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SYNTHETIC CONTROL BY MEANS OF SELECTIVE INTERMOLECULAR ASSOCIATION. SPECIFIC SYNTHESIS OF UNSYMMETRICAL OR OF SYMMETRICAL SULFIDES

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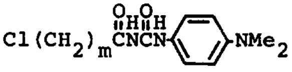
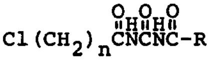
As our continuing study on "synthetic control", several attempts have been made to lead to specific synthesis and to rate acceleration on the assumption that selective intermolecular association mainly through intermolecular hydrogen bonding would control the course of an organic reaction by regulation of the orientation of molecules in solution. The previous experiments demonstrated that treatment of ethanedithiol with a pair of alkyl chlorides 1a and 1-(3-chloropropionyl)-3-(p-nitrophenylacetyl)urea gives two symmetrical bissulfides selectively[1] and that in reaction with 1b and 2c the product ratio (50 : 14) of the unsymmetrical to symmetrical bissulfide exceeds slightly the ratio (2 : 1) statistically expected.[2] The use of H_2S as a nucleophile was expected to increase the selectivity of this type of reaction in view of the fact that freedom of rotation decreases largely in going from ethanedithiol to H_2S.



1a, m = 1
1b, m = 2

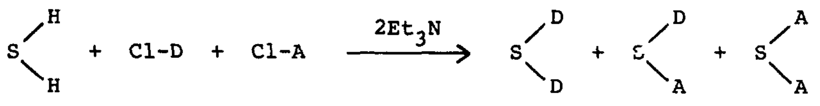


$\mathrm{Cl(CH_2)_n\overset{O}{\overset{\|}{C}}\overset{H}{N}\overset{O}{\overset{\|}{C}}\overset{H}{N}\overset{O}{\overset{\|}{C}}-R}$

2a, $R = C_6H_5$; n = 1
2b, $R = C_6H_5$; n = 2
2c, $R = CH_2C_6H_5$; n = 1

This paper describes the controlled reaction leading to the specific formation of an unsymmetrical sulfide or of two symmetrical sulfides by utilizing a pair of model compounds (1 and 2).

In general, the model reaction of H_2S with a pair of alkyl chlorides,[3] Cl-D (1, donor) and Cl-A (2, acceptor), gave three sulfides, one unsymmetrical (4) and two symmetrical sulfides (3 and 5), as shown in eq 1.



1 2 3 4 5 (1)

In a typical experiment, a solution of triethylamine (22 mmol) in 50 ml of acetonitrile was added all at once to a suspension of 1b (10 mmol, mp 186-187°) and 2a (10 mmol, mp 191.0-191.5°) in 200 ml of acetonitrile under argon with stirring at room temperature. Immediately after the addition of triethylamine, a stream of dried pure hydrogen sulfide, at the rate of ca. 30 ml/min, was passed into the suspension for 3 hr at room temperature. Work-up of the reaction mixture as described previously[1] gave 79% of the unsymmetrical sulfide 4a ($m = 2$, $n = 1$, $R = C_6H_5$), mp 187.0-187.5°, together with a small amount (3%) of 5a ($n = 1$, $R = C_6H_5$), mp 210.5-211.0° dec. The structural assignment of sulfides is based on their elemental analyses and the infrared and nmr spectra. As can be seen in Table I, highly specific synthesis of the unsymmetrical sulfides was also observed with a pair of alkyl chlorides 1b and 2c.

In contrast, when the combination of m and n, the number of the terminal methylene group, was reversed, the two symmetrical sulfides were obtained selectively: treatment of H_2S with a pair of alkyl chlorides 1a and 2b (mp 184.5-185.0°) under the same conditions as in a typical experiment gave 41% of 3a ($m = 1$), mp 213-214°, and 41% of 5b ($n = 2$, $R = C_6H_5$), mp 193.0-194.0° dec. The remarkable selectivity shown in the dialkylation of H_2S clearly indicates that this enzyme model system recognizes small changes in its own structure, i.e., the terminal methylene groups, to a large extent.

The next findings suggest the importance of selective intermolecular association in bringing about the selectivity. First, when the same reaction as in a typical experiment was carried out in DMF, the solvent unfavorable for hydrogen bonding, the yield of the unsymmetrical sulfide 4a decreased markedly from 79% to 45%. Second, the use of N-phenethylchloroacetamide (6), the compound

Table I. Reaction[a] of H_2S with 1 and 2

Chlorides		Solvent	Reaction[b]	Yield,[c] %		
Donor	Acceptor			3	4	5
1b	2a	CH_3CN[d]	A	0[e]	79	3
1b	2a	CH_3CN[d]	A	0[e]	78	3
1b	2c	CH_3CN	A	1	77	2
1b	2a	DMF	B	–[f]	45	10
1a	2b	CH_3CN	A	41	0[e]	41

[a] Carried out at room temperature under argon for 3 hr.

[b] A, heterogeneous; B, homogeneous.

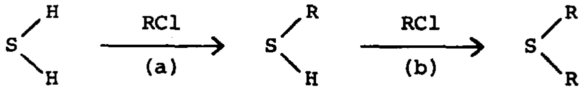
[c] Yields are calculated in such a way that complete conversion of 1 and 2 to 3 and 5 or to 4 is 50% and 50% or 100%, respectively.

[d] Typical reproducibility between completely different runs.

[e] Tlc showed that a trace amount of the corresponding sulfide was involved in the reaction mixture.

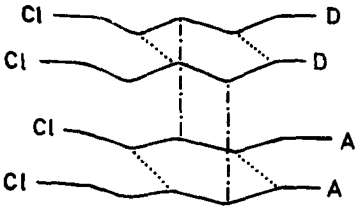
[f] The yield of this sulfide was nearly 10%. In addition, a small amount of the corresponding polysulfides was produced.

probably incapable of forming intermolecular hydrogen bonding, as an acceptor in place of 2a in a typical experiment resulted in the formation[4] of the symmetrical sulfide 3b (m = 2), mp 220-221° dec, and the symmetrical sulfide (7, mp 109-110°) derivable from 6 in 37% and 4% yields, respectively. The acceptor 6 was mainly converted to the corresponding thiol[5] (8, 56%). Third, treatment of the acceptor 2a or 6 with H_2S (flow rate: ca. 30 ml/min) in acetonitrile under argon at 35° gave the sulfide[6] 5a (more than 75%) or the thiol[5,7] 8 (73%), respectively. This result suggests that the second step b (eq 2) is largely accelerated in the case of 2a, the model compound probably capable of forming intermolecular hydrogen bonding.[8]



(2)

One possible explanation for the present results is as follows. A pair of intermolecularly hydrogen-bonded donors and acceptors might form a second tetramolecule complex[9] by means of intermolecular hydrogen bonding as shown below. The detailed structural features of this complex in acetonitrile solution are not yet clearly established. In the hypothetical tetramolecule complex, four reaction sites of two donors and of two acceptors may be kept in close proximity to one another. Therefore, the distance between the two respective terminal carbon atoms of four alkyl chlorides, which probably changes with weak molecular interactions, plays a significant role in determining the selectivity.



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1) T. Mukaiyama, T. Endo, Y. Kojima, and T. Sato, J. Amer. Chem. Soc., 94, 7575 (1972).
2) T. Endo, T. Sato, S. Sato, and T. Mukaiyama, Chem. Lett., 1201 (1973).
3) All new compounds had satisfactory analytical and spectroscopic data to support the assignment.
4) In this reaction, 6% of the donor 1b was recovered as the corresponding olefin, mp 195.0-196.0° dec.
5) Isolated practically as its disulfide, mp 127-129°.
6) Tlc showed that the residual solid consisted of a substantial amount of this sulfide and probably of elemental sulfur.
7) In addition to 8, the sulfide 7 was obtained in 9% yield.
8) It has been demonstrated that 2c forms intermolecular hydrogen bonding in CH_3CN and that infrared spectrum of 1b in CH_3CN shows a band at 3285 cm^{-1}.[2]
9) The formation of a tetramolecule complex in CH_3CN solution is suggested by the finding that a 1 : 1 solid complex between a pair of bissulfides (D-SCH_2CH_2S-D and A-SCH_2CH_2S-A), both of which have two identical acylurea linkages, was produced in some cases in contrast to the result that no complex formation was observed between a pair of alkyl chlorides (Cl-D and Cl-A), both of which have one acylurea linkage: T. Endo, T. Sato, and T. Mukaiyama, Tetrahedron Lett., 1069 (1973).