The Stereochemistry at Asymmetric Carbon in the Silylcarbinol to Alkoxysilane Rearrangement

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Abstract: X-Ray structural determination of the *p*-bromobenzoate of the predominant diastereomeric carbinol formed by reduction of benzoyl-1-naphthylphenylmethylsilane indicates that Cram's rule of asymmetric reduction does not hold in this case. This finding, coupled with the stereochemical results of the conversion of the deuterio-carbinol to the isomeric benzyloxysilane, indicates that the asymmetric carbon center undergoes inversion of configuration during the rearrangement. This stereochemistry probably also applies to the carbinols formed by addition of methyl Grignard reagent to the acylsilane and their rearrangements, previously reported to involve retention of configuration.

Some years ago the absolute configuration of (+)-1-naphthylphenylmethylsilane, R_3Si*H, was predicted on the basis of the results obtained from a Walden cycle shown in Scheme I, in which the sequence

Scheme I
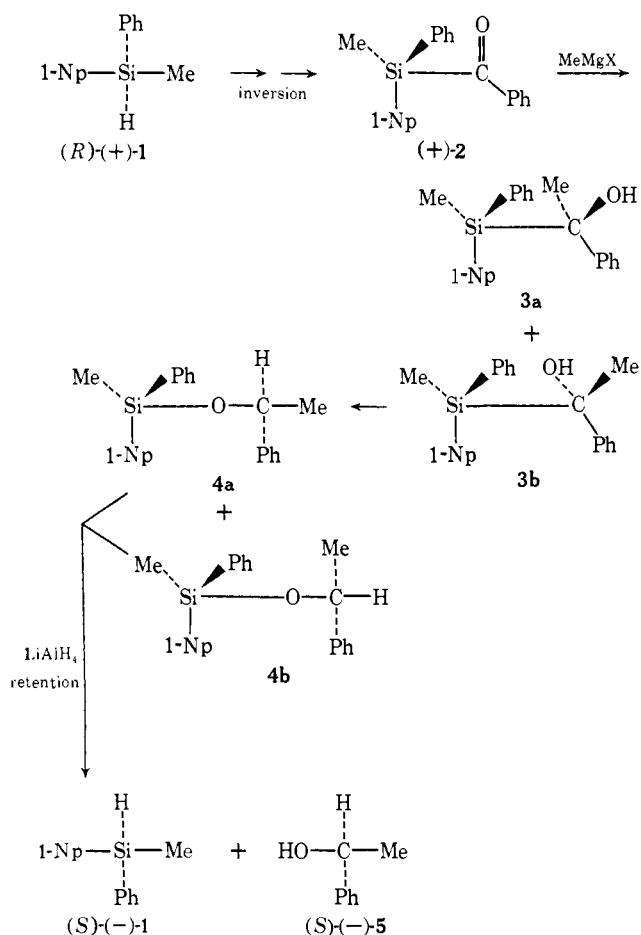
of transformations silane → acylsilane → silylcarbinol → alkoxysilane → silane and carbinol was carried out.[1] The configurational assignment of R_3Si*H was subsequently confirmed by X-ray studies of Okaya and Ashida.[2]

The assignment, which was based on the fact that in the Walden cycle shown in Scheme I the (S)-(−) enantiomer of 1-phenylethanol, **5**, predominated, contained two fundamental assumptions. One was that Cram's rule of asymmetric induction[3] could be applied to the addition of methyl Grignard reagent to the optically active acylsilane (with Me(S), Ph(M), 1-Np(L)) so that the major diastereomeric carbinol formed was assumed to have the configuration **3a**. It was presumed that 1-naphthyl would be the largest of the three groups attached to the asymmetric center, and that these groups would have the same relative steric effects on the diastereotopic faces of the carbonyl group, regardless of whether the asymmetric center was silicon or carbon. The second assumption was that there was retention of configuration at carbon in the silyl-carbinol to alkoxysilane rearrangement, *i.e.*, **3a** → **4a**.[4] This assumption was justified at the time by the stereospecificity observed for the reaction in ether solvent, which appeared consistent with Cram's evidence that carbanions in nonpolar nonprotic solvents tend to retain their configuration.[7]

Thus the predominant course of the reaction was believed to be (+)-**1** → **2** → **3a** → **4a** → (−)-**1** + (−)-**5**.

While the subsequent X-ray study of the absolute configuration of R_3Si*H and its derivatives showed the overall stereochemistry to be correct,[2] the possibility existed that both key assumptions were incorrect, and that the predominant course of the reaction was (+)-**1** → **2** → **3b** → **4a** → (−)-**1** and (−)-**5**-, a sequence which would still predict the correct configuration for (+)-R_3Si*H, but where Cram's rule did not apply and where the rearrangement involved inversion of configuration at carbon. This possibility became more real with the finding by Biernbaum and Mosher[8] that a serious conflict of evidence arose when a variety of classical methods were applied to establishing the relative configurations of two closely related carbinols **6** and **7**.

(1) A. G. Brook and W. W. Limburg, *J. Amer. Chem. Soc.*, **85**, 832 (1963).

(2) Y. Okaya and T. Ashida, *Acta Crystallogr.*, **20**, 461 (1966).

(3) D. J. Cram and F. A. Abd Elhafez, *J. Amer. Chem. Soc.*, **74**, 5828 (1952).

(4) The stereochemistry at the asymmetric silicon center in this rearrangement has been unequivocally shown to involve retention of configuration.[5,6]

(5) A. G. Brook and C. M. Warner, *Tetrahedron Lett.*, **18**, 815 (1962).

(6) A. G. Brook, C. M. Warner, and W. W. Limburg, *Can. J. Chem.*, **45**, 1231 (1967).

(7) D. J. Cram, A. Langemann, and F. Haack, *J. Amer. Chem. Soc.*, **81**, 5750 (1959).

(8) M. S. Biernbaum and H. S. Mosher, *Tetrahedron Lett.*, 5789 (1968).

Ph₃SiCHOHPh   Ph₃CCHOHPh
6   7
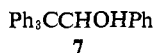
Thus the molecular rotations of a series of derivatives of **6** and **7** (Freudenberg method) and the results of asymmetric reductions suggested that (+)-**6** and (+)-**7** had the same configurations, whereas the Fredga quasiracemate technique and the Prelog atrolactic acid asymmetric synthesis suggested that (+)-**6** and (+)-**7** were of opposite configuration. ORD studies were ambiguous. These findings led us to reexamine the stereochemistry of the formation and rearrangement of asymmetric silylcarbinols.

The racemic or active benzoylsilane **2** can be reduced with any of a variety of agents to give a mixture of diastereomers **8a** and **8b** in relative proportions varying from about 2:1 to a maximum of about 4.5:1 depending on the conditions (Scheme II). The *p*-bromobenzoate

Scheme II
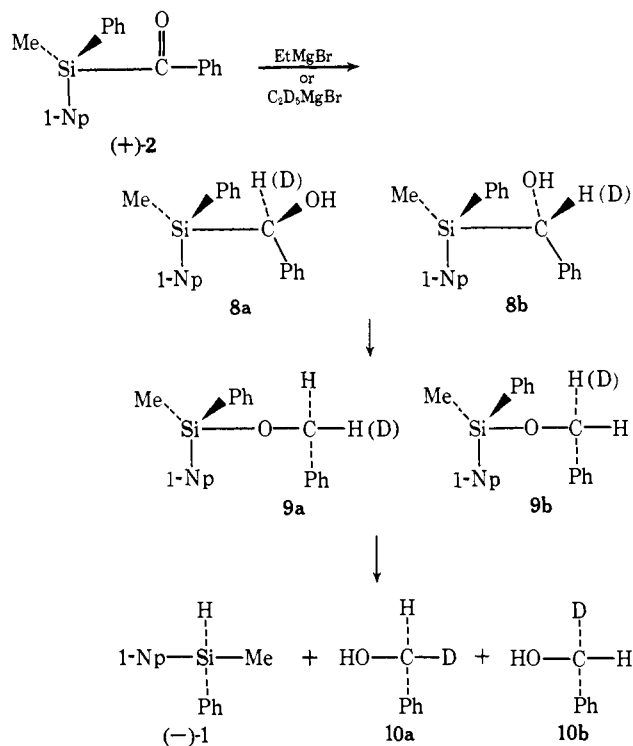
of the predominant racemic or active carbinol could be separated by fractional crystallization and the dextrorotatory optically active material was submitted to X-ray structural investigation. The structure determination,[9] including the determination of absolute configuration, which confirmed the configuration of (+)-acylsilane as **2**, clearly established that the configuration of the *predominant* diastereomer was **8b**, the product predicted by Cram's rule of asymmetric induction to be the *minor* product from reduction of the carbonyl group.

If Cram's rule does not apply for reduction of the carbonyl group in **2** (**2** → **8a** and **8b**), it seems probable that it would also not hold for the addition of methyl Grignard reagent (**2** → **3a** and **3b**) since these reactions usually follow the same stereochemical path.[3]

The optically active benzoylsilane **2** was also reduced with perdeuterioethyl Grignard reagent to give the

deuteriocarbinols **8a** and **8b**, [α]D −3.16°, with **8b** (known from the X-ray study) predominating over **8a** in a 68:32 ratio (Scheme II). Rearrangement of the mixture in ether with sodium–potassium alloy gave a mixture of diastereomeric ethers **9a** and **9b**, [α]D −15.7°, whose proportions could not be determined due to overlap of the signals from the diastereotopic groups even at 100 MHz. This mixture on reduction afforded the benzyl-α-*d* alcohols **10a** and **10b**, [α]D +0.129 ± 0.005 (neat), in which the (S)-(+)-enantiomer **10a** predominated[10] over **10b** in the ratio of 54:46. In addition, R₃Si*H, [α]D −34.5°, was obtained, as observed previously.[1]

Greater stereospecificity was obtained when the diastereomeric carbinols (ratio 78:22) were isomerized using triethylamine in chloroform at 50–60° for 6 days, the resulting benzyl-α-*d* alcohols (after work-up) having a rotation of [α]²⁰D +0.740 ± 0.005° (neat), corresponding to a 73:27 ratio of enantiomers.

These results clearly show that for the silylphenylhydrogen (deuterium) carbinols, rearrangement involves *inversion* of configuration of the asymmetric carbon center, a result which was found by Biernbaum and Mosher for O-deuterated triphenylsilylphenylcarbinol, Ph₃SiCHODPh,[12] just prior to our own findings.

If these results can be safely extrapolated to the formation of the methylcarbinols **3a** and **3b** and the rearrangement involving them, both assumptions made in predicting the absolute configuration of (+)-R₃Si*H were simultaneously wrong.[14] The reactions must involve (1) addition of Grignard reagent to the carbonyl group in (R)-(+)-**1** in a manner opposite to that predicted by Cram's rule of asymmetric induction to give **3b** as the predominant product and (2) inversion of configuration at the asymmetric carbon center in the silylcarbinol (**3b**) to alkoxysilane (**4a**) rearrangement.

Two further observations are significant. Unlike the 100% stereospecificity observed in the reaction sequence employing sodium–potassium alloy for isomerization of the methylcarbinols **3a** and **3b**, the reactions involving the deuteriocarbinols **8a** and **8b** appear to be considerably less stereospecific. However, use of triethylamine gives much higher stereospecificity, and it is presumed that the racemization occurs during the isomerization step although this cannot be rigorously established since it is not possible to establish the proportions of the diastereomeric alkoxysilanes. Secondly, it was previously noted[6] that the methylcarbinols rearranged with complete specificity regardless of whether ether or the much more polar dimethyl sulfoxide was employed as solvent. The rearrangement is known to involve a transition state with considerable carbanion character on the carbinol carbon; thus ρ (in DMSO) is 4.16.[15] The stereochemical behavior

(9) S. C. Nyburg, J. Szymanski, A. G. Brook, and J. D. Pascoe, unpublished results. (The details of this structure determination will be published later.)

(10) The absolute configuration of benzyl-α-*d* alcohol is known.[11]

(11) V. E. Althouse, D. M. Feigl, W. A. Sanderson, and H. S. Mosher, *J. Amer. Chem. Soc.*, **88**, 3595 (1966).

(12) We are exceedingly grateful to Professor Mosher for communicating his results and providing preprints of his work to us in which it is clearly established that in the rearrangement of (R)-(+)-triphenylsilylphenylcarbinol-*O-d* (Ph₃SiCHODPh), inversion of configuration at carbon occurs.[13]

(13) M. S. Biernbaum and H. S. Mosher, *J. Amer. Chem. Soc.*, **93**, 6221 (1971).

(14) Unfortunately this cannot be demonstrated at present since attempts to form the *p*-bromobenzoates of the silylmethylphenylcarbinols **3a** and **3b** (for crystal-structure work) by a variety of methods resulted instead in dehydration; apparently other methods of comparison cannot be relied upon.

Table I. Ratios of Diastereomeric Carbinols[a]

$$R_3Si^*COPh + R-H \longrightarrow R_3Si^*CHOHPh$$

Reducing agent RH	Solvent	Temp, °C	Diastereomer ratio[b]
1 N EtMgBr in Et₂O	Et₂O	−65	1.5:1
1 N EtMgBr in Et₂O	Et₂O	−100	2:1
1 N EtMgBr in Et₂O	Pentane	−65	1:1
1 N EtMgBr in Et₂O	1:1 Et₂O-pentane	−116	1.8:1
1 N EtMgBr in Et₂O	4:1 THF-pentane	−116	3.5:1 to 4.5:1
1 N EtMgBr in Et₂O	1.5:1.1:1 THP-THF-pentane	−116	3.2:1
1 N i-PrMgBr in Et₂O	4:1 THF-pentane	−116	3.8:1
1 N PhCH₂CH₂MgBr in Et₂O	3.3:1 THF-pentane	−116	3.1:1
LiAl(tert-BuO)₃H suspension in THF	THF	0	2.1:1[c]

[a] A 0.2-g sample of acylsilane was dissolved in 30–40 ml of the solvent noted and cooled to the given temperature. Reducing agent was then added very slowly to the reaction flask. Stirring was continued at reduced temperature for several hours and the reaction left to warm up slowly overnight. [b] These ratios were not always obtained, since the ratio obtained depends to a great extent upon the rate of addition of the reducing agent and to a much lesser extent upon the acylsilane concentration. [c] This reaction will give higher diastereomer ratios at lower temperatures. However, the rate is so slow at temperatures below 0° that it is impractical to carry the reaction out.

of carbanions has been shown by Cram to be sensitive to the nature of the solvent[7] and the above behavior is consistent with inversion stereochemistry at the carbanion center. It follows that in less polar solvents, retention stereochemistry might be expected. However, when a mixture of diastereomeric methylcarbinols **3a** and **3b** of known proportions was rearranged in boiling octane, benzene, or acetone, using trithylamine as isomerizing agent, or in boiling pyridine itself, the diastereomeric ratio in the alkoxysilanes was unchanged. Hence the specificity and stereochemistry of the rearrangement are completely insensitive to the nature of the solvent employed.

In summary, on the reasonable assumption that the addition of methyl Grignard reagent to optically active benzoylnaphthylphenylmethylsilane and the reduction of the acylsilane to carbinols occurs with the same stereochemistry (shown not to follow Cram's[1] rule in the latter case), it is clear that the silylcarbinol to alkoxysilane rearrangement involves inversion of configuration at the asymmetric carbon center.

Experimental Section

Reactions with organometallic reagents were carried out in an oxygen-free nitrogen atmosphere. Infrared spectra were recorded on a Perkin-Elmer 237B spectrometer and nmr spectra were recorded on either Varian T-60 or A-60 instruments. Melting and boiling points are uncorrected. Optical rotations were determined using a Perkin-Elmer 141 automatic polarimeter using a 1-dm end-filled tube.

Benzoyl-1-naphthylphenylmethylsilane, R₃Si*COPh. Benzoyl-1-naphthylphenylmethylsilane was prepared as described previously[6] or by hydrolysis in aqueous acetone-benzene with mercuric chloride-cadmium carbonate of the dithiane formed by coupling of 1-naphthylphenylmethylchlorosilane with the anion of 2-phenyl-1,3-dithiane.[16] When optically active chlorosilane, [α]D −6.3° (c 11.98, cyclohexane), was employed, the dithiane had mp 161–163°, [α]²²D 21.1° (c 10.7, CHCl₃).

Reduction of R₃Si*COPh. Small samples (0.2 g) of racemic benzoylsilanes in various solvents were treated with 2 equiv of ethylmagnesium bromide under varying conditions. After work-up with 5% hydrochloric acid in the usual manner, the crude carbinol was isolated and the proportions of diastereomers were established from the relative heights (or areas) of the two signals corresponding to the diastereotopic methyl groups on silicon observed in carbon tetrachloride at δ 0.48 (predominant diastereomer) and 0.57 ppm (minor diastereomer), or more usually, from the diastereomeric protons on the asymmetric carbon atom which

occurred at δ 5.15 (major) and 5.04 ppm (minor) for the two diastereomers. Some typical results are given in Table I.

Many attempts were made to crystallize one diastereomer of the carbinol R₃Si*CHOHPh (active or racemic) from solutions containing both diastereomers in ratios similar to those given in Table I. In all cases the carbinols separated out of solution as an oil, either when cooled, or when left to evaporate. Thin-layer chromatography of such a mixture also failed to detect a separation of diastereomers when Eastman Chromogram silica gel sheets were used. The following solvents were tried as eluents, with R_f values in parentheses: CH₃OH (0.92), C₆H₆ (0.63), CHCl₃ (0.61), toluene (0.46), trichloroethylene (0.26), CCl₄ (0.1).

Deuterioreduction of (+)-R₃Si*COPh. A solution of 8.4 g (0.024 mol) of (+)-benzoyl-1-naphthylphenylmethylsilane, [α]²²D 6.15° (c 10.8, benzene), in 320 ml THF and 80 ml of pentane was cooled to −116°. To this was slowly added 48 ml of a solution of perdeuterioethylmagnesium bromide in ether prepared from 10 g (0.092 mol) of perdeuterioethyl bromide, 2.43 g (0.10 g-atom) of magnesium, and 88 ml of ether. After being stirred to −116° overnight, work-up as usual gave the carbinols in the ratio of 2.1 ± 0.1:1 (nmr), [α]²²D −3.16° (c 7.41, benzene), yield 8.5 g (100%), as a colorless oil: ir (CCl₄) 2.78 (OH), 4.71 (C–D), 6.90 (C–Ph), 7.00 and 9.01 (Si–Ph), 7.97 (Si–Me) μ; nmr (CCl₄) δ 6.6–8.0 (Ar), 1.87 (OH, concentration dependent), 0.48 (Si–Me, major diastereomer), and 0.57 (Si–Me, minor diastereomer) ppm.

Similar reduction of 4.6 g of acylsilane in 340 ml of THF and 90 ml of pentane at −116° gave the carbinols in 100% yield, [α]²⁰D −2.98° (c 11.1, benzene), in a ratio of 78:22 (3.5:1).

Similar reductions incorporating hydrogen were effected using ethylmagnesium bromide.

p-Bromobenzoate of R₃Si*CHOHPh. A solution of 4.0 g (0.011 mol) of racemic carbinol (3.5:1 diastereomeric mixture), 3.3 g (0.15 mol) of p-bromobenzoyl chloride, 8 ml of benzene, and 3 ml of pyridine was heated for 3.5 hr at 85–95°. The reaction mixture was taken up in ether, which was washed twice with 5% sodium bicarbonate solution. After drying, the solvent was removed on the rotary evaporator and the resulting brown oil was chromatographed on a silica gel column, being eluted with 60:40 carbon tetrachloride-benzene. The colorless oil isolated had the following spectral properties: ir (CCl₄) 5.79 (C=O), 6.87 (C–Ph), 6.99 and 9.02 (Si–Ph), 7.92 (Si–Me) μ; nmr (CCl₄) (major diastereomer) δ 6.70 (C–H), 0.63 (Si–Me); (minor diastereomer) δ 6.67 (C–H), 0.68 (Si–Me); together with 6.7–8.0 (Ar). The colorless oil isolated on removal of the solvent was taken up in 100 ml of pentane. It slowly crystallized to give material melting from 119 to 131° which after several crystallizations from hexane gave plates with mp 143–144°: nmr (CCl₄) δ 6.7–8.0 (Ar, m, 21 H), 6.70 (CH, s, 1 H), 0.63 (Me–Si, s, 3 H).

In a similar manner the diastereomeric carbinols (ratio 68:32) obtained as an oil from reduction of active benzoylsilane, [α]²²D 6.08° (c 10.8, benzene), were converted to the p-bromobenzoate derivatives. An nmr spectrum of the material indicated the diastereomeric ratio was still 68:32; [α]²²D 47.6° (c 9.4, benzene). Crystallization from pentane and then many times from hexane gave needles, mp 141.5–142.5°, [α]²⁴D 123° (c 3.03, benzene), with the same ir and nmr spectra as the racemic material. The, diastereomer isolated was the one which predominated in the original mixture.

(15) A. G. Brook, G. E. LeGrow, and D. M. MacRae, *Can. J. Chem.*, **45**, 239 (1967).

(16) A. G. Brook, J. M. Duff, P. F. Jones, and N. R. Davis, *J. Amer. Chem. Soc.*, **89**, 431 (1967).

Anal. Calcd for $C_{31}H_{25}SiBrO_2$: C, 69.27; H, 4.69. Found: C, 69.16; H, 4.80.

Rearrangement of the Deuterated Silylcarbinols. A. With Sodium–Potassium Alloy. A solution of 8.4 g (0.024 mol) of carbinols, $[\alpha]^{22}D$ $-3.16°$ (*c* 7.41, benzene), diastereomer ratio 68:32, in 250 ml of dry ether, was treated with several drops of 1:5 sodium–potassium alloy under nitrogen. The reaction was followed by tlc on Eastman Chromogram silica gel sheets (Type K301R2) using benzene and was complete in 1.5 hr. The material was filtered to remove the alloy, and after washing with water and 5% HCl and drying, removal of the solvent under reduced pressure gave crude alkoxysilane, $[\alpha]^{22}D$ $-14.1°$ (*c* 6.48, cyclohexane). The material was distilled in a Kugelrohr at about 150–210° (0.09 mm) to give an oil, $[\alpha]^{22}D$ $-15.7°$ (*c* 8.18, cyclohexane). Attempts to establish the ratio of diastereomers by nmr spectroscopy (in CCl_4, $CDCl_3$, acetone, (+)-α-phenylethylamine, or (+)-2-octanol) failed, even at 100 MHz, since the Si–Me signals overlapped: ir (CCl_4) 4.67 (C–D), 6.88 (C–Ph), 7.01 and 8.97 (Si–Ph), 9.17 (Si–O–C, broad) μ; nmr (CCl_4) δ 6.9–8.15 (Ar), 4.70 (C–H, broad), 0.71 (Si–Me, no separate signals for diastereomers observed).

B. With Triethylamine. A solution of 4.6 g (0.013 mol) of carbinols, $[\alpha]^{20}D$ $-2.98°$ (*c* 11.15, benzene), in 23 ml of chloroform and 4 ml of triethylamine was stirred for 6 days at 47–60°. After removal of the amine by extraction with dilute hydrochloric acid, the crude product, $[\alpha]^{20}D$ $-14.80°$ (*c* 12.6, cyclohexane), was distilled as before to give 4.2 g (91%) of oil, $[\alpha]^{20}D$ $-17.68°$ (*c* 11.1, cyclohexane).

Reduction of the Alkoxysilanes. To 1.22 g (0.032 mol) of lithium aluminum hydride in 30 ml of dibutyl ether was added 5.4 g (0.0152 mol) of the above mixture of alkoxysilanes, $[\alpha]D$ $-15.7°$, in 25 ml of ether. The diethyl ether was distilled off until the temperature was 81°, and the mixture was heated for 21 hr. Acetone was added to destroy the excess lithium aluminum hydride, water was added, and the ether layer was separated. This and the ether extracts of the aqueous layer were washed with 5% HCl and water, and then dried over anhydrous magnesium sulfate. The ether was distilled off through a Vigreux column and the benzyl-α-*d* alcohol was distilled through a 6-in. spinning band column, bp 72–82° (8 mm). The benzyl-α-*d* alcohol was purified by glc on a 10-ft Carbowax column on Chromosorb G at 162°. The rotation of an 8.19% solution in pure benzyl alcohol was $\alpha^{22}D$ 0.011 $\pm$ 0.0005°, corresponding to $[\alpha]^{22}D$ $+0.129 \pm 0.005°$ for pure deuterated alcohol. This corresponds to an enantiomeric ratio of 54:46. The pot residue was eluted from a silica gel column with carbon tetrachloride, and, after being crystallized once from hexane, gave 3.11 g (82%) of (−)-1-naphthylphenylmethylsilane, $[\alpha]^{20}D$ $-34.5°$ (*c* 11.45, hexane).

Similar reduction of the 4.2 g of alkoxysilanes ($[\alpha]^{20}D$ $-17.68°$) followed by glc on an 8-ft SE 54 column on Chromosorb G at 115° gave 0.1386 g of deuteriocarbinol. A 12.41% w/w solution in benzyl alcohol had $\alpha^{20}D$ 0.096 $\pm$ 0.0005°, corresponding to $\alpha^{20}D$ 0.740 $\pm$ 0.005° for pure deuterated material, with a 73:27 ratio of enantiomers.

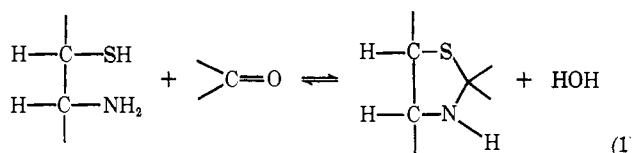# Equilibria for the Reaction of Cysteine and Derivatives with Formaldehyde and Protons[1,2]

Roland G. Kallen

Contribution from the Department of Biochemistry, School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania 19104. Received August 3, 1970

Abstract: Equilibrium constants for the major formaldehyde adducts of cysteine have been estimated from pH, spectrophotometric, and free thiol measurements of cysteine or a derivative at various formaldehyde concentrations. Equilibrium constants for the formation of *N*-hydroxymethyl-*S*-methylcysteine, *N,N*-dihydroxymethyl-*S*-methylcysteine, *S*-hydroxymethyl-*N*-acetylcysteine, and thiazolidine-4-carboxylate (TC) from formaldehyde and cysteine or a derivative are 15.9 M^{-1}, 16.0 M^{-2}, 700 M^{-1}, and 1.14 $\times$ 10^8 M^{-1} for adducts from compounds with neutral thiol and/or amino groups. Equilibrium constants for neutral and anionic *N*-hydroxymethyl-TC formation from neutral and anionic TC and formaldehyde are 7.0 and 0.7 M^{-1}, respectively. The microscopic proton dissociation constants for the eight species of cysteine which exist in the pH range 0–14 have been obtained at 25° and ionic strength 1.0 *M* from spectrophotometric measurements at different pH values, from studies on the proton dissociation of cysteine derivatives, and from mathematical relations between the constants. These data permit the calculation of the composition of cysteine solutions for precise interpretation of equilibrium and kinetic data for reactions involving cysteine.

A though reactions of carbonyl compounds with β-aminothiols, particularly cysteine, to form thiazolidines (eq 1) have been the subject of numerous previous studies,[3] measurements have not been reported

$$(1)$$

(3) (a) M. P. Schubert, *J. Biol. Chem.*, **111**, 671 (1935); (b) M. P. Schubert, *ibid.*, **114**, 341 (1936); (c) K. Shinohara, *ibid.*, **110**, 2(1935); (d) S. Ratner and H. T. Clarke, *J. Amer. Chem. Soc.*, **59**, 2(1937); (e) G. E. Woodward and E. F. Schroeder, *ibid.*, **59**, 16((1937); (f) D. Heyl, S. A. Harris, and K. Folkers, *ibid.*, **70**, 34((1948); (g) F. E. King, J. W. Clarke-Lewis, and R. Wade, *J. Chei Soc.*, 880 (1957); (h) V. duVigneaud, E. J. Kuchinskas, and A. Ho vath, *Arch. Biochem. Biophys.*, **69**, 130 (1957); (i) Y. Matsuo, *J. Ame Chem. Soc.*, **79**, 2011 (1957); (j) F. Bergel and K. R. Harrap, *J. Chei Soc.*, 4051 (1961); (k) M. V. Buell and R. E. Hansen, *J. Amer. Chei Soc.*, **82**, 6042 (1960); (l) D. Mackay and D. M. Shepard, *Biochii*