Table I. Rate Data for the Reaction of Phenylacetylene with Chlorine or Bromine in Excess Sodium Hydroxide

Solvent	Temp, °C	$[C_6H_5C{\equiv}CH] \times 10^4$, M	[NaOH],[a] M	[OCl^-] or [OBr^-],[a] M	No. of runs	k, M^{-2} $sec^{-1} \times 10^3$
H_2O	46.1	1.3–1.7	0.07–0.7	0.02–0.09	8	2.13
H_2O	25.3	1.5–1.7	0.07–0.9	0.04–0.09	7	0.462
D_2O	46.1	1.5–2.2	0.3–0.6	0.03–0.06	4	2.12
H_2O	25.0	1.27	1.82	0.049	1	1.12
H_2O	46.1	1.94	0.242	0.0946	1	3.31[b]
H_2O	46.1	1.68	0.242	0.0946	1	4.40[c]
H_2O	27.5	0.6–0.9	0.02–0.14	0.001–0.01[a]	15	7000[a]

[a] These are not initial concentrations, but those that refer to the solution determined by eq 5 and before process 4 has started. Only the last entry refers to hypobromite runs. [b] In 0.625 M NaCl. [c] In 0.625 M Na_2SO_4.

and was cleanly third order (eq 3) over the concentration range of sodium hydroxide 0–0.9 M. At higher concentrations of sodium hydroxide or with added salts, the rate constants for process 4 are markedly increased. The rate constant for chlorination in deuterium oxide is the same as that in water. The ratio of third-order rate constants $k(Br_2)/k(Cl_2) \simeq 10^4$ at 27.5°.

We propose that the mechanism of these halogenations involves the rapid proton ($k_6 \simeq 3 \times 10^3$ M^{-1} sec^{-1} at 25°)[3] exchange of eq 6 followed by rate-determining attack of hypohalite on phenylacetylide. The absence of a deuterium isotope effect in the chlorination (k_6k_7/k_{-6}) is curious, but not inconsistent with eq 6.

$$C_6H_5C{\equiv}CH + OH^- \underset{k_{-6}}{\overset{k_6}{\rightleftharpoons}} C_6H_5C{\equiv}C^- + H_2O$$

$$C_6H_5C{\equiv}C^- + OX^- \xrightarrow[k_7]{\text{slow}} (C_6H_5CCXO)^{2-} \xrightarrow{\text{fast}} C_6H_5C{\equiv}CX \qquad (6)$$

The effect of salts (and sodium hydroxide) in increasing the rate has precedent in other reactions between negative ions[4,5] and is in contrast to their effect on rate law (2).[6] Although Rappe has dismissed the doubly charged transition state as implausible,[7] it appears that we are probably dealing with such a species.

The halogenation reaction plays a key role in the theory and practice of basic catalysis of carbon acids such as ketones, nitroalkanes, cyanoalkanes, etc. Occasional variations from the relation of eq 2 to process 1 have usually been associated with extremely low halogen or carbanion concentrations.[1a,8] But rate law 2 has failed, too, *e.g.*, in certain halogenations of ketones, when $[OH^-] > 2[X_2]$ at high pH. Consequently, several mechanistic proposals concerning the slow step have been made, *e.g.*, hypohalite attacks the keto form,[7] hypohalite attacks the enol form,[8,9] or hypohalite attacks the enolate ion.[5,8] Only the last of these for the reaction of chlorine with acetone or acetophenone at high pH involves a rate law analogous to eq 3. Recognition[5,8] and revival of this rate law has some interesting and important consequences.

Three factors may contribute to the incursion of the third-order rate law. First, the weaker the carbon acid, the closer to the encounter rate will be the reaction of carbanion (C^-) with water, *e.g.*, k_{-6}. Second, at high pH, $[OX^-] >>> [X_2]^2$, and the presumably fast reaction of X_2 with C^- is negligible. Third, chlorine is "slow"; judging from the large gap in our hypobromite and hypochlorite rates, it is conceivable that in reactions with iodine or bromine or chlorine at high pH, a given carbon acid may follow either eq 2 or 3, or perhaps both. Thus, in a series of papers on the base-catalyzed reactions of 2-butanone, Rappe has reported variations in reaction rates, *e.g.*, with halogen or deuterium uptake, with pH, and with added salts.[7] In the high pH range, at least, we believe that eq 3 is consistent with his semiqualitative results.

Most halogenations, of course, follow eq 2. But certain important quantities, *e.g.*, pK values of weak carbon acids,[1a] deuterium isotope effects,[10] and tunneling in proton transfers,[11] have sometimes been determined by halogenation on the implicit assumption that mechanism 1 and eq 2 apply. Clearly, this is not always the case.

Further comments on these mechanistic problems will be made in the full paper.

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(3) E. A. Halevi and F. A. Long, *J. Amer. Chem. Soc.*, **83**, 2809 (1961).
(4) M. W. Lister, *Can. J. Chem.*, **34**, 465 (1956); A. Indelli and E. S. Amis, *J. Amer. Chem. Soc.*, **82**, 332 (1960).
(5) P. D. Bartlett and J. R. Vincent, *ibid.*, **57**, 1596 (1935).
(6) J. R. Jones and S. C. S. Rao, *Trans. Faraday Soc.*, **63**, 120 (1967).
(7) C. Rappe, *Acta Chem. Scand.*, **22**, 219 (1968), and previous papers.
(8) R. P. Bell and M. Spiro, *J. Chem. Soc.*, 429 (1953).
(9) P. D. Bartlett, *J. Amer. Chem. Soc.*, **56**, 967 (1934).
(10) J. R. Hulett, *J. Chem. Soc.*, 430 (1965).
(11) E. F. Caldin, *Chem. Rev.*, **69**, 135 (1969).

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Sulfur-Containing Polypeptides. XI. A Synthetic Route to Triscystine Peptides

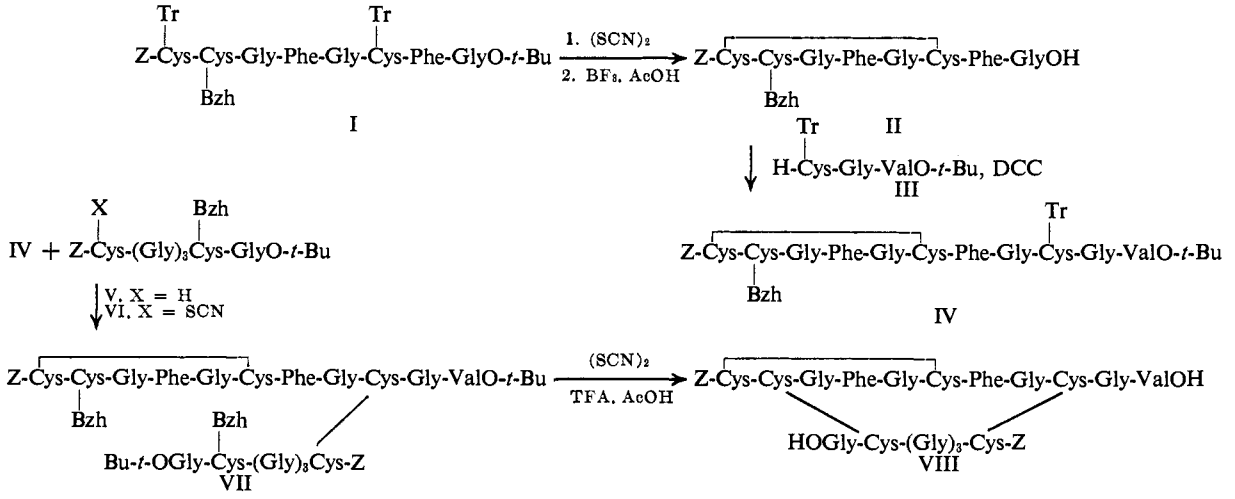
Sir:

The sulfenyl thiocyanate method of disulfide synthesis[1] has been applied to the preparation of the cross-linked polypeptide VIII. The reaction sequence allows the stepwise introduction of each of the three disulfide bonds and may provide an unambiguous route to molecules of this type or other polypeptides containing several intrachain sulfur–sulfur bonds.

The A_{1-6} sulfur–sulfur bond in VIII was generated from the octapeptide derivative I by the action of thiocyanogen followed by hydrolysis with boron trifluoride etherate in acetic acid to produce the acid II in 67% overall yield.[2] Coupling of II with C-terminal tripep-

(1) R. G. Hiskey, T. Mizoguchi, and E. L. Smithwick, Jr., *J. Org. Chem.*, **32**, 97 (1967).
(2) R. G. Hiskey and R. L. Smith, *J. Am. Chem. Soc.*, **90**, 2677 (1968).

Scheme I



tide III afforded an A chain, IV, containing the A_{1-6} loop and two differentially protected cysteine residues.[2]

The stepwise formation of the two interchain disulfide bridges in VIII was conducted under conditions previously shown to avoid disulfide interchange.[3,4] The sulfenyl thiocyanate VI was generated from the corresponding thiol[5] V and allowed to react with IV at 0° in a mixture of ethyl acetate and acetic acid. The biscystine peptide derivative VII was obtained as a crystalline solid in 76% yield:[6] mp 151–152°; $[\alpha]^{24}D$ −28.0° (*c* 0.47, DMF); mol wt (calcd) 2214, (found) 2220 (osmometric in *o*-chlorophenol); amino acid analysis after performic acid oxidation and acid hydrolysis: $CySO_3H_{6.0}Gly_{7.7}Phe_{2.0}Val_{1.0}$. The symmetrical disulfide resulting from oxidation of the B chain, V, was not observed in the thin layer chromatogram of the reaction mixture.

Selective oxidation of the two remaining S-protected cysteine residues (A_2, B_5) was accomplished by the action of thiocyanogen on VII. The cyclization was conducted in dilute solution (10^{-4} *M*) in a trifluoroacetic acid–acetic acid (1:3 v/v) solvent at 0°. The triscystine peptide derivative, VIII, was obtained in 75% yield; mp 230–236° dec; $[\alpha]^{25}D$ −37.5° (*c* 0.16, DMF); mol wt (calcd) 1938, (found) 1765 (osmometric in *o*-chlorophenol); amino acid analysis after performic acid oxidation and hydrolysis: $CySO_3H_{5.5}Gly_{7.5}Val_{1.3}Phe_{2.2}$.

These data demonstrate that multiple sulfur–sulfur bonds can be selectively introduced into reasonably complicated polypeptides. Degradative experiments, designed to verify by chemical means the apparent location of the sulfur–sulfur bonds in a triscystine derivative related to VIII, are currently in progress.

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(3) R. G. Hiskey and D. N. Harpp, *J. Am. Chem. Soc.*, 87, 3965 (1965).
(4) R. G. Hiskey and M. A. Harpold, *Tetrahedron*, 23, 3923 (1967).
(5) R. G. Hiskey and J. B. Adams, Jr., *J. Org. Chem.*, 31, 2178 (1966).
(6) Satisfactory elemental analyses were obtained for all peptides reported.

Nonunique Ordering of Solute Molecules in Nematic Solvents. Electron Spin Resonance Observation of Coexisting Modes of Solute Alignment

Sir:

We have observed superposition of distinguishable patterns of solute ordering in nematic solvents[1–4] by means of esr spectroscopy of nitroxide radicals[5–9] (Figure 1). This finding supports the hypothesis that the most stable pattern of solute ordering is that of densest packing,[10] but challenges the generality of the uniqueness of this ordering, tacitly assumed in the interpretation of high resolution nmr,[1–3] uv,[10] and ir spectra in nematic solvents.

The nitroxide groups[11–14] are located on roughly planar piperidine-derived rings.[15] The principal axes

(1) A. Saupe and G. Englert, *Phys. Rev. Lett.*, 11, 462 (1963).
(2) S. Meiboom and L. C. Snyder, *Science*, 162, 1337 (1968).
(3) A. Saupe, *Angew. Chem. Intern. Ed. Engl.*, 7, 97 (1968).
(4) A. D. Buckingham and K. A. McLauchlan, "Progress in High Resolution NMR Spectroscopy," J. W. Emsley, J. Feeney, and L. H. Sutcliffe, Ed., Pergamon Press, Oxford, 1967.
(5) H. R. Falle, G. R. Luckhurst, J. Lemaire, Y. Marechal, A. Rassat, and P. Rey, *Mol. Phys.*, 11, 49 (1966).
(6) H. Lemaire, *J. Chim. Phys.*, 64, 559 (1967).
(7) S. H. Glarum and J. H. Marshall, *J. Chem. Phys.*, 47, 1374 (1967).
(8) H. Lemaire, A. Rassat, P. Rey, and G. R. Luckhurst, *Mol. Phys.*, 14, 441 (1968).
(9) P. Ferruti, D. Gill, M. A. Harpold, and M. P. Klein, *J. Chem. Phys.*, 50, 4545 (1969).
(10) G. P. Caesar and H. B. Gray, *J. Amer. Chem. Soc.*, 91, 191 (1969).
(11) E. Z. Rosantsev and M. B. Neiman, *Tetrahedron*, 20, 131 (1964).
(12) R. Briere, H. Lemaire, and A. Rassat, *Bull. Soc. Chim. Fr.*, 3273 (1965).
(13) C. L. Hamilton and H. M. McConnell in "Structural Chemistry and Molecular Biology," A. Rich and N. Davidson, Ed., W. H. Freeman and Co., San Francisco, Calif., 1968, p 115.
(14) A. R. Forrester, J. M. Hay, and R. H. Thomson, "Organic Chemistry of Stable Free Radicals," Academic Press, New York, N. Y., 1968.
(15) The names of radicals I–IV, the synthesis of which will be described in a forthcoming work, are: I = N-4-(2,2,6,6-tetramethyl)-