Synthesis of Highly Fluorinated Chloroformates and Their Use as Derivatizing Agents for Hydrophilic Compounds and Drinking-Water-Disinfection By-Products

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A rapid, safe, and efficient procedure was developed to synthesize, on a small scale, fluorinated chloroformates often required to perform analytical derivatizations. This new family of agents allows straightforward derivatization of highly polar compounds (with multiple hydroxy, carboxy, and amino substituents) in the aqueous phase, compatible with GC and GC/MS analysis. A goal of this work was to develop a derivatization procedure that would enable the detection and identification of highly polar disinfection by-products in drinking water.

Introduction. – The characterization of highly polar substances dissolved in complex aqueous matrices is frequently challenging due to a lack of direct analytical methods and the difficulty to extract such analytes with organic solvents, especially when these substances have to be determined at trace levels [1]. Drinking-water-disinfection by-products (DBPs), which are formed by the reaction of a disinfectant (such as chlorine or ozone) with natural organic matter and/or bromide, are examples of such substances that are present at trace levels (nM – μM range). Highly polar carbonyl DBPs have been successfully detected and identified by means of derivatization agents such as 'pentafluorobenzylhydroxylamine' [2], 1-(2,4-dinitrophenyl)hydrazine [3], and 4-hydrazino-6-(4-methoxynaphthalen-1-yl)-*N*,*N*-dimethyl-1,3,5-triazin-2-amine [4]. However, experts have predicted that more-polar DBPs are likely formed, but have not been identified due to the lack of appropriate analytical methodologies to enable their detection and identification [1b]. Such potential DBPs are polyalcohols, polyacids, and polyamines, which cannot be extracted and detected by current methods [1b].

Direct-aqueous-sample derivatization represents a promising approach to make hydrophilic functional groups more hydrophobic, but finding appropriate derivatizing agents is difficult, as most of them typically undergo hydrolysis as soon as they come in contact with H_2O or other protic solvents. Alkyl chloroformates [5] have gained increasing popularity in this context, particularly the most-hydrophobic ones [6]. More recently, we and others [7] have investigated the possible use of highly fluorinated chloroformates as aqueous-sample-derivatizing agents for highly polar analytes. The use of fluorinated derivatizing agents makes analytes volatile and increases their

electron affinity, which is crucial for their gas-chromatographic (GC) separation and detection.

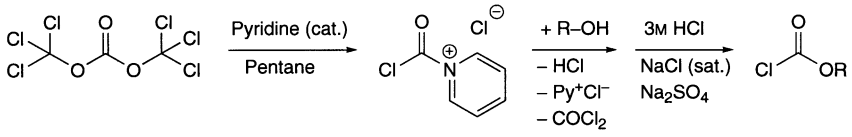
Fluorinated chloroformates are very reactive [7], but commercially not available, since they are relatively unstable and, therefore, have to be synthesized at regular time intervals (*i.e.*, every two months). This aspect hinders the widespread use of these derivatization agents, as few analytical scientists are willing to carry out organic syntheses on a regular basis unless the procedure is fast, easy, and safe. For the above reasons, we have developed a general synthetic protocol for highly fluorinated chloroformates, which, in one or two steps, can be quickly produced in high yields, with minimal manipulation.

Results and Discussion. – Our original procedure [7a] for the synthesis of 2,2,3,3,4,4,5,5-octafluoropentyl chloroformate (OFPCF) involved two critical and inherently dangerous steps: *a*) the use of gaseous phosgene ($COCl_2$) and *b*) the presence of traces of phosgene during product distillation. A high-boiling solvent, dibenzyl ether, was used to make the distillation from the low-boiling OFPCF product feasible. In the new protocol, gaseous phosgene was replaced by triphosgene (bis-(trichloromethyl) carbonate), a stable crystalline solid that can be handled with largely reduced risk. *Abe* and co-workers [8] have used triphosgene to synthesize 2,2,2-trifluoroethyl chloroformate. Based on their experience, we also used triphosgene in our syntheses, but substituted the classical three-neck reaction vessel with a 25-ml septum-sealed vial. The reagents and catalysts were introduced by appropriate syringes, so as to eliminate any risk of phosgene outgassing. Due to the minute quantity of chloroformate used in each derivatization, the limited amount of product obtainable in such a small reaction vessel is ideal for derivatizations of drinking water or other aqueous samples, safer to use than the original procedure, and allows the derivatization of hundreds of samples over the course of one month.

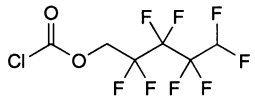
The second change that we introduced in the synthetic procedure was the elimination of the distillation step. Pentane was selected as the reaction solvent for both steps of the synthesis, namely the initial decomposition of triphosgene to phosgene and its subsequent reaction with a highly fluorinated alkyl- or aryl-alcohol to give the corresponding chloroformates. The use of a diluting solvent was necessary to minimize the formation of carbonate by-products.

The progress of the reaction was followed by GC/MS. When all the alcohol was converted to the corresponding chloroformate, the mixture was doubly extracted with HCl and NaCl solutions to eliminate the residual excess of phosgene, HCl, and pyridinium chloride (*Scheme 1*). After phase separation, the pentane extract was stored at $-20°$, before being used as derivatizing agent.

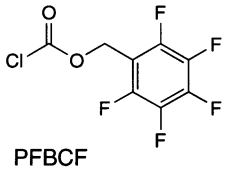
Scheme 1



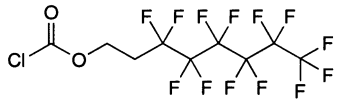
Following the above procedure, four different perfluorinated chloroformates were obtained in yields above 85%: octafluoropentyl (OFPCF), tridecafluorooctyl (TDFOCF), pentafluorobenzyl (PFBCF), and (pentafluorophenoxy)ethyl chloroformate (PFPECF). It is noteworthy that OFPCF and PFBCF, both carrying short spacers between the chloroformate group and the fluorinated moiety, were formed more rapidly and in higher yields (95% or above) than TDFOCF and PFPECF. In contrast, fluorinated alcohols without a methylene spacer, such as 2,3,4,5,6-pentafluorophenol, failed to give any observable chloroformate.



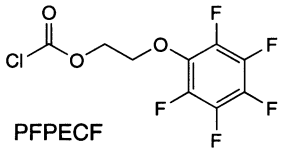
OFPCF



PFBCF



TDFOCF



PFPECF

Evaporation of the solvent (pentane) from the chloroformates was occasionally performed either to characterize the products or to achieve more-efficient derivatization of some particularly difficult analytes when the presence of a separated phase disturbed the direct aqueous-sample derivatization. However, only PFBCF, TDFOCF and PFPECF could be efficiently recovered upon solvent evaporation; the boiling point of OFPCF is too close to that of pentane to allow its concentration. Therefore, we looked for an alternative solvent that would form a single phase with H_2O in the subsequent derivatization step.

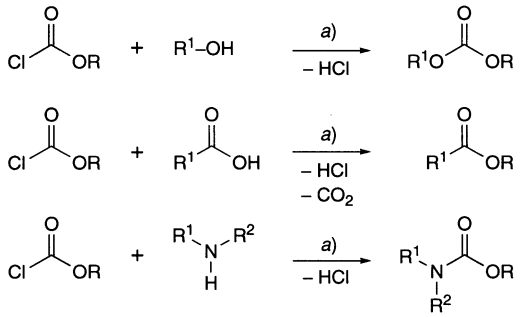
Acetone proved to be an excellent solvent to perform the synthesis of fluorinated chloroformates, yielding almost complete conversion of the fluorinated alcohols. As a consequence, the extractions with HCl and NaCl solutions could no longer be performed, as no phase separation would result. Therefore, the subsequent derivatizations were performed with the crude chloroformate mixture, with no preliminary purification, and little change of the derivatization conditions. Nevertheless, excellent results were obtained for the derivatization of both highly polar and less-polar analytes.

We concluded that acetone as the solvent for the synthesis of fluorinated chloroformates is ideal for most analytical applications of the derivatization procedure. First of all, the small excess of phosgene, still present in the crude reaction mixture, increases the stability of the chloroformates, allowing its use over longer time periods. The mixture is stored in the same sealed vial used for the synthesis, can be readily collected with a syringe and added to the sample to be derivatized in alkaline (NaOH) H_2O. This sequence of steps avoids any risk for the operator to inhale phosgene.

The second advantage of acetone as the reaction solvent is that the absence of any purification step considerably decreases the time required for the preparation of the derivatizing agent. Generally, 4 h are sufficient to prepare the chloroformates, but no loss in yield arises by allowing the reaction to proceed overnight. Details on the chloroformate synthesis in both pentane and acetone are given in the *Exper. Part*.

The derivatization of polar, highly hydrophilic compounds with chloroformates converts carboxylic acids to the corresponding esters, alcohols and phenols to carbonates, and amines to carbamates (*Scheme 2*). In primary amines, one or both NH H-atoms may undergo substitution, depending on the chloroformate used for the derivatization and, partly, on the analyte reactivity. For analytes carrying two or more polar functional groups, all these substituents undergo derivatization with excellent yields. In such a case, more than one fluorinated functional group is introduced, which results in increased sensitivity when a detection method based on electron affinity is applied.

Scheme 2



a) aq. NaOH soln. (3M), DCC, pyridine (cat.).

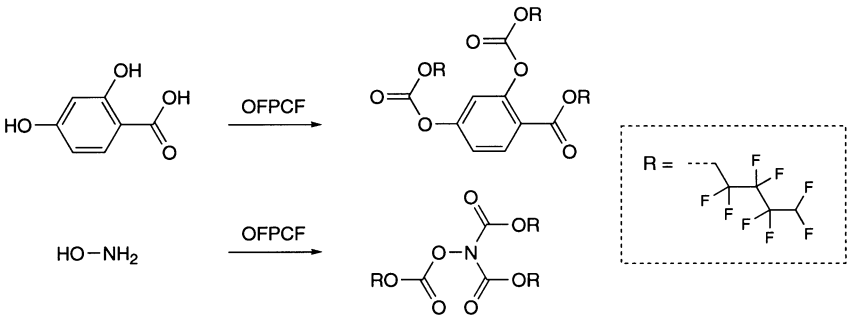
The effects on the derivatization efficiency induced by varying several experimental parameters were investigated for a large set of candidate analytes, including malic acid, resorcinol, 2,4-dihydroxybenzoic acid, hydroxylamine, 3-aminopropanol, 3-aminophenol, and valine, some of which have been suspected to be potential drinking-water DBPs. The experimental parameters investigated included *1*) the amount of derivatizing agent, *2*) the amount of catalyst, *3*) the sonication time, and *4*) the amount of base. Upon varying these parameters, a smooth variation in the derivatization yield was observed, *i.e.*, none of these parameters proved particularly critical, unless dramatically changed. The reported experimental conditions result from this optimization and guarantee effective derivatization of all the analytes tested, at least when OFPCF or PFBCF are used.

The most-critical parameter for the derivatization repeatability appears to be the efficiency of sample mixing performed by ultrasonic emission. Excellent repeatability was achieved by introducing the reaction tube in a bath where the ultrasound-emitting tip of the sonicator was maintained at a fixed position (1 cm) from the reaction tube.

All the chloroformates tested reacted similarly, but the derivatization yields and the degree of substitution on the analytes with more than one active H-atom varied considerably for the different derivatizing agents. With OFPCF, complete substitution of all active H-atoms of 2,4-dihydroxybenzoic acid and hydroxylamine was achieved, as

shown in *Scheme 3*. Extensive investigation of the reactivity differences among the four perfluorinated chloroformates is underway. Preliminary results observed for a limited set of polar substances seem to indicate that OFPCF and PFBCF have a wide applicability, whereas TDFOCF and PFPECF failed to derivatize some of the candidate analytes. A comprehensive comparison of the various perfluorinated chloroformates together with the corresponding analytical performances will be reported in in a forthcoming publication.

Scheme 3



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Experimental Part

2,2,3,3,4,4,5,5-Octafluoropentyl Chloroformiate (OFPCF). Bis(trichloromethyl)carbonate (1 g, *ca.* 3.5 mmol) was dissolved in pentane (5 ml) and cooled to $-15°$ in a septum-sealed 25-ml vial. Pyridine (160 µl, 2 mmol) was added with a syringe perforating the teflon septum, and the soln. was stirred for 1 h. Then, 2,2,3,3,4,4,5,5-octafluoropentan-1-ol (280 µl, 2 mmol) in pentane (8 ml) was slowly added *via* syringe, while maintaining the soln. at $-15°$ and eliminating equal volumes of gas from the vial with the same syringe before each addition, which were passed into an Na_2CO_3 soln. After 6 h, no more alcohol was detected in the reaction mixture. The resulting soln. was extracted with 3M aq. HCl soln. (5 ml) and brine (5 ml), within the reaction vial, and dried (Na_2SO_4). Yield: 95%. The sole reaction byproduct was bis(octafluoropentyl)carbonate (*ca.* 5%). The OFPCF pentane soln. was stored at $-20°$. Both NMR and mass spectra of the product were identical with those previously reported [7a]. The synthesis in acetone was performed as described above, but the extractions with HCl and brine were omitted, and the crude reaction mixture was used in the subsequent derivatizations. Completion of the alcohol conversion was favored by gradually raising the temp. to 0°. Yield: 95%.

2,3,4,5,6-Pentafluorobenzyl Chloroformate (PFBCF). The synthesis of PFBCF was performed as described for OFPCF, except for the following changes: *1*) the temp. was maintained at 0° throughout the entire reaction; *2*) four 2-ml aliquots of pentafluorobenzyl alcohol (396 mg, 2 mmol) in pentane or acetone were added at 20-min time intervals. The yields were *ca.* 92%, with slightly more bis(pentafluorobenzyl) carbonate formed (*ca.* 8%). Characterization of the product was reported in [7c].

3,3,4,4,5,5,6,6,7,7,8,8,8-Tridecafluorooctyl Chloroformate (TDFOCF). The same procedure described for PFBCF was used, but the four aliquots of 3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctan-1-ol (440 µl, 2 mmol) were added at 40-min time intervals, and the mixture was warmed to r.t. after the first addition to compensate for the lower reactivity of the alcohol. Yields: 90–93%. Some unreacted alcohol (*ca.* 5%) remained in the reaction mixture. ^{19}F-NMR (376 MHz, CD_3COCD_3): -82.23 (*m*, 2 F); -114.60 (*m*, 2 F); -122.97 (br., 2 F); -123.96

(br., 2 F); – 124.66 (br., 2 F); – 127.32 (br., 3 F). ^{13}C-NMR (100 MHz, pentane/$CDCl_3$ 5 :1): 150.6, 122.6 – 105.8 (*m*, 6 C); 62.7 (*t*, OCH_2, $J = 4.6$); 30.7 (*t*, CH_2CF_2, $J = 22.2$). CI-MS (isobutane): 427 (100, $[M + H]^+$), 429 (36).

2-(2,3,4,5,6-Pentafluorophenoxy)ethyl Chloroformate (PFPECF). As for TDFOCF, with 296 µl (2 mmol) of 2-(pentafluorophenyl)ethanol. Yield: 86%. The carbonate by-product accounted for 11%, and 3% of unreacted alcohol remained in the reaction mixture. ^{19}F-NMR (376 MHz, CD_3COCD_3): – 158.64 (*m*, 2 F); – 165.99 (*m*, 1 F); – 166.24 (*m*, 2 F). ^{13}C-NMR (100 MHz, pentane/$CDCl_3$ 5 :1): 150.7, 143.6, 141.1 (*m*); 139.8 (*m*); 137.3 (*m*); 133.5 (*m*); 72.3; 69.5. CI-MS (isobutane): 291 (100, $[M + H]^+$), 293 (35), 211 (81).

Derivatization Procedure. A 2-ml aliquot of the aq. sample to be derivatized was basified with 150 µl of aq. NaOH soln. (3M). Then, the chloroformate soln. was added (150 µl, *ca.* 2 µmol), while sonicating the reaction tube at optimized power and distance from the emitting tip. Immediately after, 3 µl of a sat. soln. (400 g/l) solution of dicyclohexylcarbodiimide (DCC) in pyridine were added, and the reaction was allowed to proceed for 10 min under sonication. The products were extracted with 600 µl of hexane for 1 min. The org. layer was separated and analyzed by GC/MS in the chemical ionization (CI) mode. When pentane instead of acetone was used, only 100 µl of aq. NaOH soln. (3M) was added to the aq. sample. The remaining conditions were identical. The hexane solns. of the derivatization products were stable for a few days, so several analytical samples could be derivatized and stored during the day, and automatically processed overnight.

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