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Activation of weak nucleophiles: polyfluorocarbamates from polyfluoroalcohols via a fast radical reaction

Marc Soto[a], Helena Comalrena[a], Ursula Balduzzi[a], Gonzalo Guirado[a], Vega Lloveras[b,c], José Vidal-Gancedo[b,c], Rosa María Sebastián[a,*], Jordi Marquet[a,*]

[a] Departament de Química, Universitat Autònoma de Barcelona, Cerdanyola del Vallès, 08193 Barcelona, Spain
[b] Institut de Ciència de Materials de Barcelona, Consejo Superior de Investigaciones Científicas, Cerdanyola del Vallès, 08193 Barcelona, Spain
[c] CIBER-BBN, Barcelona, Spain

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ABSTRACT

A new fast radical mechanism has been observed for the reaction of polyfluorinated alcohols and phenylisocyanate, very sensitive to the change of solvents and the concentration of reactants. The acidity of polyfluoroalcohols seems to be responsible for the observed new reactivity and evidences from kinetic studies, electron paramagnetic resonance, cyclic voltammetry, and photostimulation suggest that polyfluoroalkoxy radical is the key intermediate in the chain. To the best of our knowledge, it is the first time that a radical mechanism is described for the preparation of carbamates.

A lot of attention has been given to the synthesis of fluorinated organic materials.[1] Polyfluorinated organic compounds have very interesting properties such as high thermal and chemical stability, hydrophobicity and oleophobicity, and low surface energy,[2] and their applications range from anesthetics to oxygen transport agents among many others, especially in the fields of pharmaceutics and materials science.[3] In addition, the demonstrated usefulness of biphasic fluorinated chemistry has increased the interest in their synthesis and the study of their properties.[4] On the other hand, carbamate fragments enter into the composition of numerous drugs and pesticides and polyfluoroalkyl carbamates have been synthesized and shown to have potential applications in these fields.[5] In the area of materials, highly fluorinated polymers have found applications as thermoplastics, elastomers, coatings, membranes, etc. Among those highly fluorinated polymers, fluorinated polyurethanes represent a promising class of compounds.[6] Therefore, the study of fluorinated polyurethanes has attracted considerable interest in recent years.[7] On the whole, however, and with a few exceptions, these compounds have not yet developed all their potential, among other reasons, due to a shortage of basic knowledge on the fundamental chemistry involved in their synthesis.

The standard approach to produce carbamates consists in the reaction between an isocyanate and an alcohol.[8] However, polyfluorinated alcohols are significantly more acidic than normal alcohols (ethanol $pK_a = 29.8$; 2,2,2-trifluoroethanol $pK_a = 23.5$; iso-propanol $pK_a = 30.3$; hexafluoro-iso-propanol $pK_a = 17.9$ in DMSO)[9] and show a very low nucleophilicity in polar reactions. Thus, polyfluorinated alcohols do not react with alkyl isocyanates and react slowly with aromatic isocyanates at room temperature, catalysis (amines[5b,12c] or dibutyltin derivatives[10]), or highly electrophilic carbamates (aroxysulfonylcarbamates),[11] being necessary for the reactions to proceed. Alternative approaches include the catalyzed reaction of fluorinated carbonates with amines[12] or the electrochemically induced Hofmann rearrangement.[13]

In 2005, some of us reported a fast radical chain mechanism in the polyfluoroalkoxylation of aromatics through NO_2 group displacement.[14] Based mainly on theoretical studies we proposed a mechanism that included the intermediacy of the polyfluoroalkoxy radical. In the present Letter, we describe that in certain conditions, polyfluorinated alcohols react with phenylisocyanate in a very fast radical reaction that includes the polyfluoroalkoxy radical as a key intermediate. Full evidences come from cyclic voltammetry (CV) and Electron Paramagnetic Resonance (EPR) experiments. This finding opens a new avenue for the reactivity of very non nucleophilic polyfluorinated alcohols.

Trifluoroethanol (TFE), 1*H*,1*H*-perfluoro-1-octanol, and hexafluoro-iso-propanol (HFIP) react very fast with phenylisocyanate (PhNCO) at room temperature in DMF (Scheme 1). In Table 1, yields and reaction conditions are described.

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[*] Corresponding authors. Tel.: +34 935811029; fax: +34 935812477 (J.M.).
E-mail address: jordi.marquet@uab.cat (J. Marquet).

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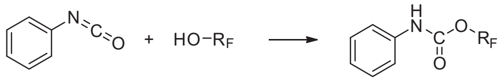


Scheme 1. Synthesis of fluorinated phenylcarbamates.

Table 1
Conversion percentage[a] at 10 min for the reaction of phenylisocyanate with alcohols in DMF

#	Alcohol[b]	Galvinoxyl[c] (%)	Conversion of PhNCO[a]		
			100[d] (mM)	10[d] (mM)	1[d] (mM)
1	CF_3CH_2OH	0	30	55	85
2		15	26	≈0	1,7
3	CH_3CH_2OH	0	29	15	–
4		15	–	17	–
5	$CF_3(CF_2)_6CH_2OH$	0	12	80	35
6		15	15	10	7
7	$(CF_3)_2CHOH$	0	55	63	47
8		15	50	19	2
9	$(CH_3)_2CHOH$	0	–	19	–

[a] Conversion determined by GC using hexadecane as internal standard.
[b] Initial ratio alcohol vs. phenyl isocyanate (2:1).
[c] Molar percentage of the radical scavenger galvinoxyl.
[d] Initial concentration of PhNCO, $[PhNCO]_0$.

The efficiency shown by these reactions constituted a surprise since polyfluorinated alcohols are well known poor nucleophiles. Therefore, a preliminary mechanistic study was undertaken on the reaction of TFE with phenylisocyanate, using as a reference the corresponding reaction of ethanol (Table 1, entries 1 and 3). Thus, no reaction was observed between ethanol and phenylisocyanate (1 mM alcohol, entry 3), whereas a 85% conversion of phenylisocyanate into the corresponding phenylcarbamate was obtained when using TFE in the same conditions and reaction time (Table 1, entry 1).

The reaction of TFE with phenylisocyanate proceeds at high rates in some polar aprotic solvents as DMF, DMSO, and HMPA, but fails completely in acetonitrile, propylenecarbonate, and acetone. On the contrary, the reference reaction of ethanol was much less sensitive to the solvent. In addition, on increasing the reactants concentration, from 10 to 100 mM (phenyl isocyanate concentration, keeping the relationship isocyanate/alcohol 1:2), the observed effect in the reaction conversion is opposite for TFE and ethanol (Table 1, entries 1 and 3).

The reaction of TFE with phenylisocyanate was carried out in the standard conditions (10 mM of phenylisocyanate, and DMF at room temperature) in the presence of a substoichiometric amount (15% molar) of galvinoxyl as a radical scavenger. The reaction was completely stopped (Table 1, entry 2), and no conversion at all was observed even after 45 min. On the contrary, the reference reaction of ethanol with phenylisocyanate in the same conditions showed no effect upon the presence of the radical scavenger (Table 1, entry 4). It reached a 50% conversion after 45 min, thus confirming the operation of a polar mechanism in this case, and suggesting the existence of a radical chain mechanism in the reaction of TFE with phenylisocyanate. This proposal of a fast radical reaction was supported by the fact that the reaction of TFE with phenylisocyanate that failed completely in ACN, could be photostimulated (30% conversion after 10 min under UV irradiation, medium vapor Hg lamp, Pyrex filter).

This behavior was general for other polyfluorinated alcohols as it is described in Table 1 (entries 5–8).

The hypothesis of a radical chain mechanism in the reaction of polyfluorinated alcohols with phenylisocyanate was deeply investigated for the case of TFE. EPR experiments supported the hypothesis since radical intermediates were detected by means of a spin trap. We used two different spin traps. 2-methyl-2-nitrosopropane (MNP) is a general spin trap and is particularly suitable for the detection of carbon-centered radicals while 3,3,5,5-tetramethylpyrroline-*N*-oxide (TMPO) works very well with oxygen-centered radicals.[15] Using TMPO as a spin trap, a double triplet absorption could be observed ($a(1\,N) = 12.70$ G; $a(1H) = 6.91$ G; $g = 2.0062$) that once properly simulated was attributed to the radical adduct of TMPO with the trifluoroethoxy radical ($CF_3CH_2O\boldsymbol{.}$), (Fig. 1a).[16]

The behavior, stability, and electrochemical properties of the trifluoroethoxy radical were studied using CV (DMF + 0.1 M n-Bu_4NBF_4, see Supplementary data). A one electron oxidation wave at 1.05 V versus SCE appears in the forward scan (from 0.0 to 1.6 V), whereas an irreversible reduction wave at −0.93 V versus SCE is observed in the cathodic back scan (from 1.6 to −1.6 V). It is important to remark that when the CV is scanned first in cathodic direction, the irreversible reduction wave at −0.93 V does not exist while the oxidation wave at 1.05 V appears uncharged on the reverse scan. The voltammogram of trifluoroethoxy anion at higher scan rates (5.0 V s^{-1}, see Supplementary data), presents a reversible one-electron oxidation wave with $E° = 0.95$ V versus SCE. That is, if there are no chemical reactions linked to electron transfer, one-electron wave is observed which corresponds to the formation of the specie A ($t_{1/2} = 1$ ms appears).[17] The specie A evolves to a second one, more stable (B), at longer times ($t_{1/2} > 1$ ms). This second specie, B, undergoes one electron reduction giving back the trifluoroethoxide anion (being also TFE detected). Hence, at this point it is fairly to think that specie A is the trifluoroethoxy radical (where the radical is centered on oxygen), whereas specie B should be the most stable isomeric radical specie where the radical is centered on the carbon (Scheme 2).[18]

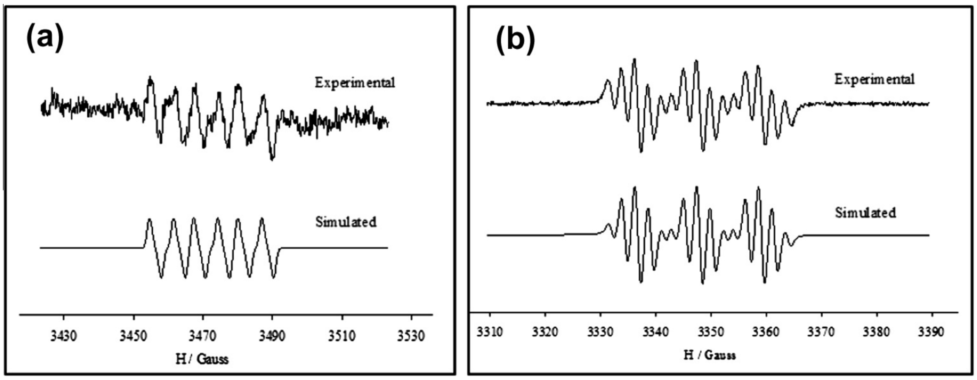
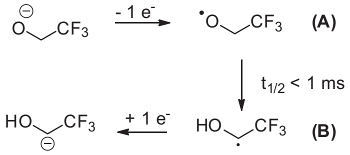


Figure 1. Experimental and simulated EPR spectra of (a) the TMPO adduct resulting from the reaction of TFE with PhNCO in the presence of TMPO, and (b) MNP and B (Scheme 2) adduct.



Scheme 2. Proposed voltammetric cycle for CF_3CH_2ONa.

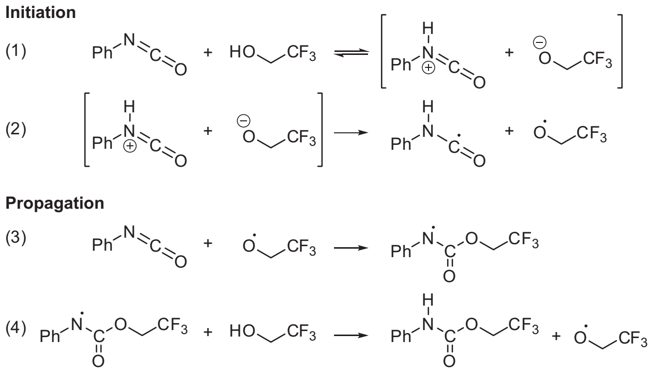
The nature of species A was confirmed by EPR. A controlled potential electrolysis of a 25 mM sodium trifluoroethoxide:MNP spin trap (1:5) solution in DMF + 0.1 M n-Bu_4NBF_4 was electrolyzed at 1.3 V for 10 min at 13 °C. Immediately after, an EPR spectrum of the electrolyzed solution was recorded. The spectrum showed the presence of a radical, that after simulation was attributed to the adduct of species B (radical centered on the α-carbon) and MNP, ($a(1N) = 11.21$ G; $a(1H) = 2.33$ G; $a(3F) = 2.39$ G; $g = 2.0062$, Fig. 1b), thus strongly supporting the voltammetric cycle proposed in Scheme 2.

The radical scavenger experiments in the presence of galvinoxyl were also carried out in the reactions of phenylisocyanate with 1*H*,1*H*-perfluorooctanol and with hexafluoro-iso-propanol (HFIP) with the same result obtained in the reaction of PhNCO with TFE and previously described (Table 1, entries 6 and 8 to compare with entries 5 and 7, respectively).

In Scheme 3 a mechanistic proposal that agrees with the reported facts is advanced. The propagation part of the mechanistic scheme has a key intermediate, the alkoxy radical. The presence of this radical in the reaction mixture has been shown by EPR experiments and its properties established by CV studies. Thus, our results suggest that this radical reacts with phenylisocyanate or, in the absence of phenylisocyanate, quickly evolves to the isomer with the radical centered on the α-carbon. This α-carbon centered radical seems to be more stable than the oxygen centered isomer in agreement with what has been reported in the literature.[19]

Theoretical calculations reported by some of us,[14] indicate that the trifluoroethoxy radical has nucleophilic properties and can compete with the corresponding anion in the elementary step of the propagation cycle. Therefore, the chain mechanism can have a kinetic advantage over the polar mechanism once the proper initiation conditions are reached.

One of the main differences between ethanol and TFE relies in their acidity, polyfluorinated alcohols being more acidic by more than five orders of magnitude.[9] Protonation of the phenylisocyanate by TFE (step 1 in the Scheme 3), even though it is not a thermodynamic favorable process, can trigger the radical mechanism since it would be coupled to an exothermic electron transfer process (step 2 in the Scheme 3). Our results (effect of the solvent) indicate that the solvent can help the proton transfer step through its 'donor properties' (Lewis basicity). Thus, the influence of the solvent in the success of the reaction does not correlate with any of the typical solvent polarity parameters.[20] Instead the results correlate with the 'Donor Number (DN)' scale,[21] and with the 'hydrogen bonding index' as defined in table 1 of Ref. 8. Following previously proposed schemes for urethane formation reactions,[8,22] the aprotic solvent is considered to solvate the complex of phenylisocyanate/alcohol at the active hydrogen to form an ion pair which in our case would undergo the electron transfer process more easily.



Scheme 3. Proposed radical chain mechanism for the reaction of TFE with phenylisocyanate.

The radical mechanism proposed in Scheme 3 can also justify the peculiar concentration effects observed in our reactions (Table 1). They are probably related with the termination steps of the chain mechanism. Thus, the major termination steps in our mechanism will be the isomerization process from oxygen radical to carbon radical, or the dismutation reactions. All termination processes are bimolecular reactions and therefore their rates are very sensitive to the concentration of the reaction mixture, the chain being sustainable only in a narrow range of concentrations. Our results (Table 1) indicate that a balance exists between 'initiation-propagation' and 'termination' steps. These groups of steps must have an opposite effect on the variation of the global rate with the concentration and on the sustainability of the radical chain.

We have demonstrated that the reactions of polyfluoroalcohols with phenylisocyanate can be carried out in very mild specific conditions that allow a new fast radical chain mechanism to become apparent. The acidity of polyfluoroalcohols seems to be responsible for the observed new reactivity and preliminary mechanistic studies indicate that the polyfluoroalkoxy radical is the key intermediate in the chain. Therefore, it seems we are in the presence of an example of a reaction type that is activated by Single Electron Transfer and that by using the appropriate conditions could be rather general for acidic poor nucleophiles. To the best of our knowledge, it is the first time that a radical mechanism has been proposed for the preparation of carbamates.

Currently we are working in establishing the scope, significance, and limitations of the reaction.

Acknowledgments

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Supplementary data

Supplementary data (experimental procedures, spectroscopic data of products, EPR spectra, data table of kinetic studies and conditions for electrochemical measurements) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.09.037. These data include MOL files and InChiKeys of the most important compounds described in this article.

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