(2) The down-field shift by approximately 1.5 ppm of one isocronus couple of the N-methylene protons of 4c compared to that of the corresponding protons of 3c (Table 1) is consistent only with a *Z* conformation around the amide bonds of 4c and the position of these protons in or close to the respective amide planes pointing towards the CO groups.[6] The *Z* conformation of N-substituted anilides is known to be the preferred one.[7]

(3) The Raman stretching at ~515 cm^{-1} indicates in the absence of α-disulfide equatorial substitutents, that the CSSC dihedral angles of 4c are not significantly distorted and thus close to the low-energy ~90°.[8] No attempt was made to confirm this by studying the position of the angle dependent UV absorption of the disulfide bond, since this absorption[9] (λ_{max} = 250–340 nm, ϵ_{max} < 500) was expected to be obscured by the strong anilide absorption, which for acetanilide has maximum at λ = 238 (ϵ_{max} = 10,500).[10]

Using the spectroscopic data listed above, models of isomers **A** and **B** of 4c could be constructed (Fig. 1).

Figure 1 shows that to adopt the conformation implied

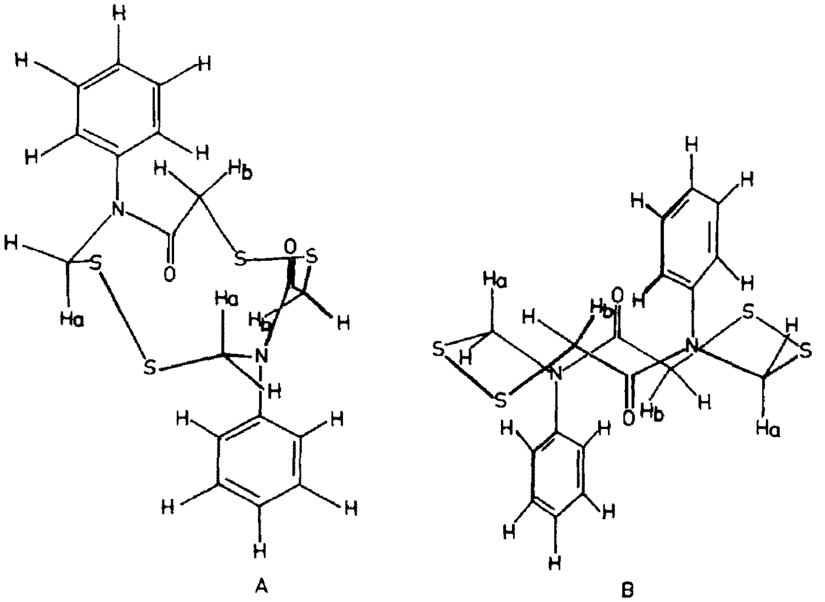


Fig. 1.

Table 2. Activation parameters for interconversion between the conformers of **4c** in $CDBr_3$

T °C	$\Delta G^{\ddagger} \pm 0.1$ kcal/mol[a]	
	$COCH_2$	NCH_2
71.4	17.2	
79.7	17.2	17.2
87.7	17.3	17.3
100.6	17.3	17.3
110.5		17.3
110.8	17.4	
122.0	17.4	17.4

[a] $\Delta H^{\ddagger} = 15.8 \pm 0.2$ kcal/mol; $\Delta S^{\ddagger} = 4 \pm 3$ cal/mol · K

by conditions (1)–(3), the planes determined by the amide functions of isomer **B** must come into close proximity. This would force-H_b and $H_{b'}$ α-CO protons into a region of strong shielding of the opposite CO functions.[11] Yet, no up-field shift of the $COCH_2$ protons is observed in the NMR spectrum of **4c** compared with **3c** (Table 1). Furthermore, the phenyl rings, which in **A** can adopt a low energy position in the planes perpendicular to the amide planes,[12] would in a similar conformation of isomer **B** strongly interact with the S atoms of the neighbouring SS groups. No such interaction in terms of unusual shifts of the aromatic protons (Table 1) is evident from the NMR spectrum of **4c**. The coplanar conformation of the phenyl rings with the respective amide bonds is expected to be highly disfavoured.[12]

Evidently, NMR and Raman spectral data indicate that compound **4c** has structure **A**. Both disulfide bonds of conformer A shown in Fig. 2 have the left-handed (M,M) chirality. Naturally, isomer A exists in solution in an equilibrium of the (M, M) and (P, P) enantiomers. The interconversion between them must involve rotation round the S-S bonds as well as rotation of the amide units round the adjacent C(3)–N and C(6)–CO single bonds.

According to the model, the rotation of the amide units seems quite unhindered and the height of the overall barrier should therefore be determined by the barrier to disulfide rotations. The barrier to inversion was determined by dynamic ^1H NMR, studying the temperature-dependent bandshapes of both methylene quartets of **4c** between 70 and 122° (Table 2). The height of the barrier, 17.3 ± 0.1 kcal/mol, lies within the range of values reported for disulfide rotations.[13]

Due to the short distance between the amide planes, the analogue interconversion between the degenerate conformers (P,M→M,P) of isomer B would have to overcome high steric hindrance and therefore should be expected to have a higher barrier than obtained for **4c**. This provides further evidence for structure A of compound **4c**.

EXPERIMENTAL

4,11 - *Diphenyl* - 4,11 - *diaza* - 1,2,7,8 - *tetrathia* - *cyclo*-*dodecane* - 5,10 - dione (**4c**).[3] Compound **4c** was prepared from **6c**[14] via crude **3c** according to the reported procedure.[3]

NMR measurements. All spectra were recorded on a Jeol-100 spectrometer equipped with standard variable temp. attachment (VT3-C). The temps were measured as previously described.[15] Toluene was used as the internal standard. The rate constants were obtained by fitting of experimental to computer-calculated spectra.

Raman measurements. The room temp. Raman spectrum of solid **4c** (soln was not possible to obtain) was recorded on a Cary 82 spectrometer with argon ion lazer excitation. The measurement was made with a band width of 15 cm^{-1}, between 450 and 600cm^{-1}. The only band in this interval, having max at ~515 cm^{-1} was assigned to the disulfide stretching.[8]

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