Complexing of α-Cyclodextrin with Sym-4,4′-Disubstituted Biphenyls

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Sym-4,4′-disubstituted biphenyls are two-site substrates for the ligand α-cyclodextrin. Since the sites are identical, the experimental binding constants for 1:1 and 1:2 complex formation are related to microscopic constants by $K_{11} = 2K_{X'X}$ and $K_{12} = a_{XX}K_{11}/4$, where $K_{X'X}$ is the microscopic constant for binding of the first ligand, and a_{XX} is a cooperativity parameter describing interaction between the sites in 1:2 complex formation. Binding constants were measured for 8 sym-4,4′-disubstituted biphenyls with α-cyclodextrin in aqueous solution at 25 °C and 0.10 M ionic strength by the solubility technique. Correlations were found of log K_{11} with −log S_0 (where S_0 is the substrate molar solubility) and of log a_{XX} with σ_X (the Hammett substituent constant), and these correlations are compared with the corresponding behavior of sym-1,4-disubstituted benzenes. Complexing of α-cyclodextrin with 4,4′-dicarboxybiphenyl is highly cooperative.

Introduction

The cyclodextrins are cyclic oligomers of six or more D-glucose units; the six-unit compound, with which the present paper is concerned, is called α-cyclodextrin or cyclohexaamylose. The cyclodextrin molecule possesses a cavity into which smaller molecules can "partition", forming so-called inclusion complexes or host–guest complexes. The formation of an inclusion complex between a cyclodextrin and a guest molecule may alter many properties of the included molecule (properties such as chemical reactivity, volatility, and absorption spectrum), and these changes in chemical and physical properties are of both theoretical and practical interest.[1] Cyclodextrins (or modified cyclodextrins) have attracted attention as enzyme models, chromatographic phases, and additives for foods and pharmaceuticals.

Our concern is with the equilibrium solution chemistry of α-cyclodextrin (the ligand, L) and some relatively simple organic guest molecules (the substrates, S), the goal being a description and understanding of the stability and properties of these complexes. It is useful to focus attention on potential binding sites on the substrates, for most organic molecules are too large to be fully enclosed within the cyclodextrin cavity. An earlier study[2] described the binding of α-cyclodextrin to a series of sym-1,4-disubstituted benzenes, X–C_6H_4–X; in these substrates there evidently exist two identical binding sites (the sites of substitution), and the solution equilibria can be represented by these equations:

$$L + XX \overset{K_{X'X}}{\rightleftharpoons} X'X$$

$$L + X'X \overset{K_{X'X'}}{\rightleftharpoons} X'X'$$

Here XX denotes the free (uncomplexed) two-site substrate, X′X is the 1:1 complex SL (the prime indicating the site bound to cyclodextrin), and X′X′ is the 1:2 complex SL_2; the definitions of the microscopic binding constants $K_{X'X}$ and $K_{X'X'}$ are implicit in the equations.

For this reaction scheme it is easily shown[2] that the microscopic constants are related to the experimentally observable stepwise binding constants by eq 1 and 2, where $a_{XX} = K_{X'X'}/K_{X'X}$. The stepwise binding constants are defined[3] as $K_{11} = [SL]/[S][L]$ and $K_{12} = [SL_2]/[SL][L]$. The interaction parameter a_{XX} is a cooperativity measure describing the interaction between the two sites in 1:2 complex formation; in fact, a_{XX} is the equilibrium constant for this process:

$$K_{11} = 2K_{X'X} \quad (1)$$

$$4K_{12} = a_{XX}K_{11} \quad (2)$$

$$2X'X \rightleftharpoons X'X' + XX$$

If, therefore, the sites are independent, $a_{XX} = 1$, and if $a_{XX} \neq 1$, the sites are not independent. (It does not follow, however, that if $a_{XX} = 1$ the sites must be independent.)

The study of sym-1,4-disubstituted benzenes revealed that a_{XX} is capable of wide variation within this series, with a_{XX} values in the range 0.07–11.7 being found.[2] These results were interpreted in terms of several contributing factors, to be discussed subsequently. Since the distance between the binding sites is expected to be a key feature in the interaction between sites, the present study was undertaken of the complexing of α-cyclodextrin with a series of sym-4,4′-disubstituted biphenyls, X–C_6H_4–C_6H_4–X. This series matches as closely as is possible the structural and electronic aspects of the binding sites in the benzene series, but incorporates a significant increase in the distance between the binding sites.

Experimental Section

Materials. α-Cyclodextrin (Sigma) was dried for 3 h at 105 °C. The substrates were from commercial sources (Aldrich, Eastman, Pfaltz & Bauer, and Tokyo Kasei Kogyo); they were recrystallized from methanol (except for the dicarboxylic acid), and melting points were consistent with literature values.

Apparatus. Spectral measurements were made with a Cary-Varian Model 2200 or a Perkin-Elmer Model 559 spectrophotometer equipped with thermostated cell compartments. Solubility measurements were carried out with a thermostated water bath fitted to rotate sample vials end over end at 32 rpm. All measurements were made at 25.0 ± 0.1 °C.

Procedure. Stability constants were measured by the solubility method.[4] The apparent solubility S_t of the substrate was determined as a function of total ligand concentration L_t. Solid substrate (in excess of its equilibrium solubility) was added to glass vials also containing the ligand solution. (The ligand solubility was never exceeded.) The vials were sealed with Teflon-lined screw caps and were rotated in the constant-temperature water bath for 24 h, which preliminary experiments showed to be more than adequate time for equilibration. The samples were filtered through 0.22-μm Teflon filters contained in 25-mm Millipore Swag-Lok filter assemblies attached to 10-cm^3 disposable syringes. An accurately measured portion was immediately withdrawn and diluted volumetrically with a methanol–water

(1) (a) Bender, M. L.; Komiyama, M. *Cyclodextrin Chemistry*; Springer-Verlag: Berlin, 1978. (b) Saenger, W. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 344. (c) Szejtli, J. *Cyclodextrins and their Inclusion Complexes*; Akadémiai Kiadó: Budapest, 1982 (D. Reidel: Dordrecht, Holland).

(2) Connors, K. A.; Pendergast, D. D. *J. Am. Chem. Soc.* **1984**, *106*, 7607.

(3) The equilibrium concentrations denoted by brackets are molar concentrations. The reference state is taken to be the experimental solvent, namely water at 25 °C, ionic strength 0.10 M.

(4) Connors, K. A. *Binding Constants: the Measurement of Molecular Complex Stability*; Wiley-Interscience: New York, 1987; Chapter 8.

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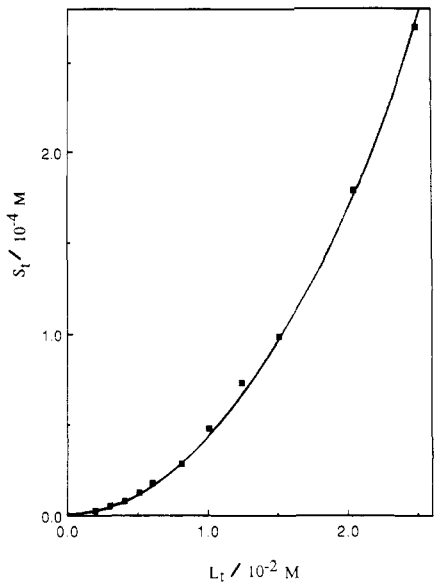

Figure 1. Plot of S_t vs L_t for the 4,4′-dichlorobiphenyl/α-cyclodextrin system.

solution to a concentration range suitable for spectrophotometric analysis. The final methanol concentration was in the range 2:1 to 4:1 (methanol:water); separate studies showed that no spectral shifts caused by complexing were present in these mixed solvents and diluted solutions. The analytical solvent for 4,4′-dicarboxybiphenyl was 5:1 *N*,*N*-dimethylformamide 0.1 N in HCl. Quantitative analysis of the total substrate concentration was carried out spectrophotometrically in 1-cm cells except for the dichloro, dibromo, and dimethyl compounds, for which 10-cm cells were used.

The medium for the solubility measurements was aqueous 0.10 M NaCl, except for 4,4′-dicarboxybiphenyl, which was studied in 0.10 N HCl to repress ionization.

Data Treatment. Equations 3 and 4 describe the system,[4-6] where S_0 is the solubility of the substrate when $L_t = 0$. In these

$$\frac{S_t - S_0}{[L]} = K_{11}S_0 + K_{11}K_{12}S_0[L] \quad (3)$$

$$L_t = [L](1 + K_{11}S_0 + 2K_{11}K_{12}S_0[L]) \quad (4)$$

equations, [L] is the equilibrium molar concentration of free ligand, which initially is unknown, so an iterative solution is used. As a first approximation [L] is set equal to L_t in eq 3 to obtain initial estimates of the stability constants, which are then used in eq 4 to give improved estimates of [L], and so on. Usually seven to nine iterations were carried out. Least-squares linear regression of eq 3 yielded the stability constants, and variance estimates were obtained by a propagation of errors treatment.

Results

Eight sym-4,4′-disubstituted biphenyls were studied as substrates for α-cyclodextrin in aqueous solution at 25 °C and 0.10 M ionic strength. The results, namely, S_0, K_{11}, K_{12}, and a_{XX}, are listed in Table I. Figure 1 shows a typical solubility diagram of S_t vs L_t, and Figure 2 is the corresponding plot of eq 3.

The intrinsic solubility S_0 of dibromobiphenyl could not be directly measured because of its very low value, although S_t was easily determined. As seen in eq 3, the linear plotting form can be used in this circumstance, since $S_t - S_0 \approx S_t$. However, an estimate of S_0 is required to obtain binding constants from the slope and intercept values. A reasonable estimate of S_0 was obtained[7] by extrapolating a plot of $S_t^{1/2}$ vs L_t to $L_t = 0$.

Table I. Binding Constants for α-Cyclodextrin Complexes with Sym-4,4′-Disubstituted Biphenyls, X-C_6H_4-C_6H_4-X[a,b]

X	$10^5 S_0$/M	K_{11}/M^{-1}	K_{12}/M^{-1}	a_{XX}
OH	19.8 (0.1)	41 (5)	345 (48)	33 (6)
CH_3	0.054 (0.005)	1000 (175)	123 (18)	0.5 (0.1)
H	4.0 (0.2)	50 (3)	63 (3)	5.0 (0.4)
Cl	0.026 (0.004)	1030 (400)	1620 (550)	6.3 (3.2)
Br	0.0062 (0.002)	4330 (1445)	5335 (1560)	4.9 (2.1)
CN	0.507 (0.07)	302 (17)	59 (13)	0.78 (0.18)
NO_2	0.046 (0.004)	855 (103)	147 (17)	0.68 (0.11)
COOH[c]	0.263 (0.02)			

[a] At 25 °C, ionic strength 0.10 M. [b] Standard deviations in parentheses. [c] $\beta_{12} = K_{11}K_{12} = 2.91 \times 10^7$ M^{-2}.

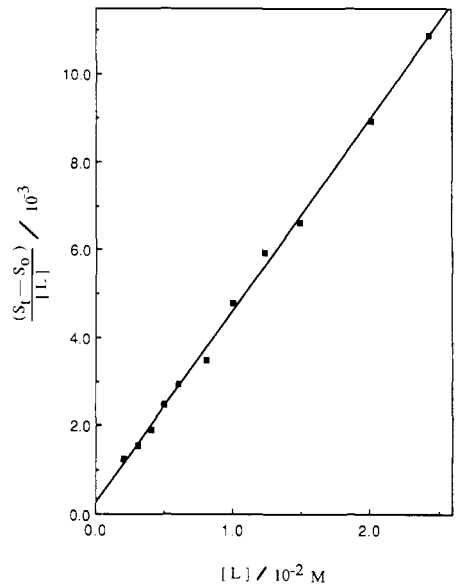

Figure 2. Plot of eq 3 for the 4,4′-dichlorobiphenyl/α-cyclodextrin system.

The dicarboxybiphenyl system did not accurately follow eq 3. It was instead found that this system appears to be described by the overall formation of a single complex SL_n according to

$$S + nL \rightleftharpoons SL_n$$

with overall stability constant

$$\beta_{1n} = \frac{[SL_n]}{[S][L]^n} \quad (5)$$

Equation 6 then follows[4] from the mass balance expression on S:

$$\log\left(\frac{S_t - S_0}{S_0}\right) = \log \beta_{1n} + n \log [L] \quad (6)$$

Figure 3 shows the plot according to eq 6, which yields the stoichiometric coefficient $n = 2.0$. For this system, therefore, it is possible to estimate β_{12} but not the individual stepwise binding constants.[8] This implies that $K_{12} >>> K_{11}$.

Discussion

In interpreting structure–stability relationships within series of cyclodextrin complexes with aromatic substrates, the following postulate has been a helpful qualitative guide:[9] complex stability (at a binding site) is enhanced

(5) Higuchi, T.; Kristiansen, H. *J. Pharm. Sci.* **1970**, *59*, 1601.
(6) Kakemi, K.; Sezaki, H.; Mitsunaga, T.; Nakano, M. *J. Pharm. Sci.* **1970**, *59*, 1597.
(7) Toledo-Velasquez, D. M.S. Thesis, University of Wisconsin–Madison, 1987.
(8) From the definitions of the equilibrium constants it is easily seen that $\beta_{12} = K_{11}K_{12}$.

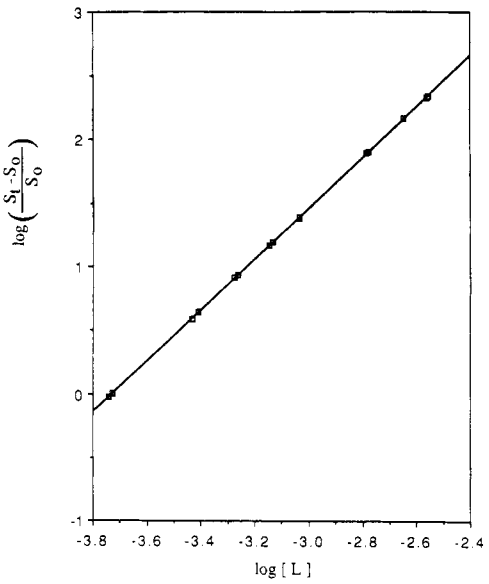

Figure 3. Plot of eq 6 for the 4,4′-dicarboxybiphenyl/α-cyclodextrin system.

by high polarizability, high electron density, and low polarity at the site. The results of this study on the disubstituted biphenyl series are most usefully viewed in comparison with the disubstituted benzene series.[2] The experiment yields two stepwise binding constants, K_{11} and K_{12}; and their interpretation according to the binding site model provides two model parameters, namely, the microscopic binding constant $K_{X'X}$ and the interaction parameter a_{XX}, is shown by eq 1 and 2.

Microscopic Binding Constant. Since $K_{X'X} = K_{11}/2$, we can conveniently discuss the results in terms of the experimental K_{11} values. It is evident from Table I that there is an inverse relationship between binding strength and substrate solubility, and this is shown graphically in Figure 4, which also shows the corresponding correlation for the disubstituted benzene series. In each series the least-squares regression line is based on seven points.[10]

The equations of the lines are

$$\log K_{11} = -0.58 \log S_0 - 0.66 \text{ (biphenyls)} \quad (7)$$

$$\log K_{11} = -0.59 \log S_0 + 0.40 \text{ (benzenes)} \quad (8)$$

The slopes of these lines are not significantly different. These relationships imply that the dissolution of a substrate (actually the reverse process, crystallization) is a good model of its inclusion in the cyclodextrin cavity, and the model is equally satisfactory for both series of substrates. There is a rough trend of log K_{11} with log P (1-octanol/water partition coefficient of the substrate), but this relationship is much poorer than that shown in Figure 4. Similar behavior was seen in the benzene series,[2] for which an analysis was given incorporating both the dissolution and partitioning processes.

The relative positions of the lines in Figure 4 can be accounted for in this way: Consider two compounds X–C_6H_4–X and Y–C_6H_4–C_6H_4–Y having the same solubility S_0. We can generally expect that, since their solubilities are the same, group X must be less polar than group Y; hence we anticipate that the benzene compound will form

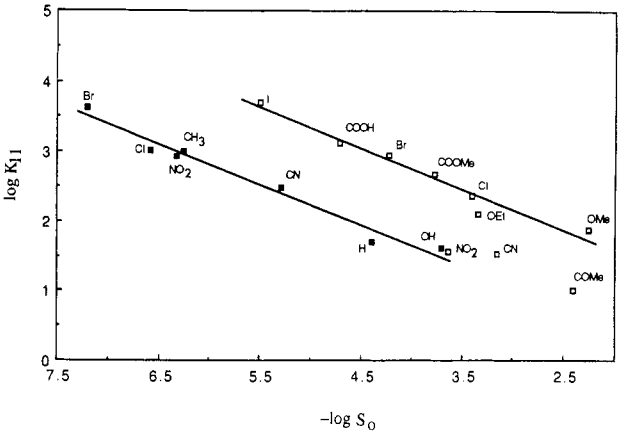

Figure 4. Plot of log K_{11} vs −log S_0 for sym-4,4′-disubstituted biphenyls (solid symbols) and sym-1,4-disubstituted benzenes (open symbols). The benzene data are from ref 2.

a stronger complex (in a polar solvent) than will the biphenyl compound. Therefore the benzene correlation line will lie above the biphenyl line. A second factor is that the portion of the substrate that is not included in the cyclodextrin complex is larger for the biphenyl member of the pair, and (since Y is more polar than X) solvation effects will tend to destabilize the biphenyl complex relative to the benzene complex.

From results on disubstituted benzenes, it had earlier[2] been inferred that the maximum possible microscopic binding constant for α-cyclodextrin at a substituted benzene site is 5.3×10^3 M^{-1}. All of the $K_{X'X}$ values for the disubstituted biphenyls in Table I are smaller than this value.

An attempt was made to resolve β_{12} for dicarboxybiphenyl into its factors. With eq 7 K_{11} was estimated from the substrate solubility, and K_{12} was then obtained from β_{12}. However, these K_{11} and K_{12} estimates failed to generate the experimental S_t, L_t data, so evidently eq 7 is not applicable to the dicarboxybiphenyl system.

Interaction Parameter. Several factors may influence the magnitude of the interaction parameter a_{XX}.

(i) The electronic effect of L bound at site X′ on the nature of site X: If the sites in XX are electron deficient (as a consequence of electron donation to the ring), upon interaction of one of them with L to give X′X there will be a partial electron transfer from L to the binding site. This has the effect of increasing the charge density at site X in X′X relative to that at X in XX. Thus binding of the second ligand will be favored relative to that of the first one (see first paragraph of Discussion), and a_{XX} will be greater than unity. Thus a_{XX} may be expected to follow a Hammett plot with a negative slope.

(ii) The repositioning effect: In the 1:1 complex the relative position of ligand and binding site is optimal with regard to lowering the total free energy of the system. Formation of the 1:2 complex will result in adjustment of all three molecules to minimize the total free energy, since in the 1:2 complex X′X′ the two bound sites are necessarily identical on average. This may require a repositioning of the substrate–ligand orientation that was reached in the 1:1 complex. Any such repositioning must therefore be destabilizing and will therefore lower a_{XX}.

(iii) The ligand–ligand interaction effect: In a 1:2 complex there is a possibility that the facing rims of the two cyclodextrin molecules may interact attractively. Such an effect could only be manifested as 1:2 complex stabilizing (increasing a_{XX}), because any destabilizing repulsive interactions would be accounted for in terms of the repositioning effect.

(9) (a) Connors, K. A.; Lin, S.-F.; Wong, A. B. *J. Pharm. Sci.* **1982**, *71*, 217. (b) Wong, A. B.; Lin, S.-F.; Connors, K. A. *J. Pharm. Sci.* **1983**, *72*, 388. (c) Lin, S.-F.; Connors, K. A. *J. Pharm. Sci.* **1983**, *72*, 1333.

(10) The deviations of three points in the benzene series were ascribed to the high polarity of the nitro, cyano, and acetyl groups.[2] That the cyano and nitro groups do not lead to deviations in the biphenyl series is unexplained.

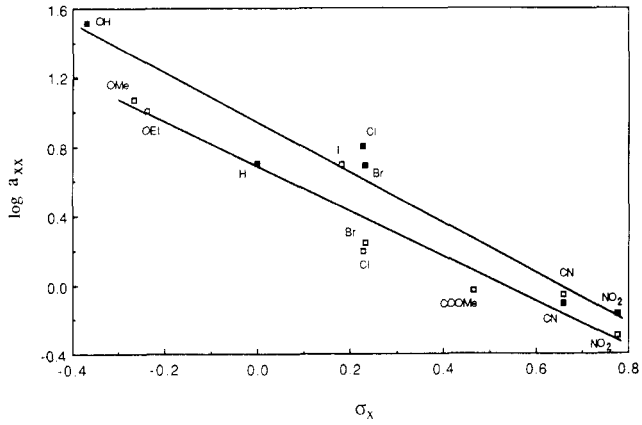

Figure 5. Hammett plot of log a_{XX} vs substituent constant for sym-4,4'-disubstituted biphenyls (solid symbols) and sym-1,4-disubstituted benzenes (open symbols). The benzene data are from ref 2.

Figure 5 is a plot of log a_{XX} against the Hammett substituent constant σ_X, for both the benzene series and the biphenyl series. The equations of the lines in Figure 5 are

$$\log a_{XX} = -1.45\sigma_X + 0.94 \text{ (biphenyls)} \quad (9)$$

$$\log a_{XX} = -1.29\sigma_X + 0.68 \text{ (benzenes)} \quad (10)$$

The standard deviations of the slopes are about 0.17 and of the intercepts about 0.07; hence the slopes are not significantly different whereas the intercepts are.

The dicarboxy member of the benzene series, terephthalic acid, is a serious negative deviator and is not included in the plot. In the biphenyl series, dimethylbiphenyl is a serious negative deviator, and dicarboxybiphenyl is an outstanding serious positive deviator (since the 1:1 complex cannot be detected). Indeed, the log a_{XX} vs σ_X correlation for the biphenyls is not, by itself, very convincing; its acceptability comes largely from the consistency of most of the points with the benzene data. The negative deviation of terephthalic acid was taken[2] as evidence of a large repositioning effect on a_{XX}, signifying that the COOH binding site is very deeply inserted in the cavity in the 1:1 complex. The positive deviation by dicarboxybiphenyl was not predicted, but it can be rationalized in a consistent manner. If, as the terephthalic acid result suggests, the carboxy group is deeply inserted in the 1:1 complex, presumably it occupies a similar position in the dicarboxybiphenyl complex. Addition of a second ligand to terephthalic acid required displacement of the first, giving a low a_{XX} value; but in the dicarboxybiphenyl case, addition of the second ligand must be highly favorable, so much so that the 1:2 complex forms with the virtually complete extinction of the 1:1 complex. It may be inferred that the spacing between sites in the biphenyl complex is optimal for avoiding the repositioning effect and for bringing the ligand–ligand interaction effect into play.

The dimethylbiphenyl behavior is anomalous. Since this compound nicely follows the correlation of log K_{11} against $-\log S_0$ (Figure 4), evidently K_{11} is normal, and so the negative deviation in a_{XX} must be a consequence of an abnormally small K_{12} value. This suggests a reduction in a_{XX} via the repositioning effect and, therefore, deep insertion of the methyl group into the cyclodextrin cavity.

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Registry No. 4,4'-$HOC_6H_4C_6H_4OH$, 92-88-6; 4,4'-$MeC_6H_4C_6H_4Me$, 613-33-2; Ph_2, 92-52-4; 4,4'-$ClC_6H_4C_6H_4Cl$, 2050-68-2; 4,4'-$BrC_6H_4C_6H_4Br$, 92-86-4; 4,4'-$NCC_6H_4C_6H_4CN$, 1591-30-6; 4,4'-$O_2NC_6H_4C_6H_4NO_2$, 1528-74-1; 4,4'-$HOOCC_6H_4C_6H_4COOH$, 787-70-2; α-cyclodextrin, 10016-20-3.

S-Alkyl Alkanesulfonothioates and *S*-1-Chloroalkyl Alkanesulfonothioates from Linear Alkanesulfinyl Chlorides[1]

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Treatment of linear alkanesulfinyl chlorides **1** with dry *N*,*N*-dimethylmethanamide (DMF), *N*,*N*-dimethylethanamide (DMA), or 1-methyl-2-pyrrolidone (NMP) in an inert atmosphere, with or without added solvent, gives *S*-alkyl alkanesulfonothioates **4** (minor products) and *S*-1-chloroalkyl alkanesulfonothioates **5**. The yield of **4** is decreased in the presence of the radical inhibitor 1,4-dihydroxybenzene. Evidence has been obtained for the formation and trapping of sulfines (including methanethial *S*-oxide) and for formation of sulfinyl radicals, *vic*-disulfoxides (α-disulfoxides), and *O*,*S*-sulfenyl sulfinates as reaction intermediates. *S*-Phenyl benzenesulfonothioate is a major product from the reaction of alkanesulfinyl chlorides and benzenesulfinyl chloride in the presence of DMF.

Although several routes have been developed for the synthesis of *S*-monooxides of thiocarbonyl compounds (sulfines), the 1,2-dehydrochlorination of alkanesulfinyl chlorides **1** containing an α-hydrogen atom with triethylamine is one of the most widely used methods for the preparation of aliphatic sulfines (eq 1).[2-8] Despite numerous attempts, none of the routes generally used for the

$$\underset{\mathbf{1}}{RCH_2\overset{\overset{O}{\|}}{S}Cl} + (C_2H_5)_3N \longrightarrow \underset{E,Z}{RCH{=}\overset{+}{S}{-}O^-} + (C_2H_5)_3NHCl \quad (1)$$

(1) Presented in part at the 186th National Meeting of the American Chemical Society, Washington, DC, September 1, 1983, ORGN 242, and the 1983 Pacific Conference on Chemistry and Spectroscopy, Pasadena, CA, October 28, 1983.

(2) Block, E. *Org. Sulfur Chem., Invited Lect. Int. Symp., 9th 1980* 1981, 15; *Chem. Abstr.* **1981**, *95*, 96267c.

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