another 10 min, and the excess palladium(II) precipitated as Pd(0) by reaction with Zn powder. The reaction mixture was then cooled to ~2 °C. A (2,4-dinitrophenyl)hydrazine solution was prepared as previously described and also cooled to 2 °C. To this solution was added the cooled reaction mixture. The solids were collected and washed with water to remove any excess hydrazine reagent. After air drying the 2,4-DNP's were dissolved in hot benzene and filtered, and the extract was cooled to crystallize the 2,4-DNP's, which were then collected, dried, and dissolved in $CDCl_3$ for NMR analysis to determine total product distribution by ^1H NMR peak integration. Fortunately each product possessed a proton whose chemical shift was different from all other protons in the reaction mixture. For example in the oxidation of crotyl alcohol the crotonaldehyde vinylic protons at 6.3 ppm, the H_b protons of 8 at 4.2 ppm, the H_c protons of 13 at 4.6 ppm, and the H_a protons of 11 at 3.9 ppm were used for this purpose. The individual 2,4-DNP's of the products were separated by column chromatography as previously described.[3] The ^1H NMR spectra of the 2,4-DNP derivatives of the products are given in Table III. The products from the deuterium-labeling experiments were separated in the same fashion and analyzed by a combination of ^1H and ^2H NMR spectroscopy.

In order to obtain yields based on Pd(II) reduced, the reactions were run in the absence of quinone and the Pd(0) formed collected and weighed. The remaining Pd(II) was then precipitated with Zn dust, the reaction mixtures again filtered, and the filtrate analyzed for total carbonyls by an oximation procedure. The procedures for running the reactions and the carbonyl analysis by oximation have been described.[3] The yield values are an average of two determinations for each allyl alcohol. The variation between runs was less than 2%.

Kinetics Studies. The reactions were run in the presence of *p*-benzoquinone (Q), which oxidized the Pd(0) formed in the oxidation back to Pd(II). The benzoquinone is reduced to hydroquinone (QH_2) in the process. The extent of reaction was determined by measuring the emf of the cell: Pt/Q, QH_2, Pd(II), HCl, $LiClO_4$, olefin/Pd(II), HCl, $LiClO_4$, Q, QH_2/Pt. The apparatus and procedure has been described.[1]

The procedure for following the isomerization of 6′ or 7′ into its allylic isomer by ^2H NMR was the same as that used to follow the isomerization of deuteriated allyl alcohol.[8]

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A Simple Conversion of 1-Chloroethyl Carbonates to Fluoroformates: Value in the Preparation of Tertiary Alkyl Fluoroformates

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When the economical and easily available 1-chloroalkyl carbonates ($RCHClOCO_2R'$) are heated neat or in solution with KF in the presence of an 18-crown-6 catalyst, they fragment to aldehydes (RCHO) and fluoroformates (FCO_2R'). If the system is evacuated during reaction and either or both products are removed as formed, then the process is driven to completion and fluoroformates are isolated in good yield. The new methodology (*which exemplifies an unusual conversion of an ester to an acid halide*) is especially valuable in the synthesis of important tertiary alkyl fluoroformates and benzyl fluoroformate (with R as CH_3 in the carbonate): *tert*-butyl fluoroformate (Boc-F, 84% yield), *tert*-amyl fluoroformate (83%), 1-adamantyl fluoroformate (76%), benzyl fluoroformate (60%). Boc-F previously has been recommended as a superior reagent for the preparation of Boc-amino acids, but earlier routes to this reagent have been expensive and impractical. When R in the carbonate reactant is Cl_3C, the reaction proceeds cleanly without the 18-crown-6 catalyst (Boc-F in 79% yield). This latter variation is most useful on a small industrial scale.

In the preferred literature synthesis of most fluoroformates (FCO_2R), the analogous chloroformates ($ClCO_2R$) are simply stirred neat at or near room temperature with excess KF activated by a little 18-crown-6.[2,3] Fluoroformate yields normally are excellent (80–97%). However, this and other halide exchange processes[2] fail as routes to tertiary alkyl fluoroformates because the required precursor chloroformates are unstable; *tert*-butyl chloroformate decomposes to *tert*-butyl chloride at 0 °C.[4,5] Because attack at the benzylic carbon is preferred (to give benzyl fluoride), the method also fails as a source of benzyl fluoroformates. Both tertiary alkyl and benzyl fluoroformates can be made in good yield by acylating the respective alcohols with COF_2 or COFCl,[2] but the method is economically impractical due to the price of COF_2 ($700/lb, bp −83 °C) and the preparative inaccessibility of both COF_2 and COFCl in a standard laboratory.[6] In

(1) Both this paper and the following paper are dedicated by this author to the memory of his childhood friend and schoolmate through graduate school, Professor Emil Thomas Kaiser of Rockefeller University, deceased July 18, 1988.

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(3) Cuomo, J.; Olofson, R. A. *J. Org. Chem.* **1979**, *44*, 1016.

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(6) For discussion, see footnote 5 in ref 2.

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the case of *tert*-butyl fluoroformate (**1**, Boc-F), this is especially unfortunate since **1** has been highly recommended as an extremely clean and efficient, stable reagent for the formation of *N*-(*tert*-butoxycarbonyl)amino acids (Boc-AA).[5,7] Today, as is well known, the Boc moiety is the most important amine protecting group in peptide synthesis despite the price of $(Boc)_2O$ ($400/kg), the acylating agent ordinarily used as the Boc source.

The investigation reported here was prompted by the serendipitous identification of **1** as a product from the attempted halide exchange of $ClCH_2OCO_2tBu$ to give FCH_2OCO_2tBu with KF/18-crown-6. In a later experiment, a mixture of ethyl fluoroformate (**3**, 93% yield) and acetaldehyde distilled into a cold trap from a heated mixture of commercial 1-chloroethyl ethyl carbonate (**2**), dried KF, and 18-crown-6 (5 mol %) in benzonitrile (30-mm vacuum).

$$\underset{\text{2 (ACE-OEt)}}{CH_3CHClOCO_2Et} + KF \xrightarrow[PhCN]{\text{18-C-6}} MeCHO + \underset{\text{3}}{FCO_2Et} + KCl$$

Formally, the transformation, **2** → **3**, depicts a conversion of an ester to an acid halide by treatment with halide ion. According to the pedagogy most teachers use to introduce the hierarchy of stability–reactivity relationships among carboxyl derivatives, this reaction should be far "uphill". Why does it occur? First, the halide nucleophilicity has been enhanced enough to change a normal nonreaction into a potential equilibrium process. Second, the leaving alkoxide, the reagent of the reverse reaction, has been destroyed in a secondary process. Finally, any equilibrium has been shifted from **2** by removing volatile products as formed.

The significance of the reaction, **2** → **3**, as the prototype of a general fluoroformate synthesis, **5** → **6**, of potential use in the preparation of tertiary alkyl fluoroformates, was magnified by the knowledge that the chloroformate presursors **4** of the carbonates **5** are cheaply accessible. For example, treatment of acetaldehyde with phosgene (1:1.1, neat) in the presence of a reusable $PhCH_2N^+(nBu)_3Cl^-$ (BTBAC) catalyst affords α-chloroethyl chloroformate (ACE-Cl[7] = **4** [R = CH_3]) in 96% distilled yield.[8-10]

$$\underset{\text{4}}{RCHOCOCl} \xrightarrow{HOR'} \underset{\text{5}}{RCHOCOR'} \xrightarrow[\text{18-C-6}]{KF} RCHO + \underset{\text{6}}{FCOR'} + KCl$$

Because of the commercial availability of ACE-Cl and the volatility of acetaldehyde, most studies of the conditions, scope, and limitations of the process, **5** → **6**, were performed with the carbonates **5** where R = CH_3. These were easily made in high yield by acylation of the respective alcohols with ACE-Cl usually with pyridine as an added acid scavenger. A list of some of the carbonates prepared is given in Table I.

Data on the synthesis of fluoroformates from the carbonates **5** is presented in Table II. *tert*-Butyl and *tert*-amyl fluoroformates were most conveniently prepared by heating the required carbonates neat at reduced pressure with 1.5–2 equiv of KF and 4–6 mol % of the 18-crown-6 catalyst. The fluoroformate and acetaldehyde were allowed to evaporate from the stirred mixture as formed and were collected in a −80 °C trap. Estimated yields (NMR) of fluoroformate in the trap ranged up to 95%, and the yields of pure distilled product were over 80%. In the synthesis of 1-adamantyl fluoroformate,[12] substitution of a simple condenser for the cold trap let the acetaldehyde pass through the collector. Then the collected product already was essentially pure (81% yield, 75% distilled of mp 30–32 °C).

Table I. Synthesis of 1-Chloroalkyl Alkyl Carbonates[a]

no.	Carbonate (RCHClOCOR') R =	R' =	yield, %[b] (method)[c]	bp, °C/mm
7	methyl	*tert*-butyl	91 (A)	58–60/10
8	methyl	*tert*-amyl	89 (A)	53–54/1
9	methyl	1-adamantyl	94 (A)	mp 63–65
10	methyl	benzyl	90 (A)	116–119/1
11	methyl	*p*-MeO-benzyl	86 (A)	oil (can't dist)
12	[ACEO$(CH_2)_6$OACE]		95 (A)	176–177/1.5
13	methyl	*n*-octyl	94 (A)	109–112/0.4
14	methyl	*n*-octadecyl	82 (A)	212–215/2
15	methyl	cholesteryl	99 (A)	amorph powder
16	methyl	CF_3CH_2	91 (A)	54–56/5
17	methyl	neopentyl	99 (A)	74–75/10
17	methyl	neopentyl	83 (B)	as above
18	methyl	phenyl	83 (A)	101–104/3
19	Cl_3C	*tert*-butyl	92 (A)	96/7 (mp 70)

[a] Made by acylation of the alcohol with the appropriate chloroformate as described in the Experimental Section. [b] Of distilled product. [c] A = pyridine used as acid scavenger. B = no added acid scavenger.

When the benzyl carbonate **10** was reacted at 80 °C, the previously unknown benzyl fluoroformate was obtained in 68% yield, but benzyl chloride was a significant side product (7%). By heating the mixture at 55 °C, this side process could be avoided, but low reaction pressure and use of a heat gun caused some **10** to evaporate with the fluoroformate. Subsequent distillation afforded pure fluoroformate in 60% yield. This side reaction became the sole process even under mild conditions when the *p*-methoxybenzyl carbonate **11** was the starting material. *p*-Methoxybenzyl chloride was obtained in 98% yield. Interestingly, only a trace of *p*-methoxybenzyl fluoride was found.

Since only one product needs to be removed as formed, the syntheses of the high-boiling fluoroformates of hexanediol (bis), octanol, and octadecanol from **12–14** were performed so that only the acetaldehyde evaporated. Distilled fluoroformate yields still were 72–86%. Workup in the octadecyl floroformate preparation even included three rapid ice–water extractions. In the reaction of the solid cholesteryl carbonate **15**, benzonitrile was included

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(8) Olofson, R. A.; Martz, J. T.; Senet, J.-P.; Piteau, M.; Malfroot, T. *J. Org. Chem.* **1984**, *49*, 2081.
(9) On an industrial scale, the current prices of acetaldehyde and $COCl_2$ are $0.37/lb and $0.55/lb, respectively. The reaction works nicely with almost all aldehydes.[10,11] For more experimental detail, see ref 8, footnote 4, or ref 10.
(10) Cagnon, G.; Piteau, M.; Senet, J.-P.; Olofson, R. A.; Martz, J. T. Eur. Pat. EP 40 153; *Chem. Abstr.* **1982**, *96*, 142281y; U.S. Pat. 4,592,874 (June 3, 1986).
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(13) See: Dang, V. A. Ph.D. Dissertation, The Pennsylvania State University, 1986. Olofson, R. A. *Pure Appl. Chem.* **1988**, *60*, 1715.

Table II. Fluoroformates Prepared from Their Respective 1-Chloroalkyl Carbonates[a]

reactant (Table I)	FCO_2R' product, R' =	yield, %[b]	KF, equiv	18-C-6, mol %[c]	solvent	temp/press, °C/mm	time, h	bp found, °C/mm
7	*tert*-butyl	84	2.3	6	none	70/37	30	40–42/175[d]
8	*tert*-amyl	83	1.4	5	none	70/14	34	35–36/36
9	1-adamantyl	76	1.5	4	none	120/1.2	36	mp 30–32[d]
10	benzyl	60	1.8	5	none	55/1.2	4	44–46/1
11	*p*-MeO-benzyl	–[e]						
12	$[FCO_2(CH_2)_6OCOF]$	77	2.8	10	none	25/3	48	102–104/3
13	*n*-octyl	86	1.7	5	none	85/14	12	74–77/4
14	*n*-octadecyl	72	1.9	8	none	90/5	30	177–180/3
15	cholesteryl	82	2.0	9	C_6H_5CN	40/3	31	mp 114–117[d]
16	CF_3CH_2	75[f]	2.5	7	C_6H_5CN	25/10	24	48–52/atm
17	neopentyl	83	1.5	6	C_6H_5CN	60/22	30	55–57/120
17	neopentyl	52	1.5	–[g]	C_6H_5CN	60/22	84	as above
18	phenyl	70	1.4	5	none	75/20	1.5	60–63/20[d]
18	phenyl	37	3.5	none	sulfolane	70/20	18	as above
19	*tert*-butyl	79	1.6	4	diglyme	50/10	8	6–8/27[d]
19	*tert*-butyl	75	1.5	none	DMF	50/20	8	as above

[a] Made by the general procedures in Experimental Section with variations given in table. [b] Of distilled or crystallized product. [c] Versus carbonate. [d] Known compound; lit. (R' =) bp: *tert*-butyl, 79–80/atm; phenyl, 61–64/21. Mp: 1-adamantyl, 31–32; cholesteryl, 112–113. [e] Even under mild conditions, the product was almost exclusively *p*-MeO-benzyl chloride. [f] Corrected for acetaldehyde contaminant. [g] Polyethylene glycol monomethyl ether (av MW 5000), 10 mol % vs carbonate, included as additive.

as a solvent. Then cholesteryl fluoroformate[3] was isolated in 82% recrystallized yield.

In the synthesis of volatile fluoroformates, a solid mixture of KF, KCl, and 18-crown-6 is left in the reaction apparatus when the process is over. To facilitate stirring in such systems, benzonitrile can be included in the reaction mixture as a nonvolatile, inert diluent with little effect on rate. In two experiments performed in that way, 2,2,2-trifluoroethyl and neopentyl fluoroformates were obtained in 75% and 83% yields, respectively. Also in a rate comparison using benzonitrile as an added solvent, *tert*-butyl, isopropyl, neopentyl, and methyl 1-chloroethyl carbonates were converted to their respective fluoroformates in 22%, 47%, 64%, and 75% yields in 1 day at room temperature. In contrast, tetraglyme was poor either as a diluent or extra catalyst. Reaction in tetraglyme at 50 °C (20 mm) afforded Boc-F in only 40% yield after 60 h.

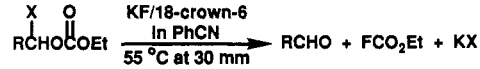
Other potential catalysts proved inferior to 18-crown-6. With BTBAC as the phase transfer agent, the yield of neopentyl fluoroformate was only ca. 5% after 18 h. Also, under conditions which afforded this fluoroformate in 83% yield after 30 h with 18-crown-6, the yield was only 52% after 84 h with PEGMe 5000 [poly(ethylene glycol monomethyl ether), av MW 5000]. Similar results were obtained with PEGMe 600 and PEG 3400, either neat or in benzonitrile, succinonitrile, *N*-methylpyrrolidinone, or sulfolane.

In a final test, treatment of the neat carbonate **18** with KF/18-crown-6 for 90 min gave phenyl fluoroformate in 70% yield. Reaction also occurred slowly (37% yield after 18 h) without the 18-crown-6 when sulfolane was used as the solvent. In this experiment, however, diphenyl carbonate was a major side product. This was not surprising since diphenyl carbonate is a side product in most known chemistry of phenyl chloroformate.

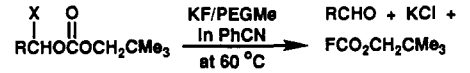
Some of the experiments outlined above were performed only to demonstrate the versatility of the new fluoroformate synthesis. The method is primarily useful in the preparation of tertiary alkyl and benzyl fluoroformates. Other fluoroformates are made more efficiently from the chloroformates by the already described simple halide exchange.[3]

Commercially, when the scale is too small to permit the economical recycling of the 18-crown-6 catalyst, an alternate route to Boc-F is attractive. In this variation, the chloral phosgene adduct **4** (R = CCl_3)[10] first is converted to the *tert*-butyl carbonate **19**[14] (92% yield). Although more expensive to prepare, **19** also should be a more reactive acylating agent than the analogous carbonate **7** from acetaldehyde: the CCl_3 substituent inductively increases the electrophilicity of the carbonyl carbon of **19** and makes 1,2,2,2-tetrachloroethoxide a better leaving group than 1-chloroethoxide.[15] Indeed, the carbonate **19** proved even more reactive than expected. When **19** was heated at 50 °C for 8 h with KF in the polar solvent DMF under a vacuum of 20 mm, Boc-F was formed without including the 18-crown-6 catalyst in the reaction medium. By simultaneous treatment of the distillate with ethylene glycol to trap the chloral byproduct, pure Boc-F was isolated in 75–79% yield.

To test the relative reactivity of polyhalogenated carbonates in nonpolar solvents, a few additional experiments were performed. The results are summarized below:



R = CH_3, X = Cl	93% yield in 13 h
R = CCl_3, X = Cl	93% yield in 2 h
R = CCl_3, X = F	88% yield in 2 h



R = CH_3	56% yield in 84 h
R = CCl_3	76% yield in 34 h
R = CCl_3	38% yield in 34 h (no PEGME)

In both the ethyl and neopentyl carbonate series, the chloral derivatives are much more reactive as expected. Even without an added catalyst, neopentyl fluoroformate is slowly generated from the tetrachloroethyl carbonate. Also surprisingly, the 1-fluoroethyl carbonate is not significantly more reactive than its chloro analogue.

Part of the incentive for this investigation came from published claims[5,7] (vide supra) that BOC-F (**1**) is a stable liquid. While considering the commercialization of **1** by the processes described here, careful stability studies were

(14) Barcelo, G.; Senet, J.-P.; Sennyey, G. *J. Org. Chem.* **1985**, *50*, 3591. Barcelo, G.; Senet, J.-P.; Sennyey, G.; Bensoam, J.; Loffet, A. *Synthesis* **1986**, 627. These authors also used **19** to directly add Boc to AA's. For synthesis and other uses of 1,2,2,2-tetrachloroalkyl alkylcarbonates, see ref 15.

(15) Bowman, M. P. Ph.D. Dissertation, The Pennsylvania State University, 1986.

performed using distilled 1 in glass, polypropylene, and Teflon containers with and without the standard chloroformate stabilizer, sodium carbonate. In the key experiments at 50 °C, the thermal stability of 1 was variable and irreproducible. The time for complete decomposition to *tert*-butyl fluoride, CO_2, and isobutene ranged from less than 2 h to greater than 96 h. A slow decomposition period was followed by a fast but not explosive process accompanied by rapid gas evolution. Thus, 1 cannot be transported from one site to another without unacceptable risk. Whether prepared in a laboratory or in a large plant, 1 should be used as soon as reasonably feasible and stored at 0 °C in the interim. Samples of Boc-F have been stored in a refrigerator for a few months without significant decomposition.

The reported excellence[5,7] of Boc-F (MW only 120) as a reagent for the formation of Boc-AA's in the laboratory has been confirmed and also has been verified on a commercial scale. With the introduction of our new route to Boc-F, the economics of the process become very attractive. The value of the methodology introduced here is further enhanced by the discoveries described in the following manuscript.[16]

Experimental Section[17]

Data were obtained with the following apparatus: ^1H NMR, Varian EM 360 or Bruker WP200 Super Con (also for ^{13}C NMR); IR, Perkin-Elmer 281B; MS, at 70 eV, Kratos MS-950 or Finnigan 3200 CI quadrupole equipped with Finnigan 6000 computer. Commercial anhydrous KF was dried in an oven at 170 °C overnight before use. Solvents were stored over Linde 4A molecular sieves. Processes requiring anhydrous conditions were performed under N_2 in oven-dried glassware (170 °C) cooled in stream of dried N_2.

1-Chloroethyl Alkyl Carbonates (5, R = Me). General Procedure A: 1-Chloroethyl *tert*-Butyl Carbonate (7). Pyridine (27.0 g, 0.34 mol) was dripped (20 min) into a stirred, cooled (0 °C) solution of α-chloroethyl chloroformate (ACE-Cl, 44.0 g, 0.31 mol) and *tert*-butyl alcohol (21.5 g, 0.29 mol) in CH_2Cl_2 (200 mL). After 15 h at room temperature, the mixture was diluted with CH_2Cl_2 (100 mL), washed with 0.5 M HCl (100 mL) and water (3 × 100 mL), dried (Na_2SO_4), concentrated, and vacuum distilled to obtain pure 7: bp 58–60 °C at 10 mm, 47.6 g (91% yield); IR (CCl_4) 1760 cm^{-1} (s); ^1H NMR (CCl_4) δ 6.45 (q, 1 H, J = 6 Hz), 1.81 (d, 3 H, J = 6 Hz), 1.52 (s, 9 H). Anal. Calcd for $C_7H_{13}ClO_3$: C, 46.55; H, 7.25. Found: C, 46.84; H, 7.49.

In the synthesis of 1-chloroethyl *p*-methoxybenzyl carbonate (11), the product (IR and NMR pure) decomposed on attempted vacuum distillation or column chromatography (silica gel). In the preparation of the 1-chloroethyl carbonates of 1-adamantanol, 2,2,2-trifluoroethanol, neopentyl alcohol, and phenol (9, 16–18), the reaction mixtures were filtered through silica (CH_2Cl_2), concentrated, and distilled. The pure cholesteryl carbonate (15) was isolated as an amorphous powder after the concentration step.

Procedure B: 1-Chloroethyl Neopentyl Carbonate (17). ACE-Cl (3.62 g, 0.025 mol) was added to neopentyl alcohol (2.23 g, 0.025 mol), and the mixture was heated at 70 °C overnight at reduced pressure (120 mm). The mixture stopped refluxing after 2 h. Traces (ca. 5%) of alcohol and ACE-Cl in the colorless mixture were removed by vacuum distillation: 4.09 g (83% yield, GC pure) of bp 74–75 °C at 15 mm; IR (CCl_4) 1765 cm^{-1} (s); ^1H NMR ($CDCl_3$) δ 6.34 (q, 1 H, J = 6 Hz), 3.81 (s, 2 H), 1.75 (d, 3 H, J = 6 Hz), 0.89 (s, 9 H). Anal. Calcd for $C_8H_{15}ClO_3$: C, 49.36; H, 7.77; Cl, 18.21. Found: C, 49.19; H, 7.55; Cl, 18.08.

When the mixture was heated above 70 °C, the solution turned brown and the yield of 17 decreased. From experience in related systems, this kind of process can be used for the synthesis of most other carbonates. However, because optimum conditions vary widely with structure, method A is preferred unless the quantities to be made are large enough to justify optimization experiments for a particular reactant.

Fluoroformate Syntheses from 5 (R = Me). General Procedure: *tert*-Butyl Fluoroformate (1). A stirred mixture of distilled α-chloroethyl *tert*-butyl carbonate (7) (20.4 g, 0.11 mol), dried KF (15.0 g, 0.26 mol), and 18-crown-6 (1.90 g, 0.0072 mol, 6.5 mol % vs 7) was heated (oil bath at 70 °C) at 37 mm. Volatile products were condensed in a −80 °C trap as formed. After 30 h, 17.0 g of a mixture of acetaldehyde and 1 had been collected (95% yield of 1, NMR) in the trap. The product mixture was heated to 50 °C to remove the aldehyde and then distilled at reduced pressure to isolate pure 1: bp 40–42 °C at 175 mm (lit.[5] bp 79–80 °C at atm pressure), 11.4 g (84% yield); IR (CCl_4) 1830 cm^{-1} (s); ^1H NMR (CCl_4) δ 1.51 (d, J = 1 Hz).

In the preparation of hexanediol bisfluoroformate, the mixture at the end of the reaction was diluted with CH_2Cl_2, filtered, concentrated, and vacuum distilled to isolate the product. This dilution step was omitted in the synthesis of octyl fluoroformate. After adding $CHCl_3$, the reaction mixture was quickly washed with ice–water (3×), dried (Na_2SO_4), and vacuum distilled to obtain octadecyl fluoroformate. After dilution with CH_2Cl_2, filtration, and concentration, cholesteryl chloroformate was isolated by recrystallization from acetonitrile. For other variations, see Discussion and Table II.

1,2,2,2-Tetrachloroethyl *tert*-Butyl Carbonate (19). Pyridine (160 g, 2.02 mol) in CH_2Cl_2 (400 mL) was added over 1 h to a stirred solution of *tert*-butyl alcohol (155 g, 2.1 mol) and 1,2,2,2-tetrachloroethyl chloroformate[10] (493 g, 2.0 mol) in CH_2Cl_2 (1 L) maintained at 0–5 °C. After stirring 4 h at 5 °C, the pyridine hydrochloride was filtered off and washed with 600 mL of CH_2Cl_2. The CH_2Cl_2 solutions were combined, washed with water to neutrality, dried ($MgSO_4$), and evaporated at reduced pressure to obtain white crystals of 19 in near quantitative yield. The product could be further purified by distillation at reduced pressure (bp 96 °C at 7 mm) or crystallization from hexane (mp 70 °C): yield 87–92%; IR ($CHCl_3$) 1770 cm^{-1} (s); ^1H NMR ($CDCl_3$) δ 6.7 (s, 1 H), 1.5 (s, 9 H).

***tert*-Butyl Fluoroformate (1) from 19.** A 2-L reactor equipped with a stirrer, thermometer, and reflux condenser, cooled with water at 20–25 °C and connected to a tube inserted into a second reactor, was charged with 19 (389 g, 1.37 mol), dried KF (115 g, 2 mol), and anhydrous DMF (700 mL). The second reactor contained a stirred mixture of anhydrous Na_2SO_4 (93 g, 0.65 mol) and ethylene glycol (140 g, 2.25 mol) kept at 30–35 °C and was equipped with a double-jacketed distillation column (Raschig rings) kept at 15 °C and connected via a trap maintained at −70 °C to a vacuum pump. The assembly of reactors and trap was maintained at a pressure of 20 mm during the entire reaction. The first reactor was heated at 50 °C for 8 h, during which the fluoroformate that formed condensed in the −70 °C trap. Vacuum distillation afforded pure 1 of bp 6–8 °C at 27 mm; 124 g (75% yield); spectra as above.

In another experiment performed as above (10-mm pressure), the first reactor was charged with 19 (300 g, 1.06 mol), dried KF (100 g, 1.7 mol), 18-crown-6 (10 g, 0.038 mol), and diethylene glycol dimethyl ether (diglyme, 300 mL) and the second reactor contained ethylene glycol (70 g), anhydrous $MgSO_4$ (60 g), and diglyme (250 mL); yield 100 g (79%).

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Registry No. 7, 98015-51-1; 8, 104483-20-7; 9, 101681-00-9; 10, 99464-81-0; 11, 125413-47-0; 12, 119448-21-4; 13, 99478-15-6; 14, 104483-25-2; 15, 104483-26-3; 16, 91507-75-4; 17, 103418-34-4; 18, 50972-20-8; 19, 98015-52-2; ACE-Cl, 50893-53-3; $HOCH_2CMe_3$, 98015-53-3; MeCHO, 75-07-0; $MeCHClOCO_2Et$, 50893-36-2; $Cl_3CCHClOCO_2Et$, 125413-46-9; $Cl_3CCHFOCO_2Et$, 117635-07-1; Me_3COH, 75-65-0; $HOC(Me)_2CH_2CH_3$, 75-85-4; HO-Ad, 768-95-6; $HO-CH_2Ph$, 100-51-6; $MeO-p-C_6H_4CH_2OH$, 105-13-5; $HO(CH_2)_6OCO_2CHClCH_3$, 629-11-8; $HO(CH_2)_7CH_3$, 111-87-5; HO(C-

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$H_2)_{17}CH_3$, 112-92-5; $HOCH_2CF_3$, 75-89-8; $HOCH_2C(Me)_3$, 75-84-3; HOPh, 108-95-2; $FCO_2C(Me)_3$, 18595-34-1; $FCO_2C(Me)_2CH_2CH_3$, 104483-21-8; FCO_2Ad, 62087-82-5; FCO_2CH_2Ph, 93942-41-7; $FCO_2(CH_2)_6OCOF$, 119448-11-2; $FCO_2(CH_2)_7CH_3$, 104483-19-4; $FCO_2(CH_2)_{17}CH_3$, 104483-24-1; $FCO_2CH_2CF_3$, 112915-23-8; $FCO_2CH_2C(Me)_3$, 63934-51-0; FCO_2Ph, 351-80-4; $Cl_3CCHClOCO_2CH_2C(Me)_3$, 105595-28-6; $MeCHClOCO_2CH(Me)_2$, 98298-66-9; $MeCHClOCO_2Me$, 80196-03-8; FCO_2Et, 461-64-3; $FCO_2CH(Me)_2$, 461-71-2; $HOCH(Me)_2$, 67-63-0; HOMe, 67-56-1; $ClCH_2OCO_2Bu$-*t*, 35180-02-0; cholesteryl fluoroformate, 65928-85-0; *p*-MeObenzyl chloride, 824-94-2; cholesterol, 57-88-5.

Supplementary Material Available: Spectral (IR, ^1H NMR, and high-resolution MS) and analytical data for carbonates and new fluoroformates (4 pages). Ordering information is given on any current masthead page.

Advantages of Fluoroformates as Carboalkoxylating Reagents for Polar Reactants[1]

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While chloroformates react explosively with DMSO and exothermically with DMF and other tertiary amides, we have found that fluoroformates are stable in these solvents below 100 °C. Several important classes of hydroxyl- and amine-containing organic compounds are insoluble in aprotic solvents less polar than DMSO and DMF and thus cannot be carboalkoxylated in inert media with chloroformates. In this paper, we show that such compounds can be easily and efficiently carboalkoxylated with fluoroformates in DMSO or DMF (NMP). Examples include the *per*-carboalkoxylation of glucose, salicin, adonitol, sucrose, and thymidine in 77–89% yield. KF, or preferably triethylamine, is used as the proton scavenger. While cellulose is only partly carboalkoxylated under these conditions, essentially all of the OH functions in polyvinyl alcohol of average MW 12000 are converted to carbethoxy groups.

Fluoroformates are easily available either by direct exchange of the corresponding chloroformates with KF[3] or by the methodology outlined in the preceding paper.[4] In this latter work, fluoroformates were generated in solvents such as DMF and *N*-methylpyrrolidinone (NMP) and were inert to the reaction medium[5] when made in DMSO.

The stability of fluoroformates in tertiary amide solvents and in DMSO contrasts sharply with the behavior of chloroformates in the same media. Chloroformates acylate DMF and other tertiary amides to give adduct salts **1**,

1 **2**

which mimic and fragment to Vilsmeier reagents.[6] N-Dealkylation, C-deprotonation (of R′), and displacement at R in **1** also occur.[6] Similar adducts **2** are formed in the highly exothermic reaction of DMSO with chloroformates. Ordinarily **2** rearranges to Pummerer type products.[7] When a weak base is included in the medium, Moffatt–Pfitzner–Barton type oxidation products also may be found.[8] Thus, unlike chloroformates, fluoroformates should be effective acylating agents in very polar solvents like DMF and DMSO. The evaluation of fluoroformates in this role is the subject of this paper.

Important classes of organic compounds which often are insoluble in aprotic media less polar than DMSO include amino acids, peptides, carbohydrates, nucleotides, and certain organic salts. It is frequently desirable to carboalkoxylate such compounds either to modify their properties as materials or as part of a synthetic scheme (e.g., introduction of protecting groups). Such acylations ordinarily have been accomplished by one of two classical methodologies. Often the polar reactant in a protic solvent such as water is treated with the chloroformate under conditions which selectively enhance the activity of the required reaction site at the expense of the solvent (e.g., Schotten–Bauman acylations). If the polar reactant contains labile protons, a mild, semipolar, aprotic base such as pyridine may be utilized both as solvent and acid scavenger. Then the medium is an equilibrium mixture including an organic salt in its conjugate base. Also, as the acid produced in the acylation step is converted to its salt, the medium becomes increasingly polar. Because some if not most of the chloroformate reacts with the solvent, both methods often are impractical.

In most experiments used to determine the value of fluoroformates as carboalkoxylating reagents, carbohydrates were chosen as test systems because extensive literature is available to demonstrate the importance of the process in synthetic chemistry and for the modification of materials.[9] Moreover, many specialized techniques and clever tricks are described in published acylation procedures[10] which indicates a continuing need to consider the acylation of each carbohydrate as a special problem and suggests a lack of generally useful methodology. Carbohydrates can also provide a stringent test of reaction efficiency: for a pentol, 90% reaction at each site translates to only a 59% yield of product. Finally, intramolecular

(1) Adapted and condensed from the Ph.D. Dissertation of V. A. Dang, The Pennsylvania State University, University Park, PA, 1986.
(2) Dedicated to the memory of Professor Emil Thomas Kaiser of Rockefeller University, deceased July 18, 1988.
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