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The Stereochemistry of Radical Additions. III. The Radical Addition of Hydrogen Sulfide, Thiophenol and Thioacetic Acid to 1-Chlorocyclohexene[1]

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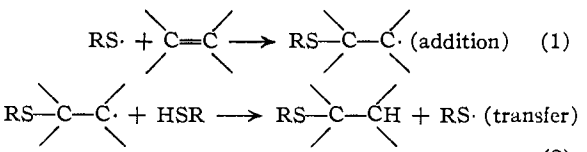
The stereochemistry of the radical-chain addition of hydrogen sulfide, thiophenol and thioacetic acid to 1-chlorocyclohexene has been investigated. The additions give 1,2-disubstituted cyclohexanes and the configurational compositions of the 1:1 addition products were determined by selective solvolysis of the more reactive *trans* isomers. Under the conditions of the present experiments the addition of hydrogen sulfide to 1-chlorocyclohexene gives primarily *cis*-2-chlorocyclohexanethiol, together with small amounts of the *trans* isomer and a mixture of diastereoisomeric bis-2-chlorocyclohexyl sulfides. The addition of thiophenol similarly results in preponderant formation of *cis*-2-chlorocyclohexyl phenyl sulfide. The addition of thioacetic acid is less stereospecific than the other additions and gives a mixture of *cis*- and *trans*-2-chlorocyclohexyl thiolacetates consisting of about 70% of the *cis* isomer. In each case the stereospecificity apparently depends upon the ratio of addendum to 1-chlorocyclohexene.

Introduction

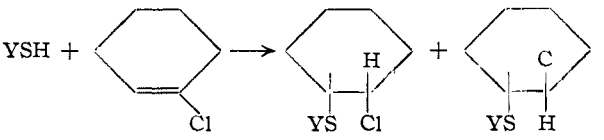
In the preceding papers of this series it has been shown that the radical addition of hydrogen bromide to 1-bromo-[2,3] and 1-chlorocyclohexene[3] gives almost exclusively the *trans*-addition product (*cis*-1-bromo-2-halocyclohexane) and evidence has been presented that the same is true for the addition of hydrogen bromide to 1-methylcyclohexene.[2] In the present work we have investigated the stereochemistry of the radical-chain addition of sulfhydryl compounds to 1-chlorocyclohexene. This system was chosen because of the anticipated ease with which the configurational composition of the 1:1 addition products (1,2-disubstituted cyclohexanes) could be determined accurately by selective solvolysis of the more reactive *trans*-1,2-disubstituted cyclohexanes.

It has been shown by other workers that sulfhydryl compounds undergo radical-chain additions to alkenes[4] and cycloalkenes[5] and that the reactions involved in the chain process are



The radical additions of hydrogen sulfide, thiophenol and thioacetic acid to 1-chlorocyclohexene proceed readily when initiated with ultraviolet light. The 1:1 adducts are 1,2-disubstituted cyclohexanes, as would be expected from earlier work concerning the orientation of radical additions.[6,7]

As illustrated below *cis*-1,2-disubstituted cyclohexanes (Ia) result from *trans* addition and *trans*-1,2-disubstituted cyclohexanes (Ib) result from *cis* addition. In each of the three cases (*i.e.*, Y = H, C_6H_5 or CH_3CO) the solvolytic reactivity of the *trans* isomer is much greater than that of the *cis* isomer—participation[8] by the neighboring sulfur atom is precluded in this *cis* isomer[9]—and the composition of the binary mixture of geometric isomers can be determined accurately by selective solvolysis of the *trans* isomer. That the additions are indeed radical and not ionic is clear from the orientation and the fact that the additions are promoted by ultraviolet irradiation or by peroxides.



Y = H, C_6H_5 or CH_3CO

Results

Addition of Hydrogen Sulfide to 1-Chlorocyclohexene.—The data obtained for the addition of hydrogen sulfide to 1-chlorocyclohexene are presented in Table I. Addition proceeds rapidly when liquid-phase mixtures of 1-chlorocyclohexene and hydrogen sulfide are irradiated at temperatures between −80 and −60° (expts. 1–6) but does not occur in the dark (expt. 7). From these observations it is clear that the radical-chain addition is completely isolated from ionic addition under the present conditions.

The radical addition results in the formation of the 1:1 adduct, 2-chlorocyclohexanethiol (I, Y = H) together with a high-boiling residue. This residue appears to be primarily bis-2-chlorocyclohexyl sulfide (formed by the addition of the initially formed 2-chlorocyclohexanethiol to 1-chlorocyclohexene), since it is oxidized in good yield to a solid sulfone with a chemical composition corresponding to that of bis-2-chlorocyclohexyl sulfone. The residue may also contain small amounts of 3,3′-dichloro-1,1′-bis-2-cyclohexenyl, a compound reported by Lindsey and Ingraham[10] to be one of the

(1) This work was supported by the United States Air Force, through the Office of Scientific Research of the Air Research and Development Command.

(2) H. L. Goering, P. I. Abell and B. F. Aycock, THIS JOURNAL, **74**, 3588 (1952).

(3) H. L. Goering and L. L. Sims, *ibid.*, **77**, 3465 (1955).

(4) (a) S. O. Jones and E. E. Reid, *ibid.*, **60**, 2452 (1938); W. E. Vaughn and F. F. Rust, *J. Org. Chem.*, **7**, 472 (1942); M. S. Kharasch, W. Nudenberg and G. J. Mantell, *ibid.*, **16**, 524 (1951); (b) see also F. R. Mayo and C. Walling, *Chem. Revs.*, **27**, 351 (1940).

(5) (a) J. I. Cunneen, *J. Chem. Soc.*, **36**, 134 (1947); (b) F. G. Bordwell and W. A. Hewett, Abs. 126th Meeting A.C.S., New York, N. Y., Sept., 1954, p. 6-O; (c) S. J. Cristol and G. D. Brindell, THIS JOURNAL, **76**, 5699 (1954).

(6) F. R. Mayo and C. Walling, *Chem. Revs.*, **46**, 191 (1950); R. N. Haszeldine and B. R. Steele, *J. Chem. Soc.*, 3747 (1954), and previous papers of this series.

(7) R. C. Fuson and J. B. Ziegler, *J. Org. Chem.*, 11, 510 (1946), have observed that the radical addition of monothioglycol to vinyl chloride gives the β-chlorosulfide.

(8) A. G. Ogston, E. R. Holiday, J. St. L. Philpot and L. A. Stocken, *Trans. Faraday Soc.*, **44**, 45 (1948).

(9) S. Winstein, *et al.*, THIS JOURNAL, **76**, 18 (1954), and previous papers of this series.

(10) R. V. Lindsey, Jr., and J. N. Ingraham, *ibid.*, **75**, 5613 (1953).

TABLE I

PHOTOINITIATED ADDITION OF HYDROGEN SULFIDE TO 1-CHLOROCYCLOHEXENE[a]

Expt.	Mole ratio[b]	Reaction time, hr.	Recovered 1-chlorocyclohexene, %	Yield of 1:1 adduct,[c] %	% *trans* isomer in adduct[d]	Yield of residue,[e] %	Material balance,[f] %
1	1	4	72.8	18.6	13.9	8.4	100
2	1	4	71.2	18.0	14.1	10.0	99
3	11	1	9.9	63.7		20.5	94
4	18	4	0.0	65.0	10.0	35.4	100
5	90	2	14.9	62.1		21.7	99
6[g]	56	4	8.3	66.2	25.2	21.4	96
7[h]	33	22	94.3	0		0	94
8	56	4	4.3	61.4	7.5	26.5	92

[a] Addition carried out without solvent by irradiating mixtures (liquid phase) of hydrogen sulfide and 1-chlorocyclohexene between −60 and −80°. [b] Mole ratio of hydrogen sulfide to 1-chlorocyclohexene. [c] 2-Chlorocyclohexanethiol. [d] Determined by selective solvolysis of the *trans* isomer; estimated accuracy of the analytical method is ±0.2%. [e] Largely bis-2-chlorocyclohexyl sulfide; yield based on 1-chlorocyclohexene. [f] Sum of the yields of products and recovered 1-chlorocyclohexene. [g] In this expt. a mixture of 0.133 mole of 1-chlorocyclohexene, 7.50 moles of hydrogen sulfide and 0.0250 mole of *trans*-2-chlorocyclohexanethiol was irradiated. [h] Without irradiation.

products of the photodegradation of 1-chlorocyclohexene. In every experiment the combined yields of products and recovered 1-chlorocyclohexene give a material balance of from 92 to 100%.

The configurational composition of the 1:1 addition product (I, Y = H), isolated in such a way as to avoid fractionation, was determined by solvolysis of the product in 80% ethanol at 100° for 45 minutes. Under these conditions pure *trans*-2-chlorocyclohexanethiol (Ib, Y = H) releases one equivalent of chloride ion whereas *cis*-2-chlorocyclohexanethiol (Ia, Y = H) releases <0.2% of an equivalent of chloride ion. As shown in Table I the binary mixtures of *cis*- and *trans*-2-chlorocyclohexanethiols (1:1 adduct) isolated in experiments 1, 2 and 4 contained 13.9, 14.1 and 10% of the *trans* isomer (*cis*-addition product), respectively. Experiments 1 and 2 represent independent duplicate experiments and illustrate that the values obtained for the configurational composition of the 1:1 adduct are reproducible. That the 1:1 adduct was indeed a binary mixture of *cis*- and *trans*-2-chlorocyclohexanethiols was indicated by its chemical composition and by the fact that the infrared absorption spectrum of this material was a composite of the spectra of the two pure components. Moreover, the initial rapid rate of solvolysis of the product (first 5% of reaction) corresponded roughly with that of pure *trans*-2-chlorocyclohexanethiol. This latter compound was prepared for comparison purposes by the reaction of cyclohexene sulfide with hydrochloric acid[11] and the pure *cis* isomer was obtained from the radical addition product by selective solvolysis of the *trans* isomer (80% ethanol at reflux for 20 hours).

It is significant that in expts. 1, 2 and 4, in which the configurational compositions of the 1:1 adduct were determined, material balances of 99 to 100% were observed. This rules out the possibility that the configurational composition of the isolated product is altered by decomposition of the isomers during the reaction or isolation. Experiment 6 was designed to determine if the conversion of the isomeric 2-chlorocyclohexanethiols to bis-2-chlorocyclohexyl sulfide during the reaction results in fractionation. In this experiment *trans*-2-chlorocyclohexanethiol was introduced at the start of a typical addition and the products were isolated in the usual manner. The observed composition of the isolated 1:1 adduct (25.2% *trans*) agrees well with that which would be expected (29% *trans*)[12] if fractionation does not occur during the reaction or isolation. From these observations it appears that the isolated 1:1 adduct corresponds to the kinetically controlled product.

Addition of Thiophenol to 1-Chlorocyclohexene.—The data for the addition of thiophenol to 1-chlorocyclohexene are summarized in Table II. These data show that the addition is promoted effectively by ultraviolet irradiation. The radical addition gives primarily *cis*-2-chlorocyclohexyl phenyl sulfide (Ia, Y = C_6H_5), the *trans*-addition product, together with small amounts of the *trans* isomer (Ib, Y = C_6H_5).

For comparison purposes pure *trans*-2-chlorocyclohexyl phenyl sulfide was prepared by the stereospecific addition of benzenesulfenyl chloride to cyclohexene. The same material was obtained by the reaction of *trans*-2-hydroxycyclohexyl phenyl

TABLE II

ADDITION OF THIOPHENOL AND THIOACETIC ACID TO 1-CHLOROCYCLOHEXENE

Expt.[a]	Mole ratio[b]	Initiator	Time, hr.	Yield of 1:1 adduct, %[c]	% *trans* isomer in 1:1 adduct[d]	Material balance, %[e]
		A. Thiophenol				
9	1	None[f]	17	17		94
10	1	None[f]	117	37	5.8	81
11	1	U.v.	2.5	32	5.2	86
12	18	U.v.	2.5	35	0.9	88
		B. Thioacetic acid				
13	1	None[f]	4	3		89
14	1	None[f]	96	4.4		88
15	1	B.P.[g]	4	13		
16	1	Asc.[h]	3	65		
17	1	Asc.[h]	18	64		
18	1	U.v.	4	80	34	80
19	18	U.v.	4	84	27	87

[a] Expts. 9, 10 and 13–17 were carried out at room temperature; in expts. 11, 12, 18 and 19 the heat given off by the u.v. lamp raised the temperature of the reaction mixture to *ca.* 50°. [b] Mole ratio of addendum to 1-chlorocyclohexene. [c] 2-Chlorocyclohexyl phenyl sulfide or 2-chlorocyclohexyl thiolacetate. [d] Composition determined by selective solvolysis of the *trans* isomer. Accuracy is ±0.2% for 2-chlorocyclohexyl phenyl sulfide mixtures; ±3% for 2-chlorocyclohexyl thiolacetate mixtures. [e] Combined yields of 1:1 adduct and recovered reactants. [f] Reaction carried out in the dark. [g] Two mole % of benzoyl peroxide added. [h] Two mole % of ascaridole added.

(11) C. C. J. Culvenor, W. Davies and N. S. Heath, *J. Chem. Soc.*, 282 (1949).

(12) Under the conditions of expt. 6, a 61% yield of 1:1 adduct (7.5% *trans* isomer) would be expected (see expt. 8). Thus 0.133 × 0.61 × 0.925 = 0.075 mole of *cis* isomer is produced. Similarly 0.133 × 0.61 × 0.075 = 0.0061 mole of *trans* is produced which together with the amount initially added is a total of 0.0311.

sulfide (prepared from cyclohexene oxide and sodium thiophenoxide) with phosphorus pentachloride. Pure *cis*-2-chlorocyclohexyl phenyl sulfide was obtained from the radical-addition product by selective solvolysis of the more reactive *trans* isomer (80% ethanol at reflux for 20 hours). The isomeric 2-chlorocyclohexyl phenyl sulfides were converted to the corresponding 2-chlorocyclohexyl phenyl sulfones by oxidation with hydrogen peroxide in acetic acid.

The radical-addition products were identified as pure binary mixtures of *cis*- and *trans*-2-chlorocyclohexyl phenyl sulfide by their chemical composition and infrared spectra. Control experiments indicated that the isomers are stable under the conditions of the reaction and the binary mixtures are not fractionated during the isolation. The configurational compositions of the 2-chlorocyclohexyl phenyl sulfide (expts. 10, 11 and 12) were determined by solvolysis of the products in 80% ethanol at 100° for 45 minutes. Under these conditions the *trans* isomer is solvolyzed completely whereas the *cis* isomer is unaffected.

Additional evidence that the addition product is in fact 2-chlorocyclohexyl phenyl sulfide rather than 1-chlorocyclohexyl phenyl sulfide (the expected product of ionic addition) is afforded by the observed instability of the latter compound under the conditions of the isolation of the 1:1 adduct. The product resulting from the reaction of dry hydrogen chloride, cyclohexanone and thiophenol at 10°, which is presumably 1-chlorocyclohexyl phenyl sulfide, was dehydrochlorinated almost completely when distilled at 120°. The radical addition products, however, were distilled at 125 to 140° without any indication of dehydrochlorination.

As shown in Table II (expts. 9 and 10) the addition of thiophenol proceeds slowly in the dark in the absence of added initiators. Evidently the reaction under these conditions is a radical addition since 2-chlorocyclohexyl phenyl sulfide (94.2% *cis* isomer) is formed instead of 1-chlorocyclohexyl phenyl sulfide.

The relative solvolytic and base-promoted dehydrohalogenation reactivities of the isomeric sulfides and the corresponding sulfones will be included in a future paper.

Addition of Thioacetic Acid to 1-Chlorocyclohexene.—The data for the addition of thioacetic acid to 1-chlorocyclohexene are included in Table II. The free radical nature of the addition is shown by the promotion of the reaction by ultraviolet light, ascaridole or to a lesser extent benzoyl peroxide.

The radical-addition product, isolated in such a way as to avoid fractionation, was found to contain a much higher percentage of *trans* isomer than was obtained in the additions of hydrogen sulfide or thiophenol. The fact that the infrared absorption spectrum of the 1:1 adduct was a composite of the spectra of the pure *cis* and *trans* isomers of 2-chlorocyclohexyl thiolacetate establishes the orientation of the addition. For comparison purposes *cis*-2-chlorocyclohexyl thiolacetate (Ia, Y = CH_3CO) was prepared by acetylation of *cis*-2-chlorocyclohexanethiol, *trans*-2-chlorocyclohexyl thiolacetate (Ib, Y = CH_3CO) was prepared by the reaction of cyclohexene sulfide with acetyl chloride.[11]

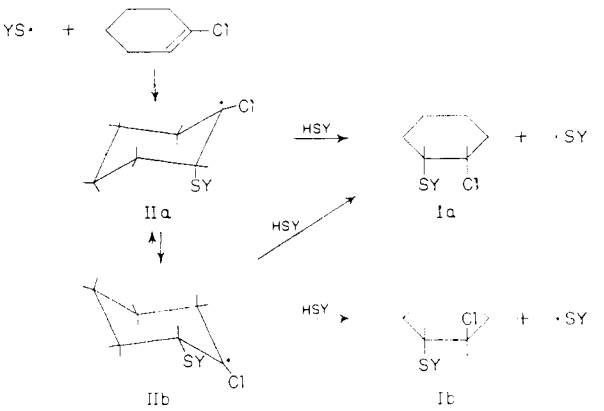
The *trans* isomer solvolyzes faster than the *cis* isomer in 80% ethanol by a factor of *ca.* 10 at 100° and a factor of *ca.* 100 at 50°. The amount of *trans* isomer in the radical-addition product was determined by solvolysis of a sample in 80% ethanol at 50° for 48 hours. Under these conditions the *trans* isomer liberates 0.275 equivalent of chloride ion and the *cis* isomer liberates 2.5×10^{-3} equivalent of chloride ion. In order to test this analytical method synthetic mixtures of *cis*- and *trans*-2-chlorocyclohexyl thiolacetate were analyzed and it was found that the composition can be determined to within 3%.

Discussion

The radical additions of hydrogen sulfide, thiophenol and thioacetic acid are not as stereospecific as the addition of hydrogen bromide.[3] However, in every case *trans* addition predominates even though the resulting *cis*-1,2-disubstituted cyclohexanes (Ia) are thermodynamically less stable than the *trans* isomers (Ib). The fact that the thermodynamically less stable isomer predominates together with the results of various control experiments indicates that the configurational composition of the isolated addition product is determined by kinetic control.

The data presented in Tables I and II show that the stereospecificity of the additions decreases in the order: thiophenol > hydrogen sulfide > thioacetic acid. The stereochemistry of the addition of thioacetic acid to 1-chlorocyclohexene (66% to 73% *trans* addition) is similar to that reported[5b] for the addition of this addendum to 1-methylcyclohexene (85% *trans* addition) and 1-methylcyclopentene (75% *trans* addition).

It appears that the present results are consistent with an explanation which was offered in an earlier paper[3] for the stereospecificity of the radical addition of hydrogen bromide to 1-halocyclohexene. As was pointed out previously[3] it seems likely that the initial conformation of the 2-substituted 1-chlorocyclohexyl radical resulting from the addition of a radical to 1-chlorocyclohexene will be the one in which the 2-substituent is in the axial position. Thus in the present system the first step of the chain process presumably results in the formation of IIa. In this conformation there is an obvious



steric advantage for the addendum (YSH) to approach the radical in the transfer step so as to give the *trans* addition product Ia. Thus if the transfer step occurs before conformational equilibration of the intermediate radical, or if IIa is a more stable conformation than IIb, a preferred *trans* addition would be expected. If the intermediate radical is converted in part to IIb both addition products would be expected since there is little or no steric advantage for the approach of the addendum so as to lead to *trans* addition.

According to the present interpretation the stereospecificity of the radical addition depends on the lifetime of the intermediate radical. This appears to be consistent with the observed correlation between stereospecificity and ratio of addendum to 1-chlorocyclohexene for each of the three cases. At a high ratio of addendum to substrate the rate of conversion of IIa to Ia is larger than at lower ratios and there is less opportunity for IIa to undergo conformational interconversion to IIb.

Experimental[13]

Materials.—Thioacetic acid, b.p. 87–91°, and thiophenol, b.p. 166–169°, were purified by distillation prior to use. Hydrogen sulfide (Mathieson Co.), benzoyl peroxide (Eastman Kodak Co.) and ascaridole (Bios Laboratories) were used without purification. 1-Chlorocyclohexene, b.p. 63–65° (61 mm.), 139–143° (738 mm.), n^{25}D 1.4784, was prepared in 68% yield by reaction of cyclohexanone with phosphorus pentachloride.[14] This material was purified by treatment with excess 2% alcoholic silver nitrate followed by fractionation and was stored in a dark bottle in a refrigerator.

cis-2-Chlorocyclohexanethiol.—Forty grams of the addition product (>85% *cis*-2-chlorocyclohexanethiol) resulting from the ultraviolet light-promoted addition of hydrogen sulfide to 1-chlorocyclohexene (see below) was mixed with 200 ml. of 80% aqueous ethanol. This mixture, which became homogeneous when warmed, was refluxed for 20 hours (>> 10 half-periods for the solvolysis of the *trans* isomer) after which 200 ml. of cold water was added. The organic layer (lower) was separated, dried (magnesium sulfate) and distilled. The pure *cis*-2-chlorocyclohexanethiol obtained in this way boiled at 90–91° (12 mm.) and was shown to be free of the *trans* isomer by its initial rate of solvolysis in 80% ethanol.

Anal. Calcd. for $C_6H_{11}ClS$: C, 47.83; H, 7.36. Found: C, 47.48; H, 7.11.

The chlorothiol was converted to *cis*-2-chlorocyclohexyl 2,4-dinitrophenyl sulfide, m.p. 155.4–156.0° (2:1 absolute ethanol–acetic acid) by reaction of the sodium salt with 2,4-dinitrochlorobenzene.[15]

Anal. Calcd. for $C_{12}H_{13}N_2O_4ClS$: C, 45.50; H, 4.14. Found: C, 45.63; H, 3.91.

Oxidation of the 2,4-dinitrophenyl sulfide with 30% hydrogen peroxide in acetic acid[16] gave *cis*-2-chlorocyclohexyl 2,4-dinitrophenyl sulfone, m.p. 138.0–138.8° (1:1 acetic acid–water).

Anal. Calcd. for $C_{12}H_{13}N_2O_6ClS$: C, 41.32; H, 3.76. Found: C, 41,64; H, 3.80.

trans-2-Chlorocyclohexanethiol.—The reaction of cyclohexene sulfide[17] with hydrochloric acid gave *trans*-2-chlorocyclohexanethiol,[11] b.p. 75.5–76.0° (8 mm.), n^{22}D 1.5175, in 34% yield. It is clear that the product obtained in this way does not contain any of the *cis* isomer since it gives 0.98–0.99 equivalent of chloride ion when solvolyzed at 99.85° for 45 minutes in 80% ethanol. Under these conditions the *cis* isomer is unaffected. Because of the discrepancy in the observed and reported refractive index (Culvenor, *et al.*, report n^{20}D 1.5015[11]) the chemical composition of the product was determined.

Anal. Calcd. for $C_6H_{11}ClS$: C, 47.83; H, 7.36. Found: C, 47.84; H, 7.14.

cis-2-Chlorocyclohexyl Phenyl Sulfide.—Twenty-four grams of addition product (*ca.* 95% *cis*-2-chlorocyclohexyl phenyl sulfide) obtained from the radical addition of thiophenol to 1-chlorocyclohexene (see below) was mixed with 400 ml. of 80% aqueous ethanol. The mixture, which became homogeneous when warmed, was refluxed for 20 hours (>> 10 half-periods for the solvolysis of the more reactive *trans* isomer). The solution was cooled and diluted with 400 ml. of cold water. The organic layer was separated, dried (magnesium sulfate) and distilled. The 11.3 g. of *cis*-2-chlorocyclohexyl phenyl sulfide obtained in this way had b.p. 133–135° (1 mm.), n^{25}D 1.5845, and was shown to be free of the *trans* isomer by its initial rate of solvolysis in 80% ethanol.

Anal. Calcd. for $C_{12}H_{15}ClS$: C, 63.57; H, 6.67. Found: C, 63.44; H, 6.55.

The sulfide was oxidized to *cis*-2-chlorocyclohexyl phenyl sulfone, m.p. 119.0–119.5° (1:1 acetic acid–water), with 30% hydrogen peroxide in acetic acid.[16]

Anal. Calcd. for $C_{12}H_{15}O_2ClS$: C, 55.70; H, 5.84. Found: C, 55.83; H, 5.86.

trans-2-Chlorocyclohexyl Phenyl Sulfide. Method A.—A solution of 9.53 g. (0.066 mole) of benzenesulfenyl chloride,[18] b.p. 69–71° (5 mm.), in 50 ml. of carbon tetrachloride was added during a period of 30 minutes to a stirred solution of 5.50 g. (0.066 mole) of cyclohexene in 50 ml. of carbon tetrachloride. The mixture was allowed to stand overnight after which the carbon tetrachloride was removed by distillation. Distillation of the residue gave 6.0 g. (38%) of *trans*-2-chlorocyclohexyl phenyl sulfide, b.p. 123–124° (1 mm.), n^{25}D 1.5802.

Anal. Calcd. for $C_{12}H_{15}ClS$: C, 63.57; H, 6.67; Cl, 15.64. Found: C, 63.14; H, 6.57; Cl, 15.32.

The sulfide was oxidized to *trans*-2-chlorocyclohexyl phenyl sulfone, m.p. 82.0–82.8° (1:1 acetic acid–water), with 30% hydrogen peroxide in acetic acid.

Anal. Calcd. for $C_{12}H_{15}O_2ClS$: C, 55.70; H, 5.84. Found: C, 55.34; H, 5.67.

Method B.—*trans*-2-Hydroxycyclohexyl phenyl sulfide, b.p. 130–132° (1 mm.), was prepared in 47% yield from cyclohexene oxide and thiophenol according to the general procedure of Gilman and Fullhart[19] for preparing β-hydroxysulfides.

Anal. Calcd. for $C_{12}H_{16}OS$: C, 69.20; H, 7.73. Found: C, 69.38; H, 7.89.

An ether solution of *trans*-2-hydroxycyclohexyl phenyl sulfide was added slowly to a suspension of phosphorus pentachloride in ether. After diluting the reaction mixture with water the organic layer was separated, dried and distilled. The product, b.p. 125–127° (1 mm.), obtained in this way was shown to be *trans*-2-chlorocyclohexyl phenyl sulfide by its chemical composition and by comparison with the product obtained by method A. The infrared spectra of the products obtained by the two methods were indistinguishable and both compounds were converted to the same sulfone, m.p. 82–83° (no depression when mixed), by oxidation with 30% hydrogen peroxide in acetic acid.[16]

cis-2-Chlorocyclohexyl Thiolacetate.—Acetylation of pure *cis*-2-chlorocyclohexanethiol (see above) with acetic anhydride in pyridine[20] gave *cis*-2-chlorocyclohexyl thiolacetate, b.p. 93.0–93.6° (1 mm.), n^{25}D 1.5182.

Anal. Calcd. for $C_8H_{13}OClS$: C, 49.86; H, 6.80. Found: C, 49.86; H, 6.76.

trans-2-Chlorocyclohexyl Thiolacetate.—Reaction of cyclohexene sulfide with acetyl chloride according to the procedure of Culvenor, *et al.*,[11] gave *trans*-2-chlorocyclohexyl thiolacetate, b.p. 120–121° (12 mm.), n^{25}D 1.5187, d^{25}_4 1.1638, MR 50.23 (calcd. 49.83) (lit.[21] b.p. 127–129° (14 mm.), n^{25}D 1.5178) in 39% yield.

(13) All melting points are corrected.

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(20) R. L. Shriner and R. C. Fuson, "Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1948, p. 165.

(21) E. E. van Tamelen, THIS JOURNAL, **73**, 3444 (1951).

Anal. Calcd. for $C_8H_{13}OClS$: C, 49.86; H, 6.80. Found: C, 49.98; H, 6.61.

Attempted Preparation and Isolation of 1-Chlorocyclohexyl Phenyl Sulfide.—A mixture of 11.01 g. (10.3 ml., 0.100 mole) of thiophenol and 9.82 g. (10.4 ml., 0.100 mole) of cyclohexanone was stirred at 10° for 45 minutes while a rapid stream of dry hydrogen chloride was passed in according to the method of Böhme.[22] The separation of water during the reaction indicated that 1-chlorocyclohexyl phenyl sulfide was formed. After drying (magnesium sulfate) the reaction mixture was distilled and 10.76 g. of product, b.p. 117–125 (1 mm.), was collected in four fractions. The percentage chloride in the product was found to be somewhat less than half of that calculated for 1-chlorocyclohexyl phenyl sulfide.

All four fractions gave positive tests for unsaturation when treated with 5% bromine in carbon tetrachloride; 2-chlorocyclohexyl phenyl sulfide does not decolorize bromine in carbon tetrachloride. Presumably the unsaturated component in the product is 1-cyclohexenyl phenyl sulfide which is formed by the decomposition (dehydrochlorination) of 1-chlorocyclohexyl phenyl sulfide during the distillation.

Radical Addition of Hydrogen Sulfide to 1-Chlorocyclohexene.—The apparatus used consisted of a test-tube-shaped reaction flask into which was fitted a specially constructed quartz-jacketed Hanovia type SC-2537 lamp (85% of the light generated in the 2537 Å. band). The reaction flask had a side arm for a reflux condenser and the reaction mixture occupied the annular space between the walls of the lamp and the reaction flask. In a typical experiment (expt. 5) 300 ml. (9 moles) of hydrogen sulfide was collected in the graduated reaction flask which was immersed in a Dry Ice–acetone-bath. After adding 15.5 g. (0.10 mole) of 1-chlorocyclohexene the lamp was inserted into the reaction flask and the mixture irradiated for two hours. During the irradiation the reaction flask was immersed in a Dry Ice–acetone-bath and the hydrogen sulfide refluxed gently from a Dry Ice–acetone cold-finger condenser inserted in the side arm. After evaporation of the excess hydrogen sulfide the residue was distilled through an 18-cm. Vigreux column and the fractions shown below were collected.

TABLE III

Fraction	Wt., g.	Yield, %	B.p. °C.	Mm.	$n^{25}D$
1	2.30	14.9	48–50	20	1.4772
2	12.41	62.1	93–96	12	1.5212
3	3.94	21.7	170–173	1	1.5491

Material balance = 98.7%

Fraction 1 was identified as unreacted 1-chlorocyclohexene by its physical properties including infrared absorption spectrum. Fraction 2 was identified as a binary mixture of *cis*- and *trans*-2-chlorocyclohexanethiols by its physical properties, including infrared spectrum, rates of solvolysis (see below) and chemical composition.

Anal. Calcd. for $C_6H_{11}ClS$: C, 47.83; H, 7.36. Found: C, 47.48; H, 7.42.

Distillation of synthetic mixtures of *cis*- and *trans*-2-chlorocyclohexanethiol showed that fractionation does not occur under the conditions of the product isolation. The configurational composition of the binary mixture was determined as described below.

Oxidation of fraction 3 with hydrogen peroxide in acetic acid[16] gave a solid sulfone, m.p. 150–168° (aqueous acetic acid), in 60% yield (after recrystallization). Evidently fraction 3 is primarily bis-2-chlorocyclohexyl sulfide since the chemical composition of the sulfone derived from it corresponds to that of **bis-2-chlorocyclohexyl sulfone.**

Anal. Calcd. for $C_{12}H_{20}O_2Cl_2S$: C, 48.15; H, 6.74. Found: C, 48.41; H, 6.64.

All of the experiments recorded in Table I were carried out in the manner described above.

Addition of Thiophenol to 1-Chlorocyclohexene.—In expts. 11 and 12 the apparatus described in the preceding section was used. In a typical experiment (expt. 12) a mixture of 90 g. (0.819 mole) of thiophenol and 5.30 g. (0.0455 mole) of 1-chlorocyclohexene was irradiated for 2.5 hours. The heat given off by the lamp raised the temperature of the reaction mixture to *ca.* 50°. Distillation of the reaction mixture gave 80 g. of unreacted starting materials, mainly thiophenol, b.p. 53–55° (10 mm.), and 3.6 g. (35%) of the 1:1 addition product, b.p. 125–133° (1 mm.), $n^{25}D$ 1.5800. The latter was identified as 2-chlorocyclohexyl phenyl sulfide by its physical properties including infrared spectrum and chemical analysis.

Anal. Calcd. for $C_{12}H_{15}ClS$: C, 63.56; H, 6.67. Found: C, 62.98; H, 6.45.

The configurational composition of the mixture was determined as described below. Distillation of synthetic binary mixtures of *cis*- and *trans*-2-chlorocyclohexyl phenyl sulfide showed that the addition product is not fractionated during the isolation.

Addition of Thioacetic Acid to 1-Chlorocyclohexene.—The apparatus described above for the addition of hydrogen sulfide was used in expts. 18 and 19. In expt. 19 a mixture of 137 g. (1.80 moles) of thioacetic acid and 11.5 g. (0.100 mole) of 1-chlorocyclohexene was irradiated for four hours. Distillation of the reaction mixture gave 100 g. of unreacted thioacetic acid, b.p. 87–91° (730 mm.), and 16.1 g. (84%) of 1:1 addition product, b.p. 115–124° (10 mm.), $n^{25}D$ 1.5191. The latter was identified as binary mixture of *cis*- and *trans*-2-chlorocyclohexyl thiolacetates by its physical properties including infrared spectrum and chemical composition.

Anal. Calcd. for $C_8H_{13}OClS$: C, 49.86; H, 6.80. Found: C, 49.60; H, 6.84.

Determination of Configurational Composition of Addition Products. (A) Hydrogen Sulfide–1-Chlorocyclohexene Addition Product.—Solvolysis of pure *trans*-2-chlorocyclohexanethiol in 80% ethanol at 100° for 45 minutes gave 0.99 ± 0.01 equivalent of chloride ion. Under the same conditions pure *cis*-2-chlorocyclohexanethiol gave <0.002 equivalent of chloride ion.

The chloride ion concentrations of solvolysis mixtures were determined as follows: A 5-ml. aliquot (25°) was delivered into 10 ml. of water. The resulting solution was extracted five times with 10-ml. portions of carbon tetrachloride and the chloride ion in the aqueous layer was determined by the Volhard method. Control experiments showed that no significant loss of chloride ion occurred during the extractions and results were reproducible to 5×10^{-4} meq. of chloride ion.

Binary mixtures of *cis*- and *trans*-2-chlorocyclohexanethiol were analyzed by solvolyzing 0.2 *M* solutions in 80% ethanol at 100° for 45 min. Under these conditions the amount of chloride ion released (determined as described above) corresponds to the amount of *trans* isomer in the mixture. From the precision of the titrations it can be determined that the composition of mixtures can be obtained to within ±0.2% *trans* by this method. In some experiments the composition of the mixture was determined by the method of Brown and Fletcher.[23] In these cases the chloride ion concentration of 0.2 *M* solutions of the mixture in 80% ethanol at 100° were determined periodically. The pure *cis* isomer has $k_1 = 2.3 \times 10^{-7}$ sec.$^{-1}$ at 100° in 80% ethanol; the *trans* isomer has $k_1 = 1.0 \times 10^{-4}$ sec.$^{-1}$ under these conditions.

(B) Thiophenol–1-Chlorocyclohexene Addition Product.—A 0.2 *M* solution of pure *trans*-2-chlorocyclohexyl phenyl sulfide in 80% ethanol at 100° for 30 minutes gives 0.99 ± 0.01 equivalent of chloride ion. Under the same conditions the *cis* isomer gives <0.002 equivalent of chloride ion. The composition of binary mixtures of the two isomers obtained from the radical additions were determined by titration (as described above) of the chloride ion resulting from the solvolysis of the products in 0.2 *M* solution in 80% ethanol at 100° for 30 minutes. Because of the large difference in the rate of solvolysis of the two isomers under these conditions the composition of mixtures can be estimated readily to within ±0.2% *trans* isomer by this method.

(C) Thioacetic Acid–1-Chlorocyclohexene Addition Product.—At 100° in 80% ethanol *trans*-2-chlorocyclohexyl thiolacetate solvolyzes less than ten times as fast as the *cis* isomer. At 50° the *trans* isomer solvolyzes *ca.* 100 times as fast as the *cis* isomer. At each temperature the rate constants for both isomers show large downward trends and for

(22) H. Böhme, *Ber.*, **69B**, 1610 (1936).

(23) H. C. Brown and R. S. Fletcher, THIS JOURNAL, **71**, 1845 (1949).

this reason the kinetic method of Brown and Fletcher cannot be used to determine accurately the composition of the mixture. The compositions of binary mixtures were determined by comparing the amount of chloride ion produced when 0.2 *M* solutions were solvolyzed in 80% ethanol at 50° for 48 hours with the amount of chloride ion resulting from each of the pure isomers under the same conditions. The chloride ion concentration was determined as described above. Analysis of these mixtures was much less accurate than for the binary mixtures described in the preceding sections. In order to test the accuracy of the method synthetic mixtures of the approximate composition obtained from the radical additions were analyzed and in each case the value obtained was within 3% of the correct value for the amount of *trans* isomer.

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[CONTRIBUTION FROM THE LABORATORIES OF THE SLOAN-KETTERING DIVISION OF CORNELL UNIVERSITY MEDICAL COLLEGE]

Studies on the Structure of Nucleic Acids. IX. Structural Changes in Solution[1]

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The interaction of the basic dye rosaniline with calf thymus deoxyribonucleic acid (DNA) isolated according to the procedure of Signer and Schwander has been examined and the results compared to those obtained with Hammarsten DNA. Two fundamental differences exist: (a) in the former, the bound dye causes structural alterations of the DNA; (b) the binding capacity of the former is significantly lower. The results are discussed in terms of structure. It is suggested that DNA in solution exists as a rather tight aggregate whose smaller units are joined by lateral forces, perhaps hydrogen bonds. It is further suggested that cleavage of this aggregate leads to degraded DNA. This type of aggregate is distinguished from one which is dependent upon concentration, *i.e.*, reversible aggregation.

In two[2,3] earlier investigations the results of the interaction of the basic dye rosaniline with deoxyribonucleic acid (DNA) were presented. These studies have now been extended using calf thymus DNA isolated according to the procedure of Signer and Schwander[4] (denoted as the SS sample), and we have shown that substantial differences exist between the present preparation and the Hammarsten sample[5] (denoted as the H sample) used previously.[2,3] The most striking difference is that the binding capacity of the SS sample varies with dye concentration in a manner indicating that structural changes occur as a result of the binding process. In addition, its binding capacity is lower.

On the basis of the earlier work[2,3] where it was shown that DNA degraded by acid or alkali had a higher binding capacity, the present results indicate that the SS sample is less degraded. It remains to be shown whether such effects have any biological significance. In this connection, it is unjustified from a biological point of view to consider any particular sample of DNA as being "better" than another because less degradation has apparently occurred during its preparation; this is obvious since the relation between physical structure and biological activity is quite nebulous at present. While this view is appreciated for the most part, there nevertheless appears to be some confusion in the literature.

Experimental

Materials.—The calf thymus DNA (sodium salt) was prepared according to the method of Signer and Schwander[4] and was the same sample used in another investigation.[6] The rosaniline was the same sample employed previously.[2,3]

Method.—Binding studies were carried out at 25 ± 0.1° and *p*H 7.2, using the method of partition analysis.[7] The details of the procedure have been given previously.[3]

Results

Figures 1 and 2 show plots of r/c *vs.* r for typical experiments where r is the average number of molecules of dye bound per phosphate group at a free dye concentration c. The upper curve in Fig. 1 is taken from previous data[3] and replotted for comparison; it was obtained using the H sample. The lower curve represents the SS sample. The broken curve in this figure approximates the binding process if both samples had behaved similarly. In Fig. 3, r *vs.* c is plotted for different DNA concentrations, showing that for any c, r increases with decreasing DNA concentration.

Discussion

In general a simple binding process is represented by eq. 1

$$r/c = k(n - r) \qquad (1)$$

where r is the average number of bound dye molecules at a free dye concentration c and k is the association constant assumed to be identical for all n available sites per DNA molecule. In the present paper r is the amount of dye bound per mole of phosphorus, rather than per mole of DNA. This has been done to avoid the use of a particular assigned molecular weight. Consequently, the maximum theoretical value of n is one, assuming that only one dye molecule is capable of being bound at each phosphate group, although it is apparent from previous and present data that the calculated value of n is less than one. That is, not all phosphates are available for binding, a situation which is discussed below.

Deviations from a straight line (eq. 1) in the r/c *vs.* r plots indicate that (a) electrostatic interactions occur among bound dye ions,[8] (b) the association constants of the sites are different[9] or (c) structural

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