Fluorinated carboxylic acids may soon become a relevant class of compounds for new materials development and as synthons in medicinal chemistry. In this report, a potential method based on a hydroboration/copper-catalyzed carboxylation reaction sequence has been computationally explored to check whether these moieties could be synthetically accessible. DFT calculations fully support the possibility of obtaining fluorinated carboxylic acids from simple fluorinated alkenes and gaseous carbon dioxide, paving the way to future preparation of this class of chemicals.

Introduction

Fluorinated carboxylic acids have become relevant synthetic targets because of their potential applications in materials science\(^1\) or as synthons in the preparation of drugs and biologically active precursors (Figure 1).\(^2\)\^-\(^7\) The preparation of fluorinated compounds has largely grown in the last decades due to the key role played by fluorine in medicine.\(^8\)\^-\(^10\) Consequently, many different methods have been developed for introducing functional groups such as CF\(_3\)\(^1\)\(^1\)\^-\(^14\) and SCF\(_3\)\(^1\)\(^5\)\^-\(^17\) into organic substrates. The addition of these fluorinated functional groups largely enhances the lipophilicity of the resulting product, increasing its ability to travel across cell membranes and boosting its metabolic stability.\(^18\) On the other hand, the carboxylic acid moiety is a widespread and versatile functional group that can be employed in the preparation of biologically active molecules or as starting point for further functionalization in drug design.\(^19\)\^-\(^21\) Methods for synthesizing fluorinated carboxylic acids are relatively scarce and usually require precious metals or harsh reaction conditions.\(^22\)\^-\(^27\) Therefore, new synthetic strategies leading to the preparation of these compounds will be soon needed.

In recent years, different metal-catalyzed systems have been reported to introduce CO\(_2\) onto organic substrates,\(^28\)\^-\(^31\) often on multiple C–C bonds.\(^32\)\^-\(^34\) One of these systems, reported by Skrydstrup and Nielsen,\(^35\) was originally devised for hydroboration/carboxylation of disubstituted alkenes and terminal alkynes but could serve as well for the obtention of fluorinated species relevant to biological and medical applications. Here, by means of a comprehensive computational study, we will explore the performance of this catalytic platform for preparing fluorinated carboxylic acids from small fluorinated alkenes and carbon dioxide.

Results and Discussion

The original reaction of Skrydstrup and Nielsen consists of two independent consecutive steps: 1) hydroboration of the double C–C bond with 9-Borabicyclo[3.3.1]nonane (9-BBN), and 2) copper-catalyzed carboxylation of the resulting borylated product with gaseous CO\(_2\) (Scheme 1). The hydroboration stage should be expected to proceed following the classical con-
certed syn addition mechanism. In the case of having a non-symmetric starting alkene two different products may be formed. Hydroboration of alkenes is known to follow the anti-Markovnikov rule, which states that the boron atom will be placed predominantly on the less substituted carbon of the alkene. In any case, when possible, both hydroboration transition states (Markovnikov and anti-Markovnikov) have been computed for all the substrates.

The general catalytic cycle for the carboxylation reaction is described in Scheme 2. The initial catalyst (I1) reacts with CsF to form species I2, this is formally an iodide/fluoride replacement, which is usually assumed to proceed smoothly and, thus, the activation energy associated to this step has not been computationally explored. The reaction proceeds by the addition of the borotray substrate to I2 to deliver complex I3. In this compound the fluoride ligand is bound to the boron atom of the incoming substrate. Then the transmetalation step (TS1) takes place and the organic moiety replaces the fluoride, producing the copper(I) organometallic intermediate I4; consequently, the fluorinated 9-BBN byproduct is released into the reaction mixture. After that, CO2 comes in, forming a non-covalently bound precursor (I5) that evolves into the metal-bound carboxylated product (I6) through the corresponding transition state (TS2). It must be noted that TS2 could correspond to front (with configuration retention) or back (with configuration inversion) S2-type transition state, TS2_F and TS2_B in Scheme 3, respectively; these two transition states, which may be both seen as an electrophilic attack of CO2 onto the copper-coordinated C atom, have been computed in all cases. Finally, the cesium salt of the desired product can be obtained by replacement of the carboxylate with CsF, which takes the catalytic cycle back to species I2. The addition of HCl at the end of the reaction furnishes the final carboxylic acid product. A recent report indicates that the carboxylation of nonbenzylic substrates requires the copper catalyst, whereas benzylic substrates can be carboxylated both with and without copper using the same catalytic platform. This pathway has also been computed for selected cases (vide infra).

The hydroboration/carboxylation reaction of cyclohexene, one of the originally reported substrates, has been studied before computationally exploring the reaction with fluorinated alkenes. In this way a proper computational methodology could be set and further employed to assess the catalytic activity towards the obtention of fluorinated carboxylic acids. The final methodology (vide infra) produces reasonable reaction barriers within a balanced time frame.

The symmetric nature of the double bond of cyclohexene indicates that only one product (9-Cyclohexyl-9-borabicyclo[3.3.1]nonane (Cy-9-BBN)) can be obtained in the hydroboration stage. The transition state barrier associated to this process (28.3 kcal mol−1, at 65 °C) indicates that it should be a a quite slow reaction, explaining the relatively long reaction time required. The carboxylation process of Cy-9-BBN (Table 1) takes place following the catalytic cycle shown in Scheme 2. The corresponding computed relative Gibbs energies can be found in Table 1.

As may be observed the overall reaction barrier, located between intermediate I3 and the front carboxylation transition state TS2_F, requires 28.8 kcal mol−1, a reasonable quantity for a reaction running at 120 °C, and similar to the values found in a previous report. The back-type S2 carboxylation transition state (TS2_B) is found more than 6 kcal mol−1 higher in energy and can be safely ruled out as a competing process.

Once a suitable computational methodology has been found, the hydroboration/carboxylation sequence can be computed for five simple fluorinated alkene substrates: 4-(trifluoromethyl)styrene (tfmstyr), 4,4,4-trifluoro-1-butene (tfmb), hexafluorisobutene (hfib), trifluormethyl vinyl sulfide (tfmvs) and allyl trifluormethyl sulfide (atfms) (Scheme 4). Contrary to cyclohexene, these substrates can form different products in the hydroboration stage, coming from either Markovnikov (M) or anti-Markovnikov (aM) additions. Table 2
shows the computed Gibbs energies for both hydroboration pathways, in all cases the anti-Markovnikov addition is clearly favored, with barriers ca. 1–3 kcal mol\(^{-1}\) lower than their Markovnikov analogues. These values indicate that, at 65 °C, the anti-Markovnikov product will be preferentially formed for all substrates, see Table 2 for the computed product ratios. In all cases except for hfib the computed anti-Markovnikov hydroboration barriers (\(\text{HB}_\text{aM}\)) are low enough (24.4–25.6 kcal mol\(^{-1}\)) to ensure this reaction stage will proceed smoothly under the experimental conditions. Since the anti-Markovnikov products (\(\text{R-B}_\text{aM}\)) are obtained in much larger amounts, only those have been employed as reactants in the computed carboxylation process; although hfib shows a very high hydroboration barrier, it has also been included for completeness.

The computed relative Gibbs energies for the copper-catalyzed carboxylation of the hydroborated fluorinated alkenes can be found in Table 3. As may be observed all the substrates show affordable overall reaction barriers at 120 °C, ranging between 24.5 and 30.2 kcal mol\(^{-1}\).

These barriers correspond always to the carboxylation transition state (TS2). The nature of this transition state is variable: front S\(_\text{E}\)2 (TS2\(_\text{F}\)) for tfmstyr, hfib and atfms, and back S\(_\text{E}\)2 (TS2\(_\text{B}\)) for tfmb and tfmvs.

Table 1. Copper-catalyzed carboxylation of Cy-9-BBN and computed relative Gibbs energies (in kcal mol\(^{-1}\)) for all the species involved in the catalytic cycle.

| Step | Relative Gibbs Energy [kcal mol\(^{-1}\)] |
|------|----------------------------------------|
| I1   | 0.0                                    |
| I2   | −0.3                                   |
| I3   | −4.5                                   |
| TS1  | 22.3                                   |
| I4   | 1.9                                    |
| I5   | 5.5                                    |
| TS2\(_\text{F}\) | 24.3                          |
| TS2\(_\text{B}\) | 30.5                          |
| I6   | −16.6                                  |
| Overall | −23.2                             |

Table 2. Plausible anti-Markovnikov (\(\text{aM}\)) and Markovnikov (\(\text{M}\)) hydroboration pathways, relative computed Gibbs energies (in kcal mol\(^{-1}\)) for all the species involved and computed product ratios at 65 °C.

| Alkene | Alkene + 1/2(9-BBN)\(_2\) | HB\(_\text{aM}\) | R-B\(_\text{aM}\) | HB\(_\text{M}\) | R-B\(_\text{M}\) | aM:M ratio |
|-------|------------------------|-----------------|-----------------|---------------|---------------|------------|
| tfmstyr | 0.0 | 25.1 | −9.7 | 26.5 | −10.3 | 88:12 |
| tfmb | 0.0 | 25.2 | −12.7 | 27.4 | −10.5 | 96:4 |
| hfib | 0.0 | 32.9 | −17.8 | 34.1 | −13.6 | 80:20 |
| tfmvs | 0.0 | 25.6 | −14.6 | 27.5 | −14.2 | 94:6 |
| atfms | 0.0 | 24.4 | −12.1 | 27.4 | −10.8 | 99:1 |

Table 3. Computed relative Gibbs energies (in kcal mol\(^{-1}\)) for all the species involved in the carboxylation catalytic cycle of fluorinated hydroborated alkenes.

| Substrate | I1 | I2 | I3 | TS1 | I4 | I5 | TS2\(_\text{F}\) | TS2\(_\text{B}\) | I6 | Overall | Barrier |
|-----------|----|----|----|-----|----|----|----------------|----------------|----|---------|---------|
| tfmstyr   | 0.0 | −0.3 | −1.8 | 12.1 | −1.5 | 2.8 | 23.5 | 22.7 | −14.3 | −21.4 | 24.5 |
| tfmb      | 0.0 | −0.3 | −4.4 | 13.3 | −1.9 | 3.2 | 23.1 | 24.6 | −14.5 | −23.2 | 27.6 |
| hfib      | 0.0 | −0.3 | −1.7 | 13.9 | −5.5 | −1.5 | 23.4 | 30.7 | −15.7 | −23.1 | 28.9 |
| tfmvs     | 0.0 | −0.3 | −6.8 | 10.2 | −4.2 | −0.4 | 24.3 | 23.4 | −14.4 | −22.5 | 30.2 |
| atfms     | 0.0 | −0.3 | −4.9 | 14.4 | −3.5 | 2.6 | 22.0 | 25.7 | −14.5 | −22.8 | 26.9 |
substrates except for hfib, cannot be correlated with any of the computed as the energy difference between the inductive effects of the fluorinated pending groups, with closer fluorinated substituents hampering the electrophilic attack of CO

The alternative copper-free CsF-catalyzed carboxylation reaction, as proposed by Hopmann et al. has been computed for tfmsty and atfms. In agreement with their results, these two nonbenzylic substrates show a much higher transmetalation barrier than their copper-catalyzed counterparts: 46.1 and 40.1 kcal mol\(^{-1}\) for tfmsty and atfms, respectively, consequently ruling out the CsF-catalyzed pathway. Given the nonbenzylic nature of the remaining fluorinated alkene substrates, this pathway has not been further explored.

Conclusion

This computational exploration clearly indicates that the synthesis of fluorinated carboxylic acids from simple alkenes and carbon dioxide could be easily achievable with the studied catalytic platform. Both the hydroboration and the copper-catalyzed carboxylation stages present affordable reaction barriers under the experimental reaction conditions. Experimental corroboration of the proposed synthetic process is currently underway and will be reported in due course.

Experimental Section

All the structures have been fully optimized in 1,4-dioxane (in PCM, see below) using the Gaussian09 suite of programs with the B3LYP functional. In the optimization process the TZVP basis set of Ahlrichs[46,47] was used for all atoms except for Cs, for which the Def2-SVPD basis set[48] along with the corresponding pseudopotential, was employed. Ultrafine integration grids have been used to ensure satisfactory convergence. This is necessary because some of the species under study present a number of low frequency vibrational modes (< 100 cm\(^{-1}\)) that contribute significantly to the entropy and have to be computed properly. In all cases the solvation energies in 1,4-dioxane are computed with the IEF-PCM[49,50] continuum dielectric solvation model using the SMD[51] radii and non-electrostatic terms. The dispersion correction terms have been included by using the D3 method of Grimme[42–45] with the Becke-Jonhson damping parameter set to zero. These computational settings are named BS1. In all cases frequency calculations are carried out to ensure the nature of stationary points and transition states. Additional single point calculations, including solvation and dispersion corrections, on the optimized geometries are employed to obtain improved Gibbs energy values with larger basis sets (BS2). In these calculations, the B3LYP functional was kept and the Def2-TZVPD basis set was employed to describe all atoms.

The computed Gibss energies were corrected to use a standard state corresponding to species in solution with a standard concentration of 1 M. The final Gibbs energies at a given temperature, computed based on the rigid rotor/harmonic oscillator approach to statistical mechanics, are obtained with the following formula:

\[
G_T = E_{BS2} + H_{corr,BS1} - TS_{BS1} + RT \ln(C(C_1 \text{atm})
\]

where \(E_{BS2}\) is the electronic energy, including the solvent and dispersion terms, obtained with the large basis sets (BS2). \(H_{corr,BS1}\) is the thermal correction to enthalpy and contains the zero-point energy plus the vibrational, rotational and translational energies. Finally, \(S_{BS1}\) accounts for the entropic correction. Both these terms are obtained with the small basis sets (BS1). Gibbs energies as output by Gaussian, which refer to an ideal gas (\(P = 1 \text{ atm}\)) standard
state, were corrected to use a standard state corresponding to species in solution with a standard concentration of 1 M. This was performed by adding an extra term to the Gaussian computed Gibbs energy of each species; this correction is computed as $RT \ln(C_{\text{Gibbs}})$ per molecule at 338.15 and 393.15 K, respectively. Numerically, these corrective terms equal to 2.23 and 2.71 kcal mol$^{-1}$ for an ideal gas at 1 atm and at 338.15 and 393.15 K, respectively. The Fukui nucleophilicity index for the carbon atom bound to copper in species $\text{I}_4$ has been computed from the NBO populations obtained in single point calculations employing the B32 computational settings. This index indicates the tendency of the carbon atom to behave as a nucleophile in a given reaction and is computed as: $f_C^+ = P(N) - P(N-1)$, where $P(N)$ stands for the population of the C atom bound to copper in $\text{I}_4$ and $P(N-1)$ is the population of the same C atom in the monovalent cationic species of $\text{I}_4$ i.e. $\text{I}_4$ minus one electron.

Given the computational nature of this study, and to assess the validity of the methodology employed, the overall reaction barrier of the Cy-9-BBN substrate has been computed with different functionals displaying variable HF amounts, namely PBE[33,34], M06[35] and M062X[36]. A single point calculation for all the species involved ($\text{I}_3$, TS$_2$, F-9-BBN, and CO$_2$) with these functionals and the BS2 functional settings has been performed while the vibrational and enthalpic corrections with B3LYP functionals along with the rest of the functionals tested, an alternative could be M06, which operating at 120 $\text{°C}$, 26 – 31

Conflict of Interest

The authors declare no conflict of interest.

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