°C for 65 h. Analysis of the clear solution by VPC (20% Carbowax 1500 on AW 60–80-mesh Chromosorb W) showed four components as 16%, 27%, 53%, and 4%, respectively. The first component (16%) was assigned the structure of *anti*-3-(hydroxymethyl)-6-oxabicyclo[3.1.0]hexyl ethyl ether (**4b**) on the basis of the following spectra properties: IR (neat) 3042 (CH stretching of epoxide ring), 1123, 1105 (vs, doublet, C–O stretching), 837 (CH bending of epoxide ring); mass spectrum, *m/e* 142. The third component (57%) was identified as *anti*-3-(hydroxymethyl)-6-oxabicyclo-[3.1.0]hexane (**4a**) on the basis of identical spectra and retention time with the authentic sample.

***p*-Bromobenzenesulfonate Ester of *syn*-3-(Hydroxydideuteriomethyl)-6-oxabicyclo[3.1.0]hexane (5c).** The same procedure was used for preparative solvolysis of **5c** in aqueous acetone which afforded a semisolid of *exo*-2-oxabicyclo[2.2.1]-heptan-3,3-d_2-6-ol as the sole product: NMR (CCl_4) a singlet at 6.95 (1 H), a broad singlet at 6.12 (1 H), an unresolved singlet at 7.49 (1 H), and a complex multiplet between 7.97 and 8.84 (5 H); mass spectrum, *m/e* 116. The alcohol **5a** was converted to its *p*-bromobenzenesulfonate ester: mp 62.5–64 °C; NMR ($CDCl_3$) a singlet at 2.20 (4 H), an unresolved doublet at 5.48 (1 H), a singlet at 5.74 (1 H), an unresolved singlet at 7.45 (1 H), and a complex multiplet between 7.88 and 8.45 (4 H).

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Registry No. 1a, 25494-14-8; **2a**, 25494-15-9; **2c**, 72598-09-5; **3a**, 72598-06-2; **3a**-*3-d*, 77662-16-9; **3c**, 72598-07-3; **3c**-*3-d*, 77662-17-0; **4a**, 72656-82-7; **4c**, 72598-08-4; **5a**, 77662-18-1; **5c**, 77662-19-2; **6a**, 36368-46-4; **6a**-*6-d*, 77662-20-5; **6a**-*1-d*, 77662-21-6; **6b**, 77662-22-7; **6b**-*6-d*, 77662-23-8; **6b**-*1-d*, 77662-24-9; **6c**, 36368-48-6; **6c**-*6-d*, 77680-03-6; 4-cyclopentenol, 14320-38-8; 4-(hydroxymethyl)cyclopentene, 25125-21-7; *p*-bromobenzenesulfonyl chloride, 98-58-8; 4-(carbomethoxy)cyclopentene-*4-d*, 77662-25-0; 4-(carbomethoxy)-cyclopentene, 58101-60-3; 4-(hydroxymethyl)cyclopentene-*4-d*, 77662-26-1; 4-(hydroxydideuteriomethyl)cyclopentene, 77662-27-2; 4-cyclopentenyl brosylate, 27721-58-0.

Neutral Trichloroacetylations of Alcohols by Hexachloroacetone

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The addition of simple alcohols in hexachloroacetone (HCA) in the presence of strong hydrogen bond acceptors (e.g., dimethylformamide) results in a high yield of the corresponding trichloroacetate (via a haloform reaction scheme). The trichloroacetylation reactions are carried out under neutral conditions, and the resultant ester can easily be separated from the reaction mixture via extraction/distillation procedures. Kinetic evidence demonstrates that the trichloroacetylation of alcohols by HCA is a stereoselective process, and further studies suggest that the catalytic role of the acceptors is of a hydrogen bonding nature.

Reports within the literature have previously described neutral haloform reactions of hexachloroacetone (HCA) in such solvents as dimethyl sulfoxide,[1] formamide,[2] and pyridine.[3] These solvents are reportedly similar with respect to their hydrogen bond accepting capabilities.[4,5] In this study, we investigated the trichloroacetylation of various alcohols by HCA in the presence of these and other hydrogen bond accepting solvents. The addition of relatively weak hydrogen bond acceptors such as dioxane, tetrahydrofuran, acetone, ethyl acetate, and cyclopentanone to alcoholic HCA solutions which are heated at reflux for several hours do not result in the trichloroacetylation of the various alcohols studied; however, the addition of relatively strong hydrogen bond acceptors such as dimethyl sulfoxide, pyridine, hexamethylphosphoramide, and dimethyl formamide (DMF) to alcoholic HCA solutions at room temperature initiate exothermic reactions resulting in the rapid formation of trichloroacetate and chloroform.

Since DMF is a relatively available and fairly inexpensive solvent, trichloroacetylation yields were maximized by utilising this reagent. Yields obtained via gas–liquid chromatographic analysis (Table I) are superior to any yields obtained by previously reported trichloroacetylation procedures.[3,6–11] Chromatographic coelution of certain trichloroacetates with either HCA or DMF necessitated the aqueous extraction of these compounds from the organic esters prior to analysis. The efficient removal of unreacted HCA from pentane solutions of the reaction mixtures appeared to be effected by the formation of the

Table I. Trichloroacetylation of Alcohols by HCA

alcohol	equiv of HCA	equiv of DMF	reaction time, h[a]	% yield[b]
methanol	1.0	1.9	1.5	98[c]
ethanol	1.5	4.0	9	98
1-propanol	1.5	5.0	9	90
2-propanol	1.5	5.0	48	74
cyclohexanol	1.5	7.0	48	75
2-methyl-2-propanol	1.0	4.0	72	0

[a] Reaction temperature was 55 °C. [b] Determined by GLC with cyclohexyl chloride as the internal standard. [c] Product isolated with a yield of 93%.

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(1) C. A. Panetta and T. G. Casanova, *J. Org. Chem.*, **35**, 2423 (1970).
(2) D. C. Dittmer and R. A. Fouty, *J. Am. Chem. Soc.*, **86**, 91 (1964).
(3) V. Migaichuk and I. G. Khaskin, *Zh. Prikl. Khim. (Leningrad)*, **50**, 2471 (1977).
(4) E. M. Arnett, L. Joris, E. Mitchell, T. S. S. R. Murty, T. M. Gome, and P. v. R. Schleyer, *J. Am. Chem. Soc.*, **92**, 2365 (1970).
(5) M. J. Kamlet and R. W. Taft, *J. Am. Chem. Soc.*, **98**, 377 (1976).
(6) M. Kulka, *J. Am. Chem. Soc.*, **72**, 1031 (1950).
(7) H. E. Simmons and D. W. Wiley, *J. Am. Chem. Soc.*, **82**, 2288 (1960).
(8) S. G. Toole and F. J. Sowa, *J. Am. Chem. Soc.*, **59**, 1937 (1971).
(9) J. F. Normant and H. Deshayse, *Bull, Soc. Chim. Fr.*, 2854 (1972).
(10) N. J. Cleve, *Suom. Kemistil. B.* **46**, 5 (1973).
(11) H. Akiyama, K. Yasunagu, and T. Komatsu, Japanese Kokai, 73 36 138 (Cl 16 C46) (1973); *Chem. Abstr.*, **79**, P31694, (1973).

0022-3263/81/1946-3519$01.25/0

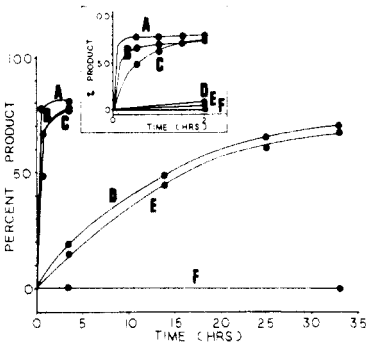

Figure 1. Trichloroacetate formation at 60 °C from equimolar solutions of HCA, DMF, and various alcohols [MeOH (A), EtOH (B), *n*-PrOH (C), *i*-PrOH (D), c-HxOH (E), and *t*-BuOH (F)].

stable water soluble HCA *gem*-diol adduct.[12] High isolated yields of the trichloroacetates (e.g., 93% for methyltrichloroacetate) could thus be obtained via this simple pentane extraction followed by distillation of the volatiles.

The results of these studies indicate that the esterification of various alcohols by HCA becomes less efficient as the bulk of the alcohol R group is increased. This can be explained on the basis of the restricted accessibility of the HCA carbonyl carbon to certain alcohols due to steric interactions with the two bulky trichloromethyl substituents. Kinetic ^{1}H NMR studies reaffirm this fact (Figure 1). The trichloroacetylation of alcohols by HCA strongly favors reaction of primary alcohols in preference to secondary alcohols. In fact, the reaction of an equimolar mixture of 1-propanol and 2-propanol with HCA in DMF resulted in trichloroacetylation of the primary alcohol with 94% specificity. The reaction of tertiary alcohols such as *tert*-butyl alcohol with HCA in DMF at 55 °C for 72 h produced no detectable trichloroacetylation.

Although the direct addition of alcohols to HCA does not result in the trichloroacetylation of any of the alcohols studied, ^{1}H NMR studies indicate that the direct addition of primary alcohols to HCA does result in rapid hemiketal formation.[13] These hemiketals of HCA were also studied by ^{13}C NMR, and the chemical shifts for these species were found to be similar to those previously reported for the HCA *gem*-diol hydrogen bond adducts.[14] Since these adducts have been identified,[12] the existence of analogous hydrogen bonded hemiketal complexes is similarly viable. Further, given the nature of these proposed complexes, the constituent hydrogen bond acceptor (e.g., DMF) could promote the trichloroacetylation reaction via hydrogen bonding catalysis. Under these circumstances, one might expect to find a deuterium isotope effect for the reaction. Trichloroacetylation kinetics of methanol vs. methanol-*d* do indeed show a rate retardation in the deuterated case (Figure 2). These results, although not conclusive, are consistent with a hydrogen bonding catalytic mechanism. Dipolar aprotic solvents such as DMF, in addition to their hydrogen bonding tendencies, have been reported to stabilize large and easily polarizable anions such as the trichloromethyl anion.[15] Such an effect would further favor the haloform reaction in the presence of these solvents.

The fact that the trichloromethyl anion exists in the trichloroacetylation reaction mixture is supported by the identification of certain minor byproducts of the reaction

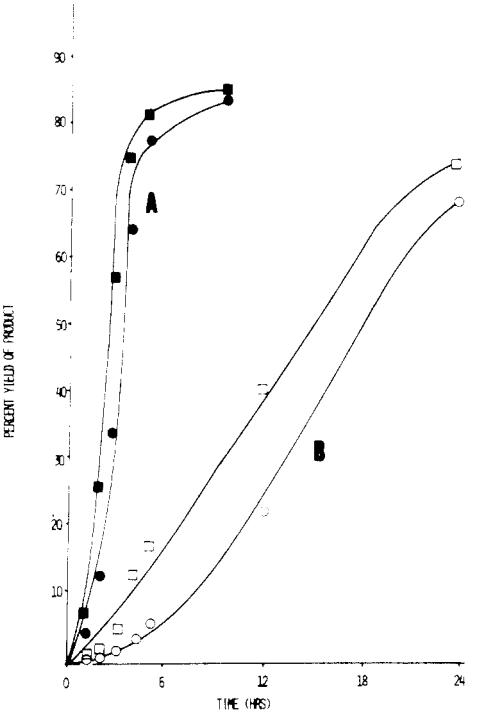

Figure 2. Trichloroacetate formation at 28 °C from equimolar solutions of methanol (A) or methanol-*d* (B) and HCA containing 0.56 equiv of DMF.

such as carbon tetrachloride by GLC, pentachloroacetone by ^{1}H NMR and GLC, and methyl dichloroacetate by GLC. The trichloromethyl anion, as a free species in solution, is apparently capable of acquiring a positive chlorine from an HCA molecule, thus forming carbon tetrachloride and a pentachloroacetonide anion. The donation of positive chlorine by HCA in enamine reactions has previously been reported by Laskovics and Schulman.[16] The pentachloroacetonide anion can then subsequently combine with a proton to form pentachloroacetone which can, as we later confirmed, undergo a haloform reaction to produce methyl dichloroacetate and chloroform.

Finally, it is interesting to note that though HCA can readily undergo a primary haloform cleavage, the release of the second trichloromethyl anion from the resultant ester is not as easily facilitated. The haloform cleavage of hexabromoacetone by sodium hydroxide reportedly yields sodium carbonate and bromoform,[17] though similar reactions with HCA reportedly result only in the formation of sodium trichloroacetate and chloroform.[18] The reaction of HCA and methoxide anion, however, does reportedly result in a dihaloform-type cleavage to yield dimethyl carbonate.[19,20] This product, however, was not identified by ^{1}H NMR in reaction mixtures of HCA and methanol containing any of the various strong hydrogen bond acceptor solvents used in this study.

Experimental Section

Carbon-13 NMR spectra were recorded at 20 MHz on a Varian CFT-20 spectrometer with proton-noise decoupling. A capillary containing D_2O was used as an internal lock signal. Proton magnetic resonance spectra were recorded on either a Perkin-

(12) E. M. Schulman, O. D. Bonner, D. R. Schulman, and F. M. Laskovics, *J. Am. Chem. Soc.*, **98**, 3793 (1976).
(13) R. S. Freedlander, Ph.D. Thesis, University of South Carolina 1980.
(14) F. M. Laskovics, Ph.D. Thesis, University of South Carolina, 1977.
(15) A. J. Parker, "Recent Advances in Physical Organic Chemistry", Vol. 5, V. Gould, Ed., Academic Press, New York, 1967, pp 184–191.
(16) F. M. Laskovics and E. M. Schulman, *Tetrahedron Lett.*, 759 (1977); *J. Am. Chem. Soc.*, **99**, 6672 (1977).
(17) A. Hantzsch and K. Schniter, *Chem. Ber.*, **20**, 2033 (1887).
(18) E. G. Edwards, D. P. Evans, and H. B. Watson, *J. Chem. Soc.*, 1942 (1937).
(19) F. W. Grant and W. B. Cassie, *J. Org. Chem.*, **25**, 1433 (1960).
(20) P. K. Kadaba and J. O. Edwards, *J. Org. Chem.*, **25**, 1431 (1960).

Elmer R-32 spectrometer at 90 MHz or a Varian EM-360 spectrometer at 60 MHz.

Reagent grade alcohols were dried over magnesium turnings containing traces of iodine at reflux for several hours. HCA and pentachloroacetone (Aldrich) were dried by refluxing the solutions at a reduced pressure of 6–7 mmHg (bp for HCA 67–70 °C) over phosphorus pentoxide for several hours. DMF was dried by refluxing the solution over calcium hydride at a reduced pressure of 33–34 mmHg (bp 62–65 °C) for 24 h and stored over molecular sieves (Davison, 5 Å). All solutions were distilled, analyzed by gas-liquid chromatography, stored under a dry nitrogen atmosphere, and protected from light. All of the trichloroacetate esters described in this paper have previously been synthesized and reported within the literature.[21] Authentic samples were prepared in a similar fashion as described within those reports.

Reaction of HCA and Alcohols. Equimolar amounts of various alcohols were added to HCA. The mixtures were stirred for several seconds until a clear solution resulted. These solutions were then studied by ^{13}C and ^{1}H NMR. Solutions were then heated at reflux for several hours and subsequently reanalyzed by NMR.

Reaction of HCA, Alcohols, and Hydrogen Bond Acceptors. Equimolar amounts of reagent grade dioxane, tetrahydrofuran, acetone, ethyl acetate, and cyclopentanone were each added to various alcoholic HCA solutions and heated at reflux for several hours. The solutions were then analyzed by GLC and ^{1}H NMR.

Equimolar amounts of dimethyl sulfoxide, pyridine, hexamethylphosphoramide, and DMF were each slowly added to equimolar solutions of certain alcohols and HCA. The mixtures were stirred in an ice bath during addition of the hydrogen bond acceptors, quickly thermostated to ^{1}H NMR probe temperature (28 °C), and analyzed.

Trichloroacetylation of Alcohols: Gas–Liquid Chromatography Yields and Product Analysis. Gas–liquid chromatography was performed on a Hewlett-Packard 5711A dual-column gas chromatograph equipped with a Vidar 6300 digital integrator. Aluminum columns ($^{1}/_{8}$ in. o.d. × 72 in.) were packed with 10% Hi-Efficiency-1-BP on 100/120 mesh Chromosorb P (AW). The analysis utilized a temperature program of 80 °C for 4 min and 8 °C/min with a final temperature of 190 °C for 2 min. The injection port and detector were regulated at 200 °C. All results were performed in triplicate. Calibration curves were obtained by using cyclohexyl chloride (bp 142 °C) as internal standard by a linear least squares computer program. Correlation coefficients of 1.00 were obtained for molar ratios of trichloroacetate to cyclohexyl chloride ranging from 1.0 to 7.0.

The reaction of various alcohols with HCA in the presence of DMF were run according to conditions outlined in Table I. The description of a typical reaction follows.

A solution of 7.5 mL of HCA (0.049 mol) and 10 mL of DMF (0.13 mol) was stirred for 10 min at room temperature under a dry nitrogen atmosphere. To this solution was added 2 mL of methanol (0.049 mol). After the addition, the vessel was sealed with rubber septa and placed in a thermostated oil bath at 55 °C for 90 min. An aliquot (0.722 g) of the reaction mixture was added to 0.0680 g of cyclohexyl chloride and diluted in 10 mL of pentane. The organic solution was washed with 2 mL of water and 2 mL of brine, dried over anhydrous sodium sulfate, and analyzed by gas–liquid chromatography.

Trichloroacetylation of Methanol: Isolated Yield. A solution containing 2 mL of methanol (0.049 mol) and 2 mL of DMF (0.026 mol) was stirred for 10 min in an ice bath under a dry nitrogen atmosphere. To this solution was added 7.5 mL of HCA (0.049 mol) dropwise. After the addition, the reaction vessel was sealed with rubber septa and placed in a thermostated oil bath at 55 °C for 90 min. The solution was diluted with 50 mL of chilled pentane, washed with 10 mL of chilled water and 10 mL of brine, and dried over anhydrous sodium sulfate, and the volatiles were removed at reduced pressure. The clear solution of methyl trichloroacetate had a weight of 8.16 g (93% yield). GLC analysis of the solution showed trace amounts of methyl dichloroacetate and pentachloroacetone.

Trichloroacetylation Kinetics. (1) Trichloroacetylation Kinetics of Various Alcohols. Equimolar solutions of HCA and the various alcohols were stirred in a dry ice bath under a positive pressure of dry nitrogen. An equimolar amount of DMF was then added to the frozen mixture. The reaction was then removed from the ice bath, sealed with rubber septa, and stirred until the solid had melted. The reaction vessel was subsequently stirred in a 60 °C thermostated oil bath. When a thermometer immersed within the reaction mixture recorded a temperature of 57 °C (approximately 5 min after immersion into the oil bath), the time was noted and recorded as time zero. Aliquots of the solution were removed via a hypodermic syringe through the rubber septum at 0.5-h intervals (and longer intervals for the secondary and tertiary alcohols) and were injected into 5-mm NMR tubes containing argon. The NMR tubes were sealed and subsequently immersed in a dry ice–methanolic bath prior to ^{1}H NMR analysis. The following ^{1}H NMR signals were integrated in order to compute kinetic results: methanol, δ 3.4 (s, 3 H); methyl hemiketal, δ 3.75 (s, 3 H); methyl trichloroacetate, δ 4.05 (s, 3 H); ethanol, δ 3.3–3.75 (q, 2 H); ethyl hemiketal, δ 3.8–4.25 (q, 2 H); ethyl trichloroacetate δ 4.15–4.6 (q, 2 H); *n*-propanol, δ 3.25–3.55 (t, 2 H); *n*-propyl hemiketal, δ 3.75–4.05 (t, 2 H); *n*-propyl trichloroacetate, δ 4.1–4.4 (t, 2 H); 2-propanol, δ 0.95–1.15 (d, 6 H); isopropyl trichloroacetate, δ 1.24–1.4 (d, 6 H); cyclohexanol, δ 3.35–3.75 (m, 1 H); cyclohexyl trichloroacetate, δ 4.8–5.1 (m, 1 H); *tert*-butyl alcohol, δ 1.2 (s, 9 H); *tert*-butyl trichloroacetate δ 1.6 (s, 9 H).

(2) Competition Trichloroacetylation Kinetics of *n*-Propanol vs. 2-Propanol. A solution containing 1 mL of 2-propanol (0.013 mol) and 1 mL of *n*-propanol (0.013 mol) was stirred under a dry nitrogen atmosphere at room temperature. A solution containing 10 mL of DMF (0.13 mol) and 2 mL of HCA (0.013 mol) was slowly added to the alcohol solution. The reaction vessel was then sealed with rubber septa and placed in a 55 °C thermostated oil bath for 9 h. The reaction mixture was then cooled, and a sample aliquot (0.770 g) was diluted in 100 mL of pentane. This solution was then washed with 20 mL of chilled water, washed with 20 mL of brine, and dried over anhydrous sodium sulfate, and the volatiles were removed at a reduced pressure. The resulting clear solution (0.125 g) corresponds to a yield of 88% trichloroacetate product. A GLC chromatogram showed that both *n*-propyl trichloroacetate and isopropyl trichloroacetate were components of this solution. The solution also contained trace amounts of *n*-propyl dichloroacetate, isopropyl dichloroacetate, and pentachloroacetone. Results of the analysis demonstrate that the trichloroacetylation showed 94% specificity for the primary alcohol.

(3) Trichloroacetylation Kinetics of Methanol and Methanol-*d* in DMF. Equimolar solutions containing 3.75 mL of HCA (0.025 mol) and 1 mL of methanol (or methanol-*d*, 0.025 mol) were added to 1.27 mL of DMF (0.014 mol) at 0 °C under a positive pressure of dry nitrogen. These reaction mixtures were quickly thermostated to ^{1}H NMR probe temperature (28 °C) and analyzed at 1-h intervals for 6 h and subsequently at 6-h intervals.

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Registry No. Methanol, 67-56-1; ethanol, 64-17-5; 1-propanol, 71-23-8; 2-propanol, 67-63-0; cyclohexanol, 108-93-0; 2-methyl-2-propanol, 75-65-0; methyl trichloroacetate, 598-99-2; ethyl trichloroacetate, 515-84-4; propyl trichloroacetate, 13313-91-2; isopropyl trichloroacetate, 3974-99-0; cyclohexyl trichloroacetate, 40410-64-8; hexachloroacetone, 116-16-5.

(21) E. H. Huntress, "Organic Chlorine Compounds", Wiley, New York, 1948.