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Ab initio study of the mechanism of the formation of *p*-rosolic acid from trifluoromethoxybenzene under HF/Lewis acid conditions

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ABSTRACT

The mechanism of the formation of *p*-rosolic acid from trifluoromethoxybenzene under HF/Lewis acid conditions was studied using *ab initio* methods. A series of cationic intermediates is initiated by the expulsion of a fluorine atom of trifluoromethoxybenzene with anomeric assistance of the trifluoromethoxy oxygen. The resulting difluorocarbonium ion is attacked by a second trifluoromethoxybenzene to generate the first carbon–carbon bond on what will be the central carbon of *p*-rosolic acid. Elimination of phenol results in the formation of cationic intermediate **4** which is susceptible to carbon-alkylation by the same phenol to form the second carbon–carbon bond. Attack on subsequent difluorocarbonium ions by trifluoromethoxybenzene strips trifluoromethyl groups from the downstream intermediates, eventually leading to *p*-rosolic acid, and continues the generation of **4**, each of which initiate a fresh mechanistic series toward another *p*-rosolic acid molecule.

1. Introduction

It was previously reported that trifluoromethoxybenzene, **1**, was observed to form the unexpected side product *p*-rosolic acid, **16**, under HF/Lewis acid conditions [1]. That study found the reaction to be general for trifluoromethoxybenzenes containing electron withdrawing groups and to occur under the influence of all the common high valence metal halide catalysts (Nb, Sb, Sn, Ta, W). This publication uses *ab initio* calculations of gas phase reactions to determine the likely mechanistic pathway by which trifluoromethoxybenzene self-condenses to form *p*-rosolic acid.

2. Computational procedures

Ab inito calculations were performed using the Gaussian 03 suite of programs [2]. Calculations were performed using the B3LYP/6-31G(d,p) model chemistry. In this work, we were interested in the relative ΔE_{rxn} for the progression of a series of intermediates. Stationary points were characterized as a local minimum structure (no imaginary frequencies) by analytical evaluation of their Hessians. When more than one isomer of a particular species existed, the more stable isomer was used in the calculations. The energies are unscaled and zero point corrected. All energies are given in kJ/mol. Energies in Hartrees and kJ/mol for each proposed intermediate or reagent are listed in Table 1. Reaction energies were determined as $\Delta E_{\mathrm{rxn}} = \Sigma E_{\mathrm{prods}} - \Sigma E_{\mathrm{reacts.}}$ There are several literature examples of *ab initio* calculations of Friedel–Crafts reactions [3].

3. Results and discussion

3.1. Main proposed mechanism of reaction (Scheme 1)

The reaction sequence was initiated by the assumed reaction, $HF + TaClF_5 \rightarrow H^+ + TaClF_6^-$ [4]. H^+ so generated reacts with trifluoromethoxybenzene **1** [5] as Reaction Step 1 to generate carbonium ion **2** through the anomerically assisted ejection of fluoride [6]. The reactive **2** is now able to carbon alkylate a second molecule of **1** in Step 2 in a Friedel–Crafts alkylation. These first two reaction steps have a negative ΔE_{rxn} to the extent of −660 and −101 kJ/mol, respectively. The next logical mechanistic step is the elimination of phenol in Step 3. This transformation is surprisingly slightly positive ΔE_{rxn} (+28 kJ/mol) but it is assumed that the energy released from Steps 1 and 2 will fuel the elimination. The alternative elimination of HF has a ΔE_{rxn} of −37.8 kJ/mol, but is a mechanistically unproductive reaction. The

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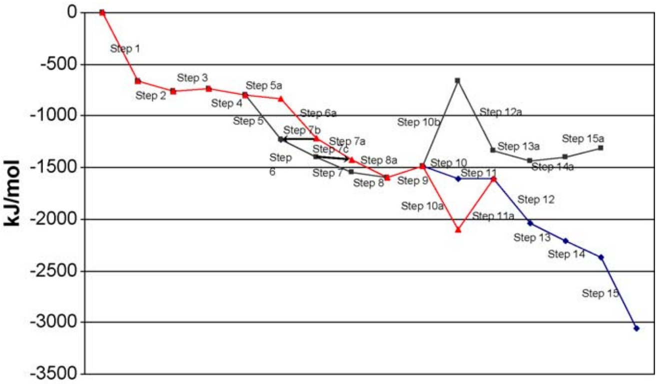
Table 1
Calculated energies of species and intermediates.

Species	$E + \text{zpc}$	
	Hartrees/mol	kJ/mol
H+	0.000000	0
HF	−100.418154	−263,648
F^-	−99.754089	−261,904
CF_4	−437.459153	−1,148,549
Phenol	−307.373652	−807,009
1	−644.402472	−1,691,879
2	−544.235760	−1,428,891
3	−1188.676651	−3,120,870
4	−881.292218	−2,313,832
4alt	−851.318148	−2,235,136
5	−1188.690274	−3,120,906
6	−1088.437658	−2,857,693
6a	−1088.286546	−2,857,296
6b	−1188.343633	−3,119,996
6c	−1188.374188	−3,120,076
7	−1732.903733	−4,549,738
7a	−988.013072	−2,594,028
7b	−1088.208314	−2,857,091
8	−851.666208	−2,236,049
8a	−1632.494625	−4,286,114
9	−751.268208	−1,972,454
10	−1395.629164	−3,664,224
10alt	−1058.616029	−2,779,396
11	−1295.258816	−3,400,702
11a	−1295.446060	−3,401,193
11b	−1395.314956	−3,663,399
12	−1295.258810	−3,400,702
13	−1195.004302	−3,137,483
13b	−1295.154612	−3,400,428
14	−1839.472480	−4,829,535
14b	−1939.592967	−5,092,401
15	−958.238628	−2,515,855
15b	−1058.286233	−2,778,530
16	−957.836659	−2,514,800



Graph 1. Energy diagram for proposed mechanism.

co-product of Step 3 is **4**. Intermediate **4** can be targeted by the just eliminated phenol for another Friedel–Crafts alkylation in Step 4, forming the second of the requisite C–C bonds for *p*-rosolic acid in a step with negative ΔE_{rxn}. The combination of Step 3 and Step 4 is effectively a Fries Rearrangement with a net energy change of −36 kJ/mol.

At this point, the mechanism can take divergent pathways that parallel each other and converge later to a common intermediate. The series of Steps 5 → 6 → 7 → 8 is most likely, due to the triple digit negative ΔE_{rxn} for each of the first three steps. However, the series of Steps 5a → 6a → 7a → 8a only lags by 16.9 kJ/mol by the end of Step 6a and is actually at lower energy by the end of Step 7a. It is possible that some of intermediate **7** may convert to intermediate **8a** for the −24 kJ/mol advantage, thus crossing over to the otherwise less advantageous pathway. None-the-less, both pathways converge back to the same intermediate, **9** and, of course, the same overall ΔE_{rxn}. It is important to note that Step 7 and Step 8a both generate a molecule of **4** which is feedstock for Friedel–Crafts alkylation by trifluoromethoxybenzene, **1**, thus propagating another mechanistic sequence. This propagation step is shown as Step 4alt (Step 4 alternative) as it mimics Step 4.

The conversion of intermediate **9** to *p*-rosolic acid can proceed without further divergence. Step 9 suffers from a positive ΔE_{rxn} (+109 kJ/mol) but every step of the sequence of Steps 10 → 11 → 12 → 13 → 14 occurs with negative ΔE_{rxn} to intermediate **15**, the protonated form of *p*-rosolic acid. It is likely that **15** is the terminal species for this reaction, as, in practice, the product was isolated simply by distillative removal of excess HF. In this case, by only de-solvating the system, the stabilized carbonium fluoride salt of **15** would be isolated. However, it is *p*-rosolic acid, **16**, that is the silica gel chromatographically purified product. We have emulated the proton scavenging effect of silica by using F^- as base in Step 15. Conversion of **15** to **16** in this manner is strongly exothermic.

The overall energetics for the above mechanistic sequence is diagrammed in Graph 1.

3.2. Evaluation of alternative mechanism steps (Scheme 2)

Early in this study, simple de-trifluoromethylation of **3** by nucleophilic attack by fluoride was evaluated. This is represented as Step **3alt** and is unfavorable to the value of +199 kJ/mol. It was this observation that instigated the consideration of de-trifluoromethylation sequences that involved generation of the difluorocarbonium intermediates such as **2**, **6**, **7a**.

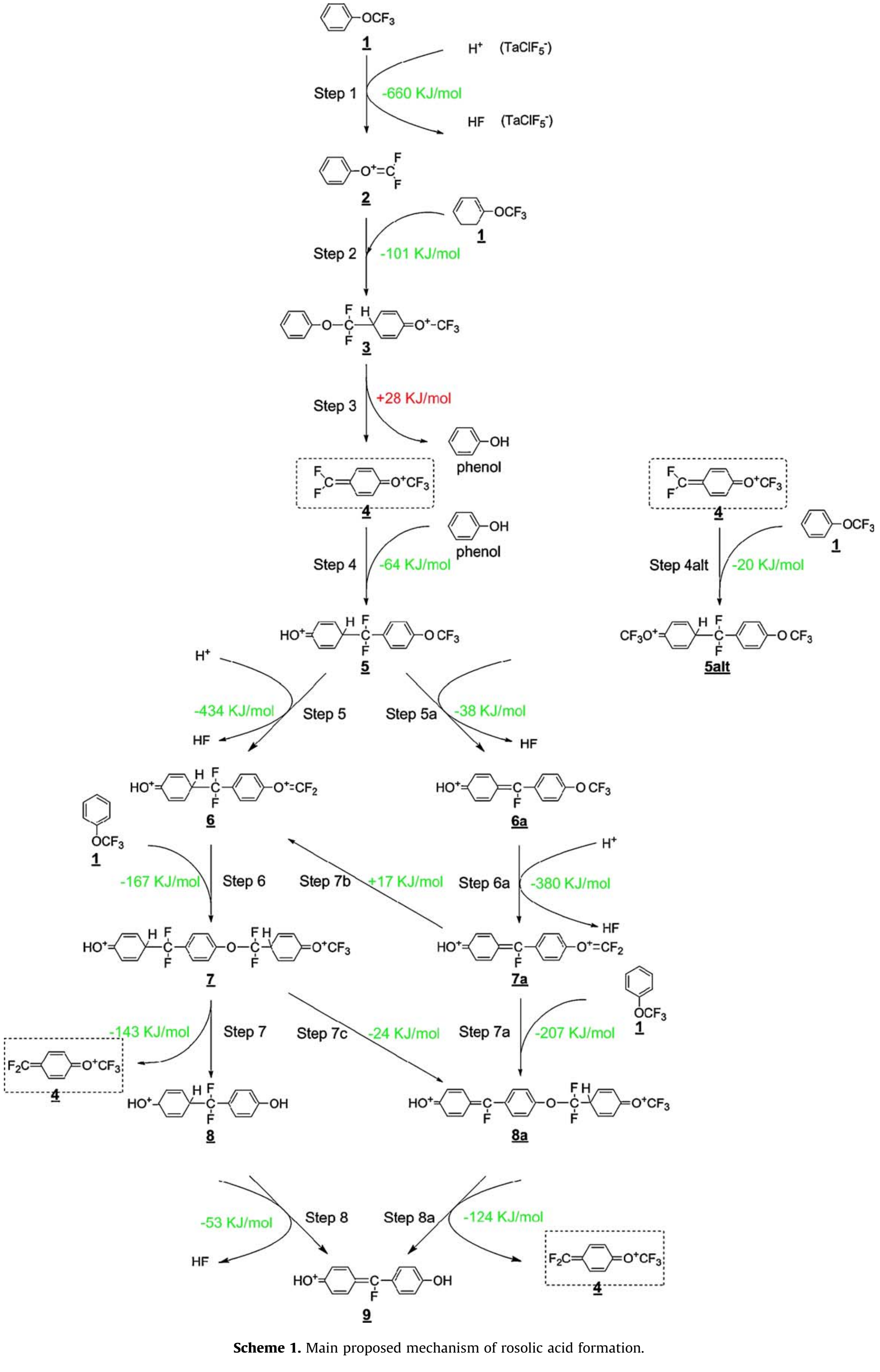
3.3. Evaluation of alternative mechanism steps (Schemes 3 and 4)

Scheme 3 shows several alternative mechanistic steps that were considered for extending the mechanism beyond intermediate **5**. Simple deprotonation of **5** to **6b** is unfavorable by +910 kJ/mol (Step 5b). Likewise, aromatization of **5** to **6c** is ΔE_{rxn} positive with +830 kJ/mol (Step 5c). Another example of an unfavorable neutralization/aromatization is the conversion of **6** to **7b** in Step 6b, Scheme 4. Throughout this study, all attempts to generate neutral species, including aromatizations, resulted in large positive ΔE_{rxn} penalties.

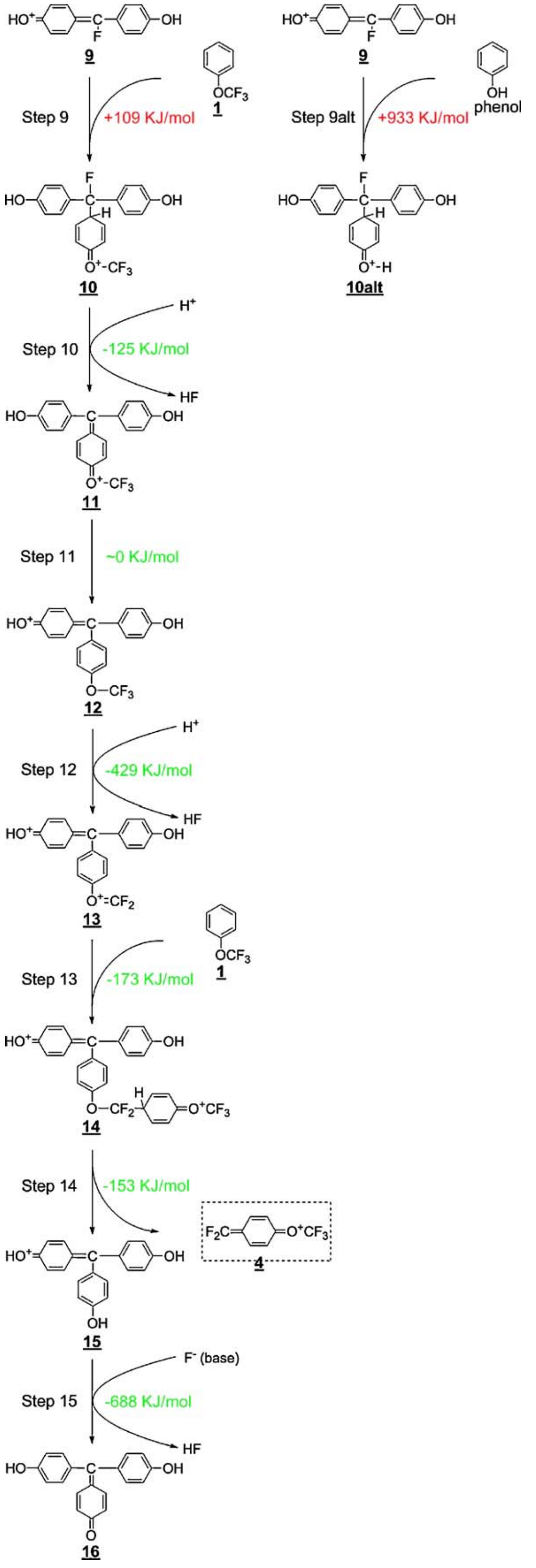
3.4. Evaluation of alternative mechanism steps (Scheme 5)

We have shown that intermediate **10** introduces the remainder of the main mechanistic sequence. However, two alternative pathways were also investigated. The first, conversion of **10** to **11a** (Step 10a) is extremely favorable at −617 kJ/mol! However, the logical following Step 11a is an unfavorable +492 kJ/mol. None-the-less, the combined sequence is −125 kJ/mol and is considered possible. The final product of this sequence is **12** which is the same intermediate generated by Step 11, in effect converging back onto the original mechanistic pathway.

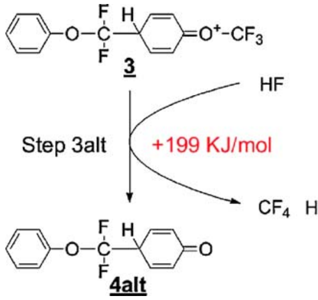
The second alternative pathway is much less likely. Aromatization of **10** as shown in Step 10b is unfavored by +825 kJ/mol (another unfavored aromatization). Even if one were to envision **11b** as a transition and carry the electron-pushing through Step 12a and 13b to intermediate **14b**, the energy cost would still be +35 kJ/mol. This mechanistic series continues with modest, but



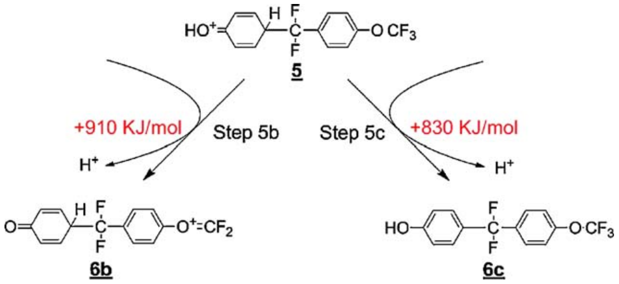
Scheme 1. Main proposed mechanism of rosolic acid formation.



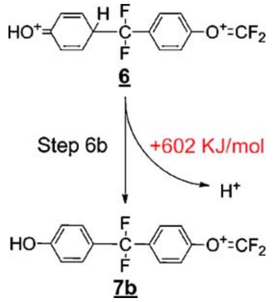
Scheme 1. (*Continued*).



Scheme 2. Step 3 alternative.



Scheme 3. Unfavorable alternative steps.

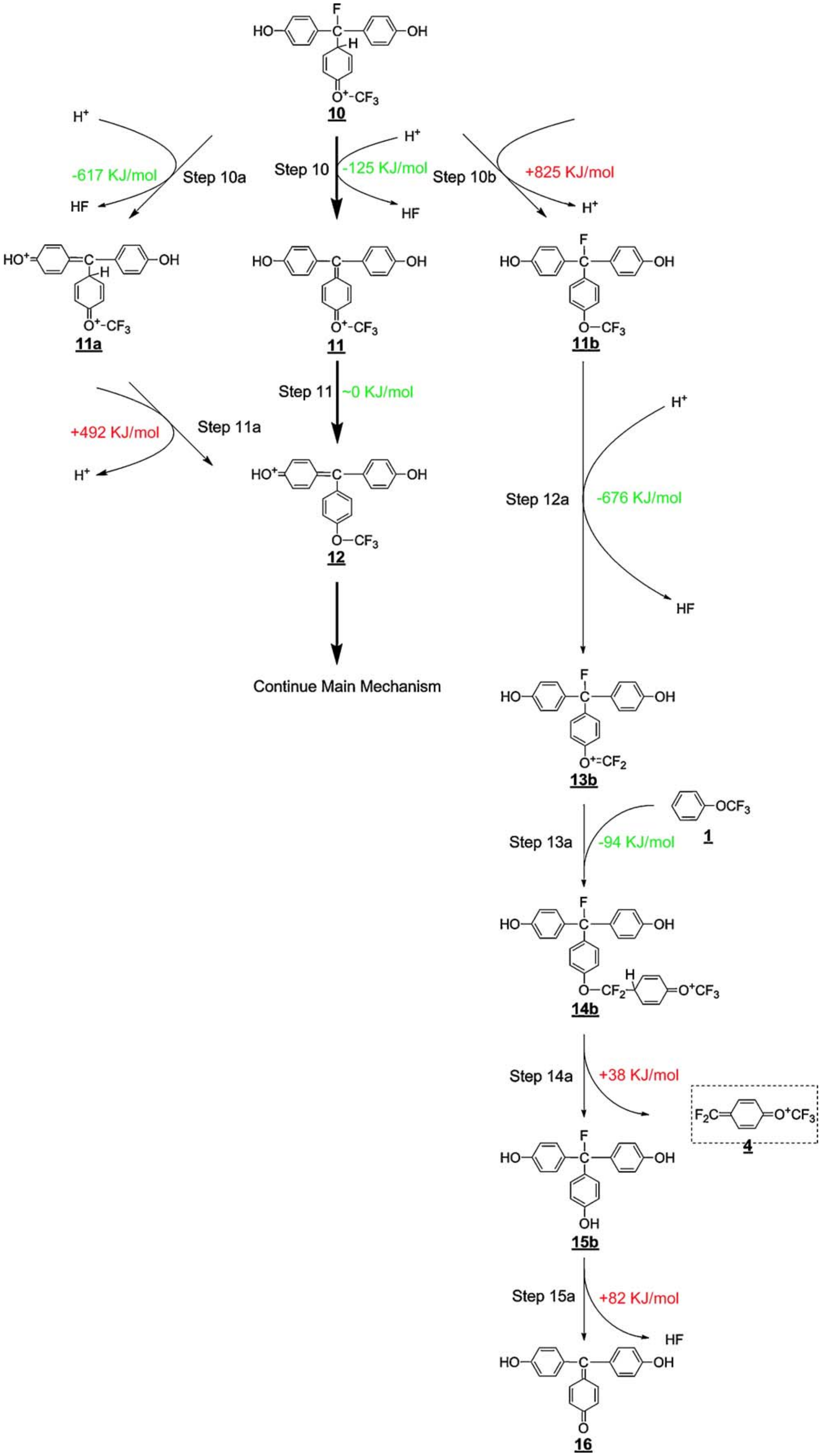


Scheme 4. Unfavorable alternative step.

persistant energy costs to final product **16** after Step 15a. The original proposed sequence of Steps 10 → 11 → 12 → 13 → 14 surely predominates.

3.5. Re-evaluating the endothermic steps

As it stands, the proposed mechanism has ΔE_{rxn} positive reactions at Step 3 and Step 9. The ΔE_{rxn} at Step 3 is +28 kJ/mol and is quite modest. However, the positive ΔE_{rxn} at Step 9 is +109 kJ/mol and, while just a bump in the road (see Graph 1), is of more concern. We sought to circumvent this disfavored step by changing Step 9 from the addition of trifluoromethoxybenzene, **1**, to intermediate **9** to the addition of phenol to intermediate **9**. This transformation (Step 9alt) unfortunately was found to have ΔE_{rxn} of +933 kJ/mol and is therefore not an acceptable alternative. As an aside, in order to access a phenol molecule for this alternative Step 9, it would have to be with-held from Step 4. That could be done by using a molecule of trifluoromethoxybenzene, **1**, as the nucleophile in Step 4 rather than phenol. This Step 4alt is modestly favorable with a ΔE_{rxn} of −20.1 kJ/mol and, as mentioned above, is the means by which molecules of **4** initiate new mechanistic series.



Scheme 5. Step 10 alternatives.

4. Conclusion

The mechanism proposed here for the formation of *p*-rosolic acid from trifluoromethoxybenzene progresses through a series of steps initiated by the formation of cationic species **2**. As such, all subsequent intermediates are cationic or even dicationic. The first two carbon–carbon bonds are introduced within the first four mechanistic steps. However it isn't until six steps later that the third carbon–carbon bond is established.

Each trifluoromethyl group is detached from oxygen as the result of HF/Lewis acid catalyzed transformation to a difluorocarbonium ion that is subsequently attacked by a trifluoromethoxybenzene nucleophile in a Friedel–Crafts reaction. Elimination of phenol or more complex phenolic species generates intermediate **4** which recycles to an earlier mechanistic step (Step 4alt) initiating the formation of another molecule of *p*-rosolic acid even before the first molecule has been formed. In fact, each *p*-rosolic acid sequence spawns the formation of two others (Steps 7 or 8a and 14).

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