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Base-Induced Cleavage of Sulfur-Sulfur Bond in Several Disulfides Having α-Hydrogens

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Several disulfides having α-hydrogens were decomposed by lithium diisopropylamide (LDA) into the corresponding thioaldehydes and thiolate anions. The thioaldehyde undergoes competitively one-electron transfer from LDA leading to a radical anion or nucleophilic attack by the thiolate anion simultaneously formed leading to a thiolate anion of hemidithioacetal. The radical anion was further converted to the corresponding thiolate anion by a hydrogen radical abstraction from solvent and/or the corresponding dithiolate dianion by dimerization.

KEY WORDS: Lithium diisopropylamide/ Benzyl phenyl disulfide/ 1,1′-[1,2-Bis(methylthio)-1,2-ethanediyl]bisbenzene/ 2,3-Benzodithian/ α,α′-Bis(methylthio)-*o*-xylene/ Dialkyl 2,2′-dithiobisacetates/ Dialkyl 2,3-bis(methylthio)butanedioates

In a recent paper[1] we reported that the lithium diisopropylamide (LDA)-induced fragmentation of dibenzyl disulfide at low temperature followed by the trapping with some alkyl halides afford 1,1′-[1,2-bis(alkylthio)-1,2-ethanediyl]bisbenzenes and alkyl α-alkylbenzyl sulfides. The reaction proceeds mainly *via* the fragmentation of α-carbanion generated from dibenzyl disulfide into thiobenzaldehyde and α-toluenethiolate anion; the former thiobenzaldehyde is converted to a radical anion by one-electron transfer from LDA followed by alkylation-dimerization sequence providing 1,1′-[1,2-bis(alkylthio)-1,2-ethanediyl]bisbenzenes, and the latter α-toluenethiolate anion is converted to alkyl α-alkylbenzyl sulfide by alkylation-deprotonation-alkylation sequence. Twenty years ago, Hiskey and Dennis[2] reported the potassium ethoxide-induced conversion of α,α′-dithiobis(acetophenone) and of diethyl 2,2′-dithiobisacetate affoding 1,4-diphenyl-1,4-butanedione-2,3-dithiol and diethyl 2,2′-thiobisacetate-2-thiol, respectively. The reaction proceeds *via* the process involving sulfur-sulfur bond cleavage of α-carbanion generated from α,α′-dithiobis(acetophenone) or diethyl 2,2′-dithiobisacetate providing two intermediate fragments, the corresponding thiolate anion and thioaldehyde; these fragments combine leading to the final product with or without further deprotonation-rearrangement sequence. However, none of well-known disulfides, except three kinds of disulfides above-mentioned, has been submitted to such the base-induced fragmentation.

Thus, we have studied the LDA-inducced cleavage of sulfur-sulfur bond in some of easily available disulfides having α-hydrogens. In a few cases lithium 2,2,6,6-tetramethylpiperidide (LTMP) was used instead of LDA as the base. Initially, benzyl

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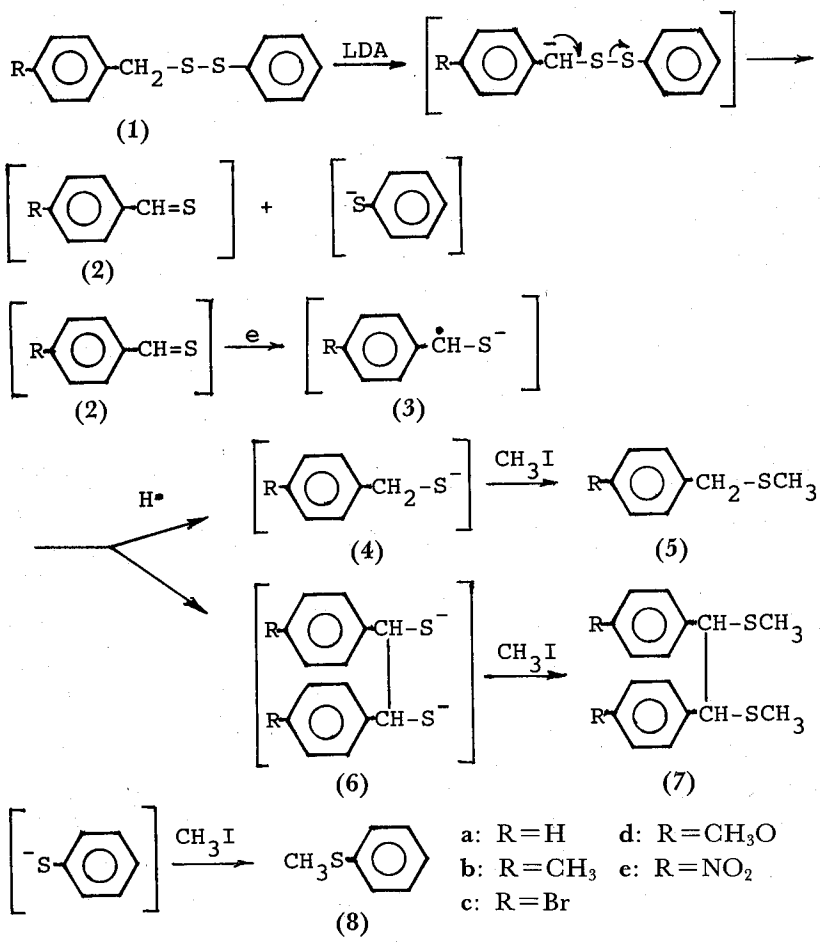
Table I. Base-Induced Fragmentation of Several Disulfides Having α-Hydrogens, Followed by Trapping with Methyl Iodide

Run[a]	Starting[b] disulfide	Base used	Product[c] (yield/%)
1	**1a**	LDA	**7a** (26), **8** (57)
2	**1a**	LDA+TMEDA[d]	**7a** (24), **8** (45)
3	**1b**	LDA	**5b** (35), **7b** (8), **8** (65)
4	**1c**	LDA	**7c** (16), **8** (63)
5	**1c**	LTMP	**8** (26)
6	**1d**	LDA	**5d** (40), **8** (55)
7	**1d**	LTMP	**8** (53)
8	**1e**	LDA	**5e** (10), **7e** (33), **8** (44)
9	**1e**	LTMP	**7e** (25), **8** (29)
10	**9**	LDA	**13** (55)
11	**9**	LTMP	**13** (21)
12	**14a**	LDA	**19a** (24)
13	**14b**	LDA	**19b** (26)
14	**14c**	LDA	**19c** (19)
15	**14d**	LDA	**19d** (22)
16	**14e**	LDA	**19e** (18)

a) In all runs the presence of a few minor products was recognized by thin-layer chromatography. These minor products, however, were not isolable by column chromatography.
b) Besides **1**, **9** and 14, benzyl *t*-butyl disulfide was allowed to react with LDA in THF. This, with trapping with methyl iodide, afforded 25% yield of **7a** together with significant amounts of *t*-butyl methyl sulfide.
c) In all runs the unaltered disulfides could not be recovered.
d) TMEDA: *N, N, N′, N′*-Tetramethylethylenediamine. TMEDA (0.30 g, 0.26 mmol) was added to the solution of LDA in THF prepared at the beginning. Then, this mixture was used as the base under the same conditions.

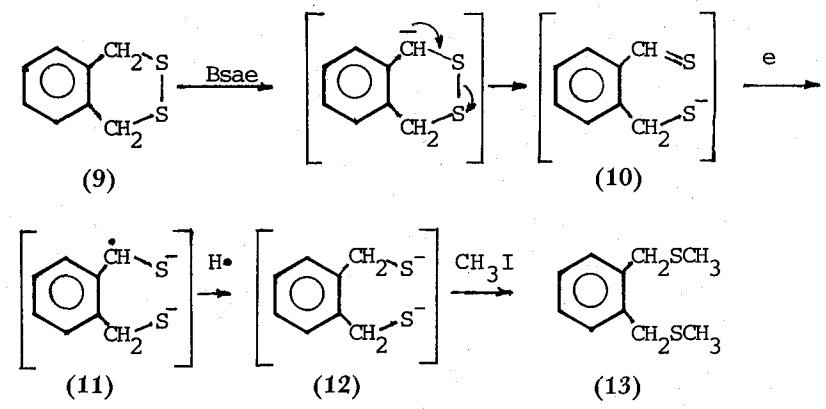
phenyl disulfide (**1a**) was treated with an excess of LDA in tetrahydrofuran (THF) at low temperature. This, with trapping with methyl iodide, led to 1,1′-[1,2-bis(methylthio)-1,2-ethanediyl]bisbenzene (**7a**) together with methyl phenyl sulfide (**8**). The results of analogous reactions using *p*-substituted benzyl phenyl disulfides (**1b, 1c, 1d** and **1e**) as the starting disulfide as well as those using LTMP instead of LDA as the base are collected in Table I. As can be seen from Table I, LTMP is apparently unsuitable base for this kind of reaction; 25% yield of 4,4′-[1,2-bis(methylthio)-1,2-ethanediyl]bis(nitrobenzene) (**7e**) together with **8** was isolated in only Run 9. In Runs 1, 2, 3, 4, 6 and 8 either one of the compounds **5** and **7** or both were isolated together with significant amounts of **8**. None of *p*-substituted benzaldehyde methyl phenyl dithioacetal or its related compounds was isoalted, meaning that there is no process involving the combination of intermediate thioaldehyde with benzenethiolate anion simultaneously formed. The process is probably minor one if it were. Thus, the reaction of **1** with LDA followed by trapping with methyl iodide seems to proceed as follows.

Next, 2,3-benzodithian (**9**) was submitted to the analogous base-induced fragmentation at low temperature followed by trapping with methyl iodide. The product isolated



was α,α'-bis(methylthio)-*o*-xylene (**13**) alone (see Table I). The reaction seems to proceed *via* the process involving α-deprotonation, sulfur-sulfur bond cleavage giving *o*-thioformyl-α-toluenethiolate anion **10**, one-electron transfer from the base giving the radical anion **11**, hydrogen radical abstraction from THF as well as charge neutralization by methyl iodide. None of 3-methylthio-1,3-dihydrobenzo[c]thiophene was isolated. This means that there is no appreciable interaction between $-CH_2S^-$ and the thioformyl group of **10**.

Lastly, several dialkyl 2,2′-dithiobisacetates (**14**) were allowed to react with LDA in THF followed by trapping with methyl iodide under the same conditions. The products isolated were dialkyl 2,3-bis(methylthio)butanedioates (**19**) alone. In all of Runs 12–16 none of alkyl (methylthio)acetates was isolated. This means that the initially formed alkyl thioformylcarboxylate **15** and alkoxycarbonylmethylthiolate anion **16** combine exclusively leading to the formation of intermediate species **17** which undergoes deprotonation-rearrangement sequence to afford the dithiolate dianion **18**. Thus, the reaction seems to proceed as follows.



$$ROCOCH_2\text{-}S\text{-}S\text{-}CH_2COOR \xrightarrow{LDA} \left[ROCO\bar{C}H\text{-}S\text{-}S\text{-}CH_2COOR\right] \longrightarrow$$

(14)

$$\left[ROCOCH{=}S + {}^{-}S\text{-}CH_2COOR\right] \longrightarrow \left[ROCO\overset{S^-}{\overset{|}{C}}H\text{-}S\text{-}CH_2COOR\right]$$

(15) (16) (17)

$$\rightarrow \left[ROCO\overset{S^-}{\overset{|}{C}}H\text{-}S\text{-}\bar{C}HCOOR\right] \longrightarrow \left[ROCO\overset{S^-}{\overset{|}{C}}H\text{-}\overset{S^-}{\overset{|}{C}}HCOOR\right]$$

(18)

$$\xrightarrow{CH_3I} ROCO\overset{SCH_3}{\overset{|}{C}}H - \overset{SCH_3}{\overset{|}{C}}HCOOR$$

(19)

a: R=CH_3 **d**: R=i-C_3H_7
b: R=C_2H_5 **e**: R=n-C_4H_9
c: R=n-C_3H_7

In conclusion, α-lithiodisulfides, as unstable intermediates occurring in the reaction of disulfides having α-hydrogens with LDA, undergo fragmentation into thioaldehydes and thiolate anions. The thioaldehyde undergoes competitively one-electron transfer from LDA leading to a radical anion or nucleophilic attack by the thiolate anion simultaneously formed leading to a thiolate anion of hemidithioacetal. The radical anion is further converted to the corresponding thiolate anion by a hydrogen radical abstraction from solvent and/or the corresponding dithiolate dianion by dimerization. On the other hand, the thiolate anion of hemidithioacetal undergoes deprotonation followed by intramolecular rearrangement leading to the corresponding dithiolate dianion if the deprotonation is possible. In our experiments, the thioaldehyde **2** or **10** underwent one-electron transfer by LDA, on the other hand, the thioaldehyde **15** underwent nucleophilic attack by the thiolate anion **16** simultaneously formed. This difference seems to be caused by the structural difference between these thioaldehydes, but with some uncertainty.

Table II. ^{1}H-NMR Spectral and Analytical Data of Some Products Obtained

Compound[a]	Mp (°C) or Bp (°C/mmHg) (lit.)	^{1}H-NMR (δ in $CDCl_3$)	Found (Calcd) (%)		
			C	H	N
7a	98–100 (99.3–101)[7]	1.78 (s, 6H), 4.03 (s, 2H), 6.8–7.4 (m, 10H)	69.74 (70.02)	6.55 (6.61)	
7b	Not measured	1.78 (s, 6H), 2.21 (s, 6H), 4.06 (s, 2H), 7.0–7.2 (m, 8H)	71.33 (71.47)	7.36 (7.33)	
7c	Not measured	1.82 (s, 6H), 4.05 (s, 2H), 6.9–7.4 (m, 8H)	44.49 (44.46)	3.60 (3.73)	
7e	Not measured	1.88 (s, 6H), 4.22 (s, 2H), 7.2–8.1 (m, 8H)	52.42 (52.73)	4.27 (4.43)	7.48 (7.69)
13	116/1.0–1.5 (114/1.0)[8]	2.04 (s, 6H), 3.85 (s, 4H), 7.0–7.4 (m, 4H)	60.56 (60.55)	6.94 (7.11)	
19a	69–71 (71–72)[9]	2.19 (s, 6H), 3.60 (s, 2H), 3.79 (s, 6H)	40.18 (40.32)	5.98 (5.92)	
19b	Not measured	1.31 (t, 6H), 2.20 (s, 6H), 3.57 (s, 2H), 4.25 (q, 4H)	44.87 (45.09)	6.80 (6.81)	
19c	Not measured	0.97 (t, 6H), 1.6–1.8 (m, 4H), 2.20 (s, 6H), 3.59 (s, 2H), 4.15 (t, 4H)	48.80 (48.95)	7.66 (7.53)	
19d	Not measured	1.28 (d, 12H), 2.19 (s, 6H), 3.51 (s, 2H), 5.0–5.2 (m, 2H)	48.74 (48.95)	7.53 (7.53)	
19e	Not measured	0.93 (t, 6H), 1.3–1.5 (m, 4H), 1.6–1.7 (m, 4H), 2.19 (s, 6H), 3.57 (s, 2H), 4.18 (t, 4H)	51.85 (52.14)	8.08 (8.13)	

a) The compounds in Table II, except **13**, are the mixture of stereoisomers.

Danehy and Parameswaran[3] researched upon the decomposition of several disulfides in aqueous or nonaqueous solution. They reported that no one mechanistic scheme governs the alkaline cleavage of disulfides. Probably, half or more parts of the starting disulfides used in our experiments should be decomposed by LDA during the course of reaction leading to many compounds of low molecular weight which are soluble or insoluble in water. However, the process proposed by us seems to be the governing one in the reaction of disulfides with base such as LDA although it compete with many other minor processes, none of which is definite.

EXPERIMENTAL

Materials. The disulfides **1** were prepared by converting benzyl bromide or its *p*-substituted derivatives into the corresponding thiosulfates followed by treatment with sodium benzenethiolate[4]. 2,3-Benzodithian (**9**) was prepared by converting 1,2-bis(bromomethyl)benzene into the corresponding Bunte salt followed by treatment with one equivalent of iodine. The disulfides **14** were prepared as follows. Disodium (*S*-carboxymethyl)thiosulfate, prepared from sodium chloroacetate and sodium thiosulfate, was converted by iodine and water into 2,2′-dithiobis(acetic acid). It was allowed to react with appropriate alcohols in the presence of *p*-toluenesulfonic acid[5,6].

Base-Induced Fragmentation of Several Disulfides (1, 9 and 14) Followed by the Trapping with Methyl Iodide. General Procedure: A solution of LDA (or

LTMP) in THF was prepared by the well-known method using diisopropylamine (0.32 ml, 2.3 mmol) [or 2,2,6,6-tetramethylpiperidine (0.39 ml, 2.3 mmol)] in THF (6 ml) and 1.50 molar solution (1.47 ml, 2.2 mmol) of butyllithium in hexane. Only in Run 2, TMEDA (0.30 g, 2.6 mmol) was added to this solution of LDA in THF. To a stirred, cooled (−78°C) solution of **1**, **9** or **14** (1.0 mmol) in THF (4 ml) was added, under nitrogen, the solution of LDA (or LTMP) in THF above-mentioned. After addition, the reaction mixture was allowed to warm to −15°C and the stirring was continued for 1 h at that temperature. The reaction mixture was cooled again to −78°C and methyl iodide (0.47 g, 3.3 mmol) was added with stirring. The stirring was continued for 1 h at −10～−5°C and then for 24 h at room temperature. The reaction mixture was quenched with a saturated aqueous solution (20 ml) of ammonium chloride, and then extracted with ether (3 × 15 ml). The combined ethereal extract was washed with brine (20 ml), dried over magnesium sulfate and concentrated under reduced pressure to afford a residue, which was subjected to column chromatography on silica gel using 95% hexane-ethyl acetate as eluent.

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