the mixture was cooled, EtOAc was removed by concentration in vacuo. The product was dried under high vacuum to yield an off-white, gummy solid: 0.613 g (~100%): ^{1}H NMR ($CDCl_3$) δ 9.3 (br s, 1 H), 7.6 – 7.1 (m, 15 H), 4.35 (br m, 1 H), 5.36 (d, J = 8.5 Hz, 1 H), 4.8 (s, 2 H), 2.75 (d of d, J = 6 Hz, 1 Hz, 2 H); IR 1745, 1730 cm^{-1}; $[\alpha]^{25}_D$ +7.78 ($CHCl_3$); mass spectrum, m/e 537 (M^+); R_f 0.3 with 80:20:0.1 cyclohexane–ethyl acetate–acetic acid as eluant.

***N*-((Allyloxy)carbonyl)-*S*-trityl-L-cysteine (3).** A suspension of *S*-tritylcysteine (5.45 g, 15 mmol) in EtOAc (300 mL) was treated with allyl chloroformate (3.16 g, 26 mmol, 1.75 equiv) and then heated at reflux for 24 h to give a yellow solution. Evaporation of the solvent in vacuo gave a yellow oily solid: 6.1 g (91%); ^{1}H NMR ($CDCl_3$) δ 9.15 (br s, 1 H), 7.6–7.1 (m, 15 H), 6.05–5.65 (m, 1 H), 5.3 (d, J = 9 Hz, 1 H), 5.3–5.1 (m, 2 H), 4.55 (d, J = 4 Hz, 2 H), 4.2 (m, 1 H), 2.7 (d, J = 5 Hz, 2 Hz); IR 1745, 1730 cm^{-1}; mass spectrum, m/e 447 ($M + H^+$); R_f 0.33 with 8:2:0.1 cyclohexane–ethyl acetate–acetic acid as eluant.

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Registry No. **1**, 37888-25-8; **2**, 96845-11-3; **3**, 96865-72-4; Cbz-L-Ala-OH, 1142-20-7; Cbz-Gly-OH, 1138-80-3; Cbz-L-His-OH, 14997-58-1; Cbz-L-Leu-OH, 2018-66-8; Cbz-DL-Met-OH, 4434-61-1; Cbz-L-Phe-OH, 1161-13-3; Cbz-L-Pro-OH, 1148-11-4; Cbz-L-Val-OH, 1149-26-4; L-Ala-OH, 56-41-7; Gly-OH, 56-40-6; L-His-OH, 71-00-1; L-Leu-OH, 61-90-5; DL-Met-OH, 59-51-8; L-Phe-OH, 63-91-2; L-Pro-OH, 147-85-3; L-Val-OH, 72-18-4; *O*-benzyltyrosine, 16652-64-5; 2,2,2-trichloroethyl chloroformate, 17341-93-4; *S*-trityl-L-cysteine, 2799-07-7; allyl chloroformate, 2937-50-0; benzyl chloroformate, 501-53-1.

Thiol–Disulfide Exchange Reactions of Bis(1-methyl-1*H*-tetrazol-5-yl) Disulfide Studied by ^{1}H Nuclear Magnetic Resonance Spectroscopy

Masayuki Narisada,* Yoshihiro Terui, Masumi Yamakawa, Fumihiko Watanabe, Mitsuaki Ohtani, and Hiroshi Miyazaki

Shionogi Research Laboratories, Shionogi & Co., Ltd., Sagisu, Fukushima-ku, Osaka 553, Japan

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Recently, 1-methyl-1*H*-tetrazole-5-thiol (**1**) and its disulfide **2** have been proposed to inhibit in vitro an enzyme system for the γ-carboxylation of the glutamyl residue of a model prothrombin precursor.[1] Since little was known about their chemical properties, we examined them in detail using NMR and UV spectroscopies as well as polarography. Here, we report observations that oxidation of **1** giving **2** is more difficult than that of dithiothreitol **3**, that decomposition of **2** giving **1** and **6** in neutral aqueous solution proceeds rapidly, that facile thiol–disulfide exchange reactions of **2** with **1** and **3** proceed in $CDCl_3$, and that the latter reaction, carried out in neutral aqueous solution, precedes the decomposition, if the concentrations of **2** and **3** are above 1.0 mmol/L.

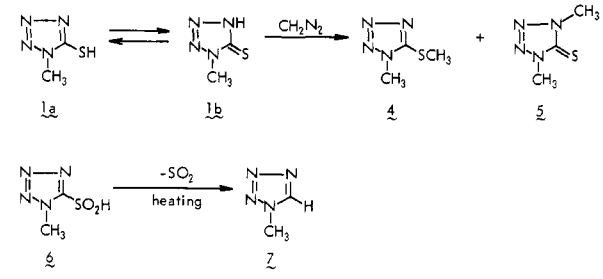
Disulfide **2** was prepared by oxidizing **1** with ferric chloride, mp 112.5–113.0 °C.[3] Spectral data for **1**, which predominantly takes a thioamide form,[2] and **2** are shown in Table I. The fact that the potentials observed at pH 7.0 for **1** ($E_{1/2}^{oxd}$ = –0.08 V vs. SCE) and **2** ($E_{1/2}^{red}$ = ca. –0.3 V vs. SCE[3]) are respectively differentiated from the $E_{1/2}^{oxd}$ values for **3** or cysteine[4] (–0.465 or –0.46 V, respectively) and from the $E_{1/2}^{red}$ values for **10** or cystine[4] (–0.965 or –0.86 V, respectively) suggests that **1** possesses poor susceptibility to oxidation and high reducibility. In fact, although oxygen oxidation of **3** proceeded slowly, that of **1** did not proceed at all even after 3 days.

Table I. UV and NMR Spectra of 1 and 2

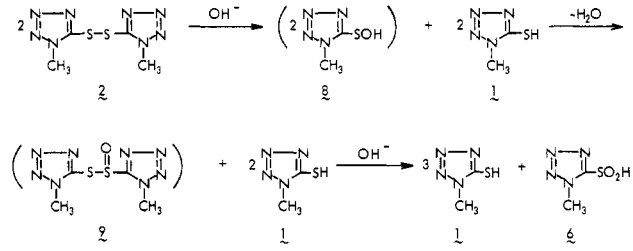
compd	1	1[a]	1	2
		UV		
solv	0.1 N H_2SO_4	H_2O[b]	CH_3CN	0.1 N H_2SO_4
λ_{max}, nm	241.0	223.5	246.0	210[c]
ε	14 000	11 800	14 200	11 000
		NMR[d]		
solv	0.1 N DCl	D_2O[e]	$CDCl_3$	$CDCl_3$
^{1}H NMR, δ				
NCH_3	3.88	3.84	3.933	4.189
^{13}C NMR, δ				
NCH_3	34.7	34.2	34.1	35.0
ring	164.1	165.5	164.2	151.1

[a] N-Anion. [b] A phosphate buffer solution (pH 7.0). [c] End absorption. [d] Me_4Si or DSS was used as an internal reference. [e] Added with $NaHCO_3$ (pH 9.5).

Scheme I



Scheme II



Decomposition of 2 in Aqueous Solution. Gradual decomposition of compound **2** ($\tau_{1/2}$ ca. 40 h at 25 °C) in dilute sulfuric acid (pH 1.25) and formation of **1** were indicated by the change of the ultraviolet absorption intensities at 210 and 241 nm. At pH 7.39, however, **2** decomposed very rapidly, and formation of 3 mol of **1** from 2 mol of **2** was suggested from the UV maxima at 223.5 nm ($\epsilon^{1\%}$ = 1540) at pH 7.39 and 241.0 nm ($\epsilon^{1\%}$ = 1810) at pH 1.41.[5] Acid-quenching experiments with 30-s intervals revealed that the decomposition went to completion within the first 30 s at 25 °C. Polarographic measurements also revealed that **2** decomposed gradually at pH 1.80 and rapidly at pH 7.01, showing an oxidation wave corre-

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(3) Estimated from the value (ca. 0.01 V) observed at pH 1.80 with a shift of –0.06 V/pH.

(4) Dubbos, D. In "Electrochemical Data"; Elsevier Science Publishing: New York, 1975.

(5) Analysis by ^{1}H NMR measurement suggested that 1.00 mol of **2** produced 1.67 mol of **1** and 0.33 mol of **7** (after 430 min at 37 °C) via an unstable intermediate.

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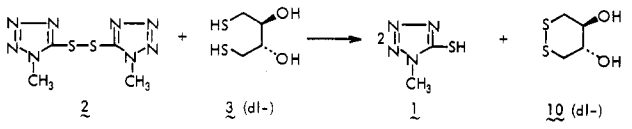
Table II. Effects of Concentrations of 2 and 3 (10 mmol/L) on Yields of 10 in a Buffer Solution (pD 7.0) at 25 °C

conc of 2, mmol/L	0	1.0	2.3	3.0	4.3	5.6	8.3	10.1
yield of 10, %	4.0	13.0	24.4	36.4	37.5	55.3	84.6	100.0

Scheme III



2 3 (dl-) 1 10 (dl-)

sponding to 1 and a low reduction wave ($E_{1/2}^{red}$ = −0.46 V vs. SCE) for a minor product with an unassignable structure. The formation of 1 was verified by the isolation of 1 as its *S*- and *N*-methyl derivatives 4 and 5, while the formation of a labile byproduct 6 was deduced by the isolation of 7,[6] which was obviously the desulfination product of 6 (Scheme I).

From the results described above, we propose Scheme II for the principal path of the decomposition of 2 in a neutral aqueous solution. Although similar decomposition of *p*-nitrophenyl disulfide by alkali under more drastic conditions has been already described,[7] it is noteworthy that decomposition of 2 is quite rapid in neutral aqueous solution even at room temperature.

Thiol–Disulfide Exchange Reaction of 2 with 1. A facile thiol–disulfide exchange reaction between 2 and 1 was indicated by the fact that mixtures of 2 and 1 in $CDCl_3$ at 23 °C invariably exhibited a singlet ^1H NMR signal of *N*-methyl at a position intermediate between those for 2 and 1.[8] The position (*Y* ppm) depends linearly on X = 2[2]/(2[2] + [1]), where brackets indicate molar concentration, ($Y = 0.253X + 3.933$; $n = 6$, $r = 0.999$). Similarly, a (1:2) mixture of 2 and 1 in $CDCl_3$ exhibited only two ^{13}C NMR signals for *N*-methyl and the ring carbon atom at 34.5 and 157.7 ppm, respectively. The phenomena are the first example for an uncatalyzed rapid thiol–disulfide exchange reaction observed by ^1H NMR spectroscopy, although the titration study on a base-catalyzed thiol–disulfide exchange reaction and ^1H NMR study on rapid exchange reactions between activated disulfides and sulfide species have been already reported.[9,10] From the increases in band width of ^1H NMR signal of the *N*-methyl of mixtures 2 and 1, we estimated the order of the rate of the exchange (k) to be ca. 10^5 mol^{-1} s^{-1}.[10d] On the contrary, we concluded that no exchange reaction between 3 and 10 took place in Me_2SO-d_6 or D_2O (pD 9.0) at 23 °C.

Thiol–Disulfide Exchange Reaction of 2 with 3. ^1H NMR spectroscopy indicated that the exchange reaction between 2 and 3 shown in Scheme III proceeded rapidly and quantitatively in $CDCl_3$ (1.0 mol/L each). UV measurements revealed that the reaction in acetonitrile (0.032 mmol/L each) ended within 30 s at 25 °C. Isolation of the disulfide 10[11] confirmed its formation.

All three reactions examined indicate that, as compared with a typical disulfide, 2 has extraordinarily high reactivity to HO^- and RS^- which is hypothetically attributable to the electron-withdrawing character of the tetrazole ring[12] of 2. The resulting low electron density at the sulfur atoms in 2 will facilitate the attacks of the nucleophiles.

Thiol–Disulfide Exchange Reaction of 2 with 3 in Neutral Aqueous Solution. One of two reactions should predominate in a neutral aqueous solution: the decomposition reaction of 2 or the thiol–disulfide exchange reaction between 2 and 3. Since the rate of the latter reaction yielding 10 must be affected by the concentrations of 2 and 3, we examined their effects on the yield of 10 with calculations based on the ^1H NMR intensities of methylene signals for both 3 and 10 (Table II). A linear correlation was found between the various concentrations of 2 (X mmol/L) and the yields of 10 (Y %) obtained by the reaction carried out at 25 °C and pD 7.0 using the constant concentration of 3 (10.0 mmol/L) ($Y = 9.55X + 3.09$; $n = 8$, $r = 0.99$). At lower concentrations of 2 and 3 (1.0 mmol/L each), a yield of 90% of 10 was obtained with less accuracy.

Experimental Section

Melting points were measured in a capillary glass tube with a Büchi apparatus. Infrared (IR) spectra were recorded on a Hitachi 215 spectrometer. Proton nuclear magnetic resonance (^1H NMR) spectra were obtained on a Varian XL-200 NMR spectrometer operating at 200.057 MHz with tetramethylsilane (Me_4Si) or sodium 2,2-dimethyl-2-sila-5-pentane sulfonate (DSS) as an internal reference. Carbon-13 NMR (^{13}C NMR) spectra were obtained on a Varian XL-100-12 NMR spectrometer at 25.160 MHz in buffer solutions (dioxane as an internal reference, δ 67.4) and in $CDCl_3$ (Me_4Si as an internal reference, δ 0.0). Ultraviolet (UV) spectra were recorded on a Hitachi 323 spectrometer. Polarographic potentials of 1, 2, 3, and 10 were determined in buffer solutions of pH 7.0–7.1 (KH_2PO_4 + NaOH + NaCl, μ 0.5) and pH 1.80 (AcONa + HCl + NaCl, μ 0.5) at 25 ± 0.1 °C. The measurements were carried out with a dropping mercury electrode and a saturated calomel electrode (SCE) on a Yanagimoto P-8 polarograph after removal of oxygen from the solutions by bubbling them with argon. For column chromatography, silica gel (Merck silica gel 60) deactivated by adding 10% water was used.

Preparation of Bis(1-methyl-1*H*-tetrazol-5-yl) Disulfide (2). To a solution of 1-methyl-1*H*-tetrazol-5-yl mercaptan (1, 10.0 g) in 95% ethanol (40 mL) was added portionwise a solution of $FeCl_3 \cdot 6H_2O$ (116.4 g) in 95% ethanol (60 mL), and the resulting solution was stirred at room temperature for 24 h. The reaction mixture was concentrated in vacuo, and the concentrate was diluted with water and extracted with dichloromethane. The organic solvent was washed with water, dried (Na_2SO_4), and evaporated in vacuo. The residue was recrystallized repeatedly from acetone–ether until a constant melting point, mp 112.5–113.0 °C, was attained, and pure 2 (5.95 g, 59.5%) was obtained. Although thin-layer chromatogram (silica gel, ethyl acetate–benzene 4:1) of 2 indicated the presence of 1, compound 1 was considered to have resulted from the hydrolytic decomposition of 2 during the chromatography. Measurement of the melting point curve of the admixture of 2 with 1 revealed that 2 obtained was pure. 2: spectral data, see text. Anal. Calcd for $C_4H_6N_2S_2$: C, 20.86; H, 2.63; N, 48.66; S, 27.85. Found: C, 20.95; H, 2.68; N, 48.68; S, 27.74. Oxidation of 1 with bromine in an aqueous potassium bicarbonate solution proceeded smoothly to yield 2 in a satisfactory yield. An attempt to prepare 2 by bubbling oxygen into a phosphate buffer solution (pH 7.0) of 1 at room temperature for

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(7) (a) Schiller, R.; Otto, R. *Chem. Ber.* **1876**, *9*, 1637. (b) Fromm, E.; Wittmann, J. *Ibid.* **1908**, *41*, 2264.

(8) Although the temperature was lowered down to −70 °C, no sign of band splitting was indicated.

(9) Fava, A.; Iliceto, A.; Camera, E. *J. Am. Chem. Soc.* **1957**, *79*, 833.

(10) (a) Ryle, A. P.; Sanger, F. *Biochem. J.* **1955**, *60*, 535. (b) Benesch, R. E.; Benesch, R. *J. Am. Chem. Soc.* **1958**, *80*, 1666. (c) See also: Kice, J. L.; Favstritsky, N. A. *Ibid.* **1969**, *91*, 1751. (d) Smallcombe, S. H.; Caserio, M. C. *Ibid.* **1971**, *93*, 5826.

(11) Luettringhaus, A.; Kabuss, S.; Prinzbach, H.; Langenbucher, F. *Justus Liebigs Ann. Chem.* **1962**, *653*, 195.

(12) The electron-withdrawing character of the tetrazole ring is illustrated by the low pK_a value of thiol 1 (pK_a 3.31 at 22 °C).

72 h failed, and the starting material was recovered; although the same treatment of **3** yielded **10** in a yield of 70%.

Measurements of Decomposition of 2 in Aqueous Solution. (1) In Acid Solution. A solution of **2** in dilute H_2SO_4 (0.685×10^{-4} mol/L, pH 1.25) was kept at 25 °C for 24 h. Absorption coefficients at 210 (ϵ 10730) and 241 nm (10790) indicated that decomposition of 30–40% of **2** had occurred. These values imply that the half life $\tau_{1/2}$ of **2** is 32–47 h.

(2) In Neutral Solution. Since the rate of the decomposition of **2** in a buffer solution of pH 7.39 (Michaelis phosphate) was too rapid to follow, the increase in intensity at 241 nm arising from the generation of **1** was measured instead. To the stirred buffer solution (100 mL) was added a solution (2.00 mL) of **2** in acetonitrile (2.00 mL, 3.50 mmol/L) at 25 °C, and from the resulting solution, several aliquots (each 5.00 mL) were removed at 30-s intervals and quenched with 2 N HCl (0.10 mL). The extinction coefficient of every aliquot was almost the same, indicating that the decomposition was completed in less than 30 s.

(3) Isolation of Alkaline Hydrolysis Products of 2. To a stirred solution of sodium hydroxide (1.0 mol/L, 30 mL), immersed in an ice–water bath, was added portionwise **2** (2.76 g, 12 mmol), and then the resulting solution (pH above 11.0) was stirred for 1.5 h after removal of the bath. The solution was acidified with 2 N HCl to pH 1.5. The acid solution was treated with an excess of ethereal solution of diazomethane, and the resulting mixture was extracted with ethyl acetate. The organic layer was washed with water and dried (Na_2SO_4), and then the solvent was removed. The residue was chromatographed on silica gel, and elution with benzene–ethyl acetate (2:1) afforded a 3:1 mixture of **4** and **5** in a yield of 96.8% calculated by the equation shown in Scheme II. Repeated chromatography gave pure samples of **4** and **5**, which were identified respectively with authentic samples of **4** and **5** prepared by similar treatments of pure **1**. **4**: UV λ_{max}^{EtOH} (ϵ) 223.0 nm (3700); ^{1}H NMR ($CDCl_3$) δ 2.80 (s, 3 H, SMe), 3.95 (s, 3 H, NMe); ^{13}C NMR ($CDCl_3$) δ 15.3 (SMe), 33.3 (NMe), 155.0 (ring carbon). **5**: UV λ_{max}^{EtOH} (ϵ) 246.0 nm (14500); ^{1}H NMR ($CDCl_3$) δ 3.90 (s, NMe); ^{13}C NMR ($CDCl_3$) δ 34.9 (NMe), 164.7 (ring carbon).

The aqueous layer was freeze-dried under high vacuum, giving a colorless powder, which was dissolved in methanol. Removal of the inorganic salts by filtration and concentration of the methanol solution in vacuo gave an oil, which was purified by bulb to bulb distillation at 90 °C (10 μmHg). Crystallization of the distillate from ethanol–*n*-hexane gave **7**, mp 34–35 °C (lit.[6] mp 36 °C), in a yield of 50% calculated by the equation in Schemes I and II. **7**: IR $\nu_{max}^{CHCl_3}$ 3160, 1715, 1496 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.18 (s, 3 H, NMe), 8.65 (s, 1 H, =CH); ^{13}C NMR ($CDCl_3$) δ 34.66 (NMe), 143.33 (=CH). Anal. Calcd for $C_2H_4N_4$: C, 28.57; H, 4.80; N, 66.64. Found: C, 28.59; H, 4.99; N, 66.26.

Thiol–Disulfide Exchange Reaction between 2 and 1. (1) ^{1}H NMR Spectra of Mixtures of 1 and 2. ^{1}H NMR spectra of mixtures of various ratios of **1** to **2**, dissolved in $CDCl_3$ (10 mg/0.60 mL), were measured at 23 °C under the following conditions for FT NMR measurements: spectral width, 2200 Hz; acquisition time, 5.0 s; pulse width, 4 μs (pulse flipping angle, 27°); number of data points, 22K; number of transients, 4. A single sharp signal of the NMe group was observed for each mixture, and the observed δ values for the mixtures with the molar ratios of **1** to **2**, shown in the parentheses, were as follows: 3.933 (100/0); 3.988 (88.9/11.1); 4.032 (75/25); 4.083 (57.1/42.9); 4.135 (33.3/66.7); 4.182 (0/100).

(2) Measurement of Line Widths of ^{1}H NMR Signals of a Mixture of 1 and 2. The half-height widths of the ^{1}H NMR signals of the mixtures of various ratios of **1** to **2**, dissolved in $CDCl_3$ (1.00 mL), were measured at 23 °C under the following conditions for FT NMR measurements: spectral width, 2000 Hz; acquisition time, 7.998 s; pulse width, 3 μs; number of data points, 32K; number of transients, 4. The observed half-height widths (Hz) for the mixtures, of which weights (mg) of **1** and **2** are shown in parentheses, were as follows: 0.62 (0.0, 10.0); 0.63 (0.5, 10.0); 0.66 (5.0, 10.0); 0.58 (5.0, 0.0). The observed increases in the half-height widths were within the experimental error (0.10 Hz), and the order of the rate of the exchange (k) was estimated to be larger than 10^5 mol^{-1} s^{-1}, which was calculated from the increase in line width ($\lesssim$0.1 Hz) by using the equations for a rapid two-site exchange process given by Smallcombe and Caserio.[10d]

Thiol–Disulfide Exchange Reaction between 2 and 3. (1) Isolation of 10. To a solution of **3** (925 mg) in dichloromethane (25 mL) was added portionwise **2** (1.451 g) under a nitrogen stream, and the resulting mixture was stirred at room temperature for 1.5 h. Colorless crystals precipitated and were collected by filtration and then washed with dichloromethane, giving **10** (358 mg, 39%), mp 131–132 °C. **10**: ^{1}H NMR (Me_4SO-d_6, 90 MHz, Varian EM-90 NMR spectrometer) δ 2.74, 3.03 (AB q, d, J = 13, 10, 1.5 Hz, 4 H, CH_2), 3.40 (m, 2 H, CHO), 5.16 (d, J = 4 Hz, 2 H, OH). Anal. Calcd for $C_4H_8O_2S_2$: C, 31.55; H, 5.31; S, 42.12. Found: C, 31.22; H, 5.07; S, 42.11. The structure was also confirmed by comparison of its IR spectrum and melting point with those reported previously.[11]

(2) UV Measurements of the Rate of the Exchange Reaction in Acetonitrile. Since the rate of the exchange reaction of **2** with **3** even in a diluted acetonitrile solution was too rapid to follow, the increase in the intensity at 241 nm arising from the generation of **1** was measured instead. A solution of **2** in acetonitrile (0.065 mmol/L, 2.00 mL) was shaken in a cell with a solution of **3** in acetonitrile (0.065 mmol/L, 2.00 mL) at 25 °C, and the UV spectra of the resulting solution were measured in a rapid-scan mode with a Hitachi 320 UV spectrometer after 30, 90, 120, and 480 s. The intensity at 241 nm of the first measurement remained constant thereafter, confirming that the reaction had been completed in less than 30 s.

(3) ^{1}H NMR Measurements of Yields of the Exchange Reaction between 2 and 3 in Neutral Aqueous Solution. In order to prepare a D_2O phosphate buffer solution (0.2 mol/L, pD 7.0, μ 0.5) with a lower content of H_2O, a D_2O solution of $Na_2HPO_4 \cdot 12H_2O$ (366.4 mg), $NaH_2PO_4 \cdot 2H_2O$ (152.4 mg), and NaCl (55.8 mg) was freeze-dried, and the residue was dissolved in D_2O (10.0 mL). To a solution of **3** (10 mmol/L) in the D_2O buffer solution were added various amounts of **2** corresponding to the concentrations shown in Table II, and the ^{1}H NMR spectra of the resulting solutions were measured at 37 °C immediately after complete dissolution under the following conditions for FT NMR measurement: spectral width, 1100 Hz; acquisition time, 5.0 s; pulse width, 7 μs; pulse interval 10 s; number of data points, 10K; number of transients, 128. Although the SCH_2 signals for **3** [δ ca. 2.72 (m) and ca. 2.76 (m)] and **10** [δ ca. 2.93 (m) and ca. 3.15 (m)] were well separated and the yield of **10** was calculated on the basis of the ratio of the intensity of the SCH_2 signal for **10** to the summations of both the intensities of the SCH_2 signals for **3** and **10**, it is noteworthy that a long pulse interval (10 s) was necessary to obtain the accurate ratio of the intensities because of the T_1 problem. Since some error in weighing the samples of **2** was inevitable, the molar ratio was determined exactly by the ratio of the integrated intensity of the NMe signal for the generated **1** to the summation of the intensities of the SCH_2 signals for both **3** and **10**.

Registry No. **1**, 13183-79-4; **2**, 62671-38-9; (±)-**3**, 27565-41-9; **4**, 68700-68-5; **5**, 54986-14-0; **7**, 16681-77-9; (±)-**10**, 86023-22-5.

Mechanism of Friedel–Crafts Acetylation of Acetylene with Acetyl Chloride

Sydney Brownstein,* Anne Morrison, and Liang K. Tan[1]

Division of Chemistry, National Research Council of Canada, Ottawa, Canada K1A OR9

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The Friedel–Crafts acylation of alkynes, leading to the formation of β-chlorovinyl ketones has long been known.[2] The addition of acid chlorides to acetylene in the presence of aluminum chloride at 0 °C in carbon tetrachloride yields solely *trans*-β-chlorovinyl ketones.[3] Other workers re-

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