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Nucleophilic Radiofluorination Using Tri-*tert*-Butanol Ammonium as a Bifunctional Organocatalyst: Mechanism and Energetics

Young-Ho Oh ¹, Sandip S. Shinde ^{2,*}  and Sungyul Lee ^{1,*}

¹ Department of Applied Chemistry, Kyung Hee University, Deogyong-daero 1732, Yongin-si 17104, Gyeonggi-do, Korea; chem_yhoh@daum.net

² Department of Nuclear Medicine, Molecular Imaging and Radiochemistry, Friedrich-Alexander University Erlangen-Nürnberg (FAU), 91054 Erlangen, Germany

* Correspondence: shinde88@gmail.com (S.S.S.); sylee@khu.ac.kr (S.L.)

Abstract: We present a quantum chemical analysis of the ¹⁸F-fluorination of 1,3-ditosylpropane, promoted by a quaternary ammonium salt (tri-*tert*-butanol)-methylammonium iodide (TBMA-I) with moderate to good radiochemical yields (RCYs), experimentally observed by Shinde et al. We obtained the mechanism of the S_N2 process, focusing on the role of the –OH functional groups facilitating the reactions. We found that the counter-cation TBMA⁺ acts as a bifunctional promoter: the –OH groups function as a bidentate ‘anchor’ bridging the nucleophile [¹⁸F]F[–] and the –OTs leaving group or the third –OH. These electrostatic interactions cooperate for the formation of the transition states of a very compact configuration for facile S_N2 ¹⁸F-fluorination.

Keywords: ¹⁸F-fluorination; tri-*tert*-butanol ammonium; organocatalysis; mechanism



Citation: Oh, Y.-H.; Shinde, S.S.; Lee, S. Nucleophilic Radiofluorination Using Tri-*tert*-Butanol Ammonium as a Bifunctional Organocatalyst: Mechanism and Energetics. *Molecules* **2022**, *27*, 1044. <https://doi.org/10.3390/molecules27031044>

Academic Editor: Viktor O. Iaroshenko

Received: 28 December 2021

Accepted: 1 February 2022

Published: 3 February 2022

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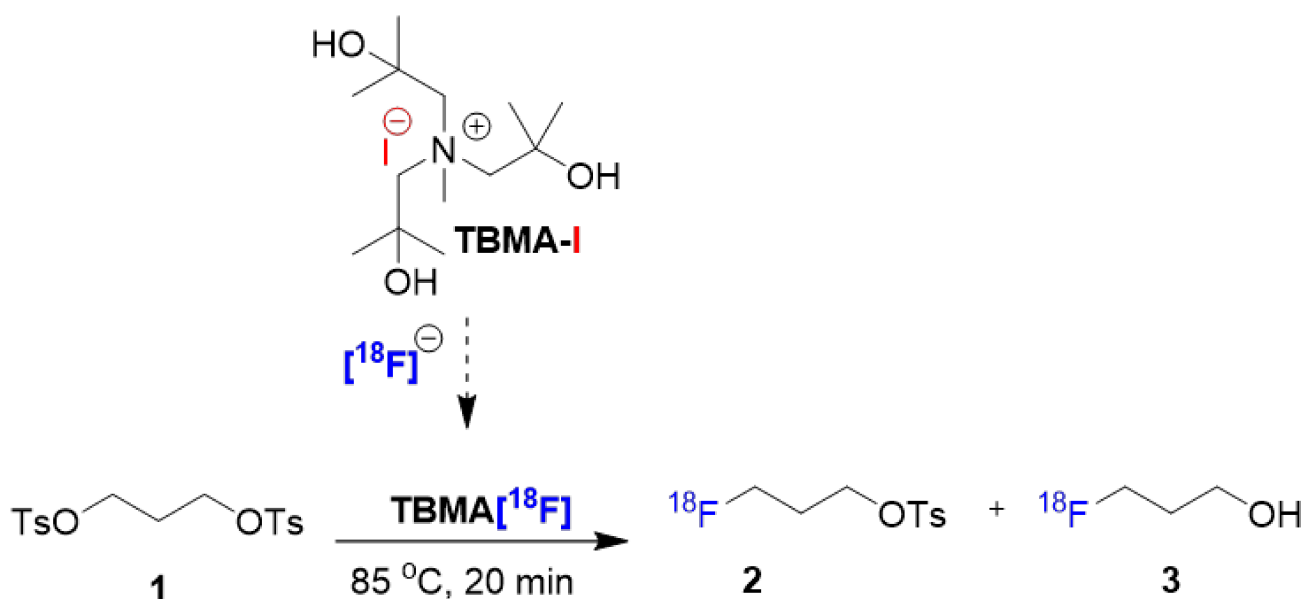
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1. Introduction

The ¹⁸F-fluorination [1–20] of organic compounds is gaining considerable importance for synthesizing chemicals that can be employed as radiotracers for the diagnosis of various diseases [21–23] by the highly sensitive imaging technique of positron emission tomography (PET) [24,25]. Electrophilic substitution reactions [26–28] using the carrier added [¹⁸F]F₂ gas were the earlier method for this purpose, but this approach usually suffers from poor radiochemical yields (RCYs) and from the difficulty of handling the [¹⁸F]F₂ gas. The nucleophilic incorporation of [¹⁸F]fluoride may be considered as a favorable alternative, but so far, this approach mainly requires azeotropic drying and multistep synthetic routes. Generally, this is undesirable for radiofluorination, as ¹⁸F possesses a relatively short half-life of 109.77 min. Various non-radioactive nucleophilic fluorination methods [29–35] have been developed using various phase-transfer catalysts (PTCs) for their application in radiopharmaceutical chemistry in which hydrogen bonding between protic PTC and nucleophile [¹⁸F]fluoride enhances the reaction and selectivity [36,37]. The recent development of tri-*tert*-butanol)-methylammonium [¹⁸F]fluoride (TBMA-¹⁸F) [13] as a promoter for radiofluorination demonstrated an excellent [¹⁸F]fluoride elution efficiency under the reduced basicity of [¹⁸F]fluoride, with moderate to good obtained RCYs. This technique seems to allow a single-step reaction scheme for the synthesis of ¹⁸F-labeled substances, which would be a significant advance. Shinde and co-workers proposed that these excellent organocatalytic properties of the counter-cation may be attributed to the coordinating capacity of the two functional groups (ammonium and hydroxyl) in TBMA⁺. This rate enhancement, promoted by the counter-cation, which would be the first such example for ¹⁸F-fluorination, exhibits significant advantages over more conventional methods using alkali metal cations, M⁺ (M = K, Rb, Cs), because in the latter case the Lewis base promoters such as bulky alcohols [8,32], oligoethylene glycols [8,31,32], ionic liquids [8,33], or crown

ethers [34,35] are required to suppress the harmful Coulomb forces of the counter-cation on the nucleophile.

Here we elucidate the mechanism of the rate enhancement of ^{18}F -fluorination by a quaternary ammonium salt (tri-*tert*-butanol)-methylammonium iodide (TBMA-I) (Scheme 1) by quantum chemical methods. We present the analysis of the ^{18}F fluorination of 1,3-ditosylpropane (**1**), finding that the counter-cation TBMA^+ acts as a bifunctional promoter: the $-\text{OH}$ groups in TBMA^+ act as a bidentate ‘anchor’ by forming hydrogen bonds with the nucleophilic ^{18}F fluoride and the tosylate ($-\text{OTs}$) leaving group or the third $-\text{OH}$. These electrostatic interactions cooperate for the formation of the transition state (TS) of a very compact configuration for facile $\text{S}_{\text{N}}2$ ^{18}F -fluorination. The fluorinating agent TBMA^{18}F reacts with substrate **1** as a contact ion-pair, in which the counter-cation TBMA^+ and the nucleophile $^{18}\text{F}\text{F}^-$ are in close contact.



Scheme 1. Structure of TBMA-I and the ^{18}F -fluorination of 1,3-ditosylpropane [13].

2. Results

Scheme 1 presents the structure of TBMA-I, which is transformed to TBMA^{18}F by Shinde and co-workers' procedure [13], along with the ^{18}F -fluorination of the model substrate 1,3-ditosylpropane **1**. Carrying out the reaction in CH_3CN selectively produced the ^{18}F -labeled product ^{18}F **2** with an RCY of 20% in CH_3CN (Table 1). In Shinde and co-workers' experiments, TBMA^{18}F is recovered from QMA cartridges after treatment with methanolic TBMA-I, and the counter-cation TBMA^+ accelerates the ^{18}F -fluorination, thus the reaction given in Scheme 1 would be the key process.

Table 1. Reactivity of TBMA^{18}F for ^{18}F -substitution of 1,3-ditosylpropane (**1**) [13].

Entry	Promoter	Recovery of ^{18}F fluoride [%]	Solvent (0.5 mL)	RCY[%] (Radio-TLC)	
				^{18}F 2	^{18}F 3
1	TBMA-I	98.8	CH_3CN	21	-

Reactions were carried out using 15.0 μmol of (**1**), K_2CO_3 (1 M, 15 μL), and 39.0 μmol of TBMA-I at 85 $^\circ\text{C}$ for 20 min.

We carried out density functional theory (DFT) calculations for the reaction in CH_3CN and obtained the reaction mechanism and energetics shown in Figures 1 and 2, in which the TSs (structures of pre- and post-reaction complexes and Cartesian coordinates are listed in Supplementary Materials, Figure S1) and the energy profile are depicted.

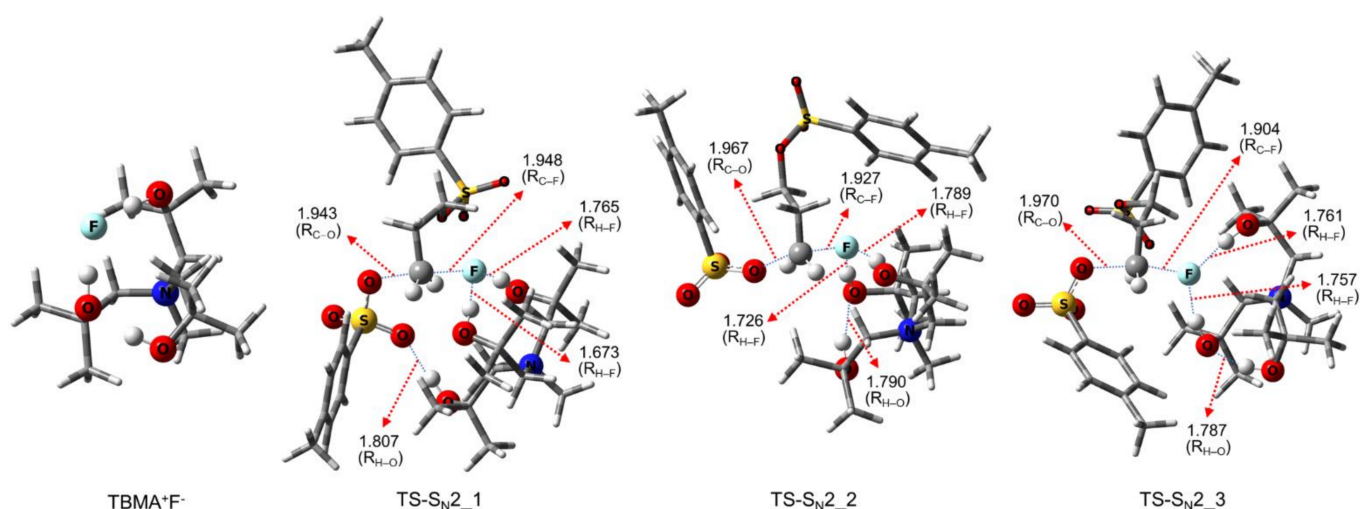


Figure 1. Calculated structures of the free reactant TBMA^+F^- and the transition states of ^{18}F -fluorination using $\text{TBMA-}^{18}\text{F}$ in CH_3CN .

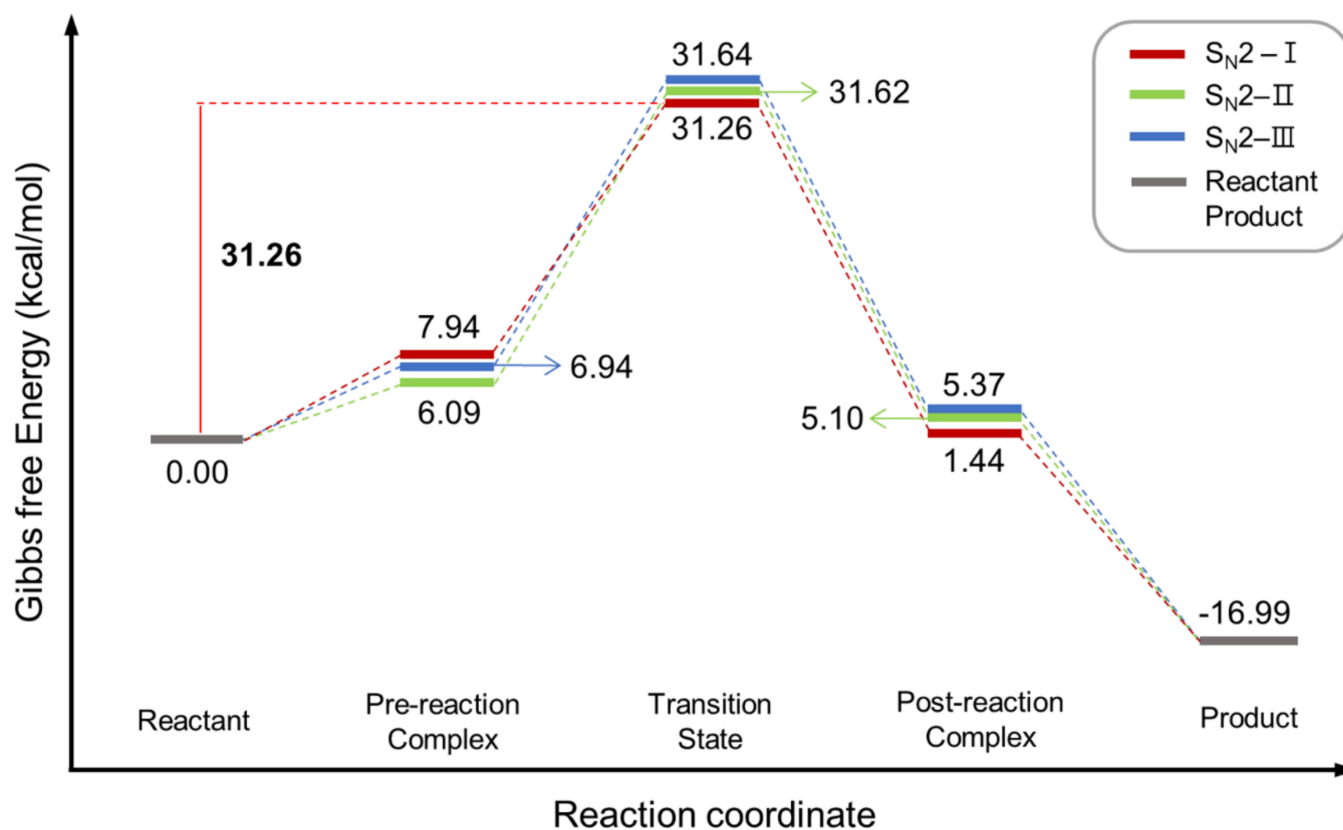


Figure 2. Energetics of ^{18}F -fluorination using $\text{TBMA-}^{18}\text{F}$ in CH_3CN .

We found three $\text{S}_{\text{N}}2$ mechanisms with different TSs and energetics (Figure 1). In all TSs ($\text{TS-S}_{\text{N}}2_1$, $\text{TS-S}_{\text{N}}2_2$, $\text{TS-S}_{\text{N}}2_3$), the ammonium TBMA^+ and the nucleophile $[^{18}\text{F}]\text{F}^-$ are in close contact ($R_{\text{N-F}} = 3.568\text{--}3.735 \text{ \AA}$), indicating that the reaction proceeds via the contact ion-pair (CIP) mechanism. In these TSs, hydrogen bonding between the two hydroxyl $-\text{OH}$ s, the third $-\text{OH}$, or the tosylate ($-\text{OTs}$) leaving group are shown to play a crucial role in the reaction mechanism. Two of the $-\text{OH}$ s bind to the nucleophile $[^{18}\text{F}]\text{F}^-$ in all TSs. The role of the 3rd $-\text{OH}$, however, is somewhat different: in $\text{TS-S}_{\text{N}}2_1$, it interacts with the leaving group $-\text{OTs}$, assisting their departure, whereas in two other TSs, it forms

a hydrogen bond with –OH. These electrostatic interactions help to form compact pre-reaction complexes and TSs (see Supplementary Materials, Figure S1) and TSs that are favorable for S_N2 fluorination. Thus, the two –OH groups act as a bidentate ‘anchor’, and the counter-cation $TBMA^+$ plays its role as a promoter for the ^{18}F -fluorination by providing these two –OHs. The structures of the three TSs in Figure 1 are similar, the difference being in the relative orientation of the –OTs leaving group and $TBMA^+$.

The relative feasibility of the three CIP mechanisms may be assessed by invoking the Curtin–Henderson principle [38]: if the transformation from free reactants to the pre-reaction complex is irreversible (that is, no equilibrium between the two), the reaction path with the lowest Gibbs free energy of the TS (that is, with lowest Gibbs free energy of activation G^\ddagger with respect to the free reactants) is favored, irrespective of the Gibbs free energies of the pre-reaction complexes along the reaction routes. The calculated G^\ddagger for the three reaction routes are 31.3, 31.6, and 31.6 kcal/mol (Figure 2), suggesting that they may contribute almost equally (the difference of 0.3 kcal in G^\ddagger for the case 1 and case 3 routes amounts to a ~1:1.5 ratio of reaction rates at the reaction temperature of 85 °C).

It would be interesting to compare the mechanism of ^{18}F -fluorination by $TBMA$ - ^{18}F shown here with the mechanism [39] of promotion of (non-radiative) fluorination by $[bmim][F]$ in a solvent-free environment, experimentally demonstrated by Magnier and co-workers [40]. In the latter process, the acidic H-atom in the counter-cation $bmim^+$ facilitates the detachment of the leaving group, whereas in the present case it is the –OHs interacting with the leaving group. It is to be noted that in both reactions the fluorinating agents ($TBMA$ - ^{18}F , $[bmim][F]$) act as promoters for the reactions as well. Strong Coulombic attraction between the nucleophile and the counter-cation forces them to react as a CIP.

The relative Gibbs free energies of the pre-reaction complexes in Figure 2, with respect to those of free reactants, are worth mentioning: the (stationary) pre-reaction complexes are predicted to lie higher than free reactants, in contrast with most S_N2 reactions we have studied. Although some theoretical studies [41–43] have suggested that pre-reaction complexes could not be obtained in some cases, the origin of the ‘well-skipping’ S_N2 reactions predicted here is not clear.

One of the salient features of Shinde and co-workers’ procedure is that it produced the S_N2 ^{18}F -labeled product $[^{18}F]2$ exclusively, without E2 elimination [44] products, and this observation is worth mechanistic scrutiny. This aspect of Shinde’s method is very important, because the exclusion of E2 products may be much more significant than the S_N2 yield itself, especially for radiofluorination. Additional purification steps would be critically harmful when using the radiofluorinated product for clinical/diagnostic purposes due to the short lifetime of ^{18}F . Figures 3 and 4 present the two TSs (structures of pre- and post-reaction complexes and Cartesian coordinates are listed in Supplementary Materials, Figure S2) and the corresponding energetics, respectively, of the E2 elimination of **1** in CH_3CN . The Gibbs free energies of activation G^\ddagger for the elimination process are calculated to be 34.1–35.5 kcal/mol (Figure 4), which are considerably higher (by 2.8–4.2 kcal/mol) than those for the S_N2 ^{18}F -fluorination (Figure 2), accounting for the experimentally observed exclusive formation of S_N2 products. Thus, it seems that although the hydrogen bonding between the two –OHs and the nucleophile $[^{18}F]F^-$ may retard the S_N2 fluorination to a certain degree, these electrostatic interactions may also promote the reaction by facilitating the formation of a pre-reaction complex and TS that are much more advantageous for the S_N2 over the E2 process.

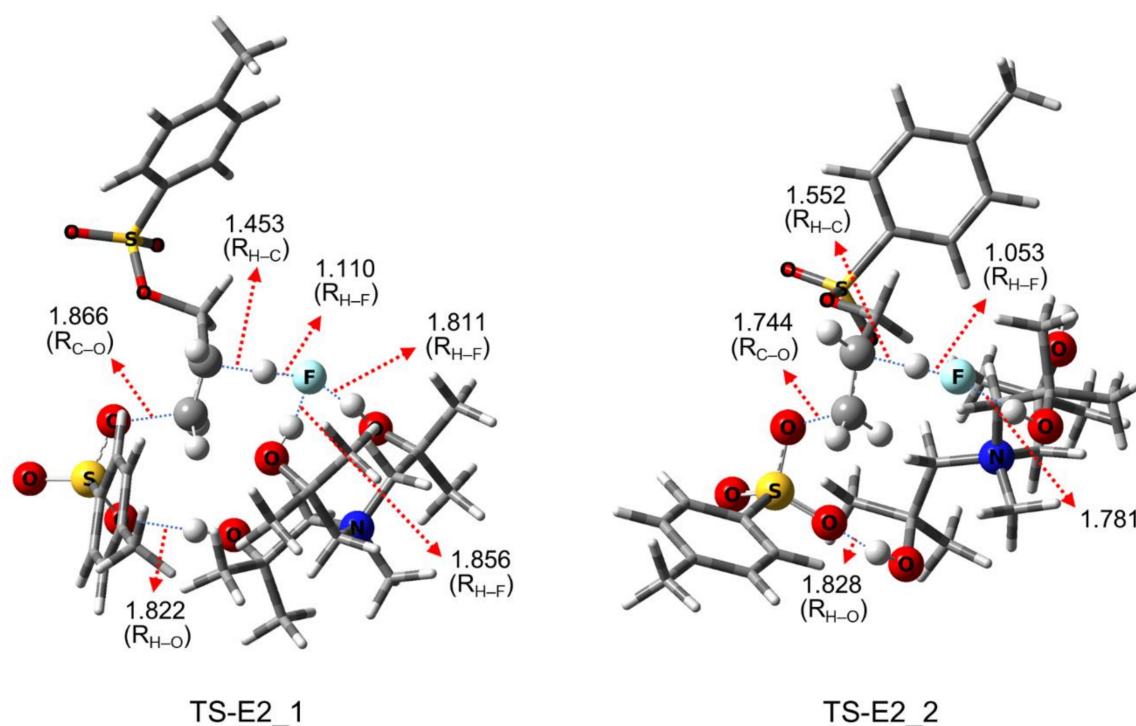


Figure 3. Calculated transition states of the E2 elimination of 1 in CH_3CN .

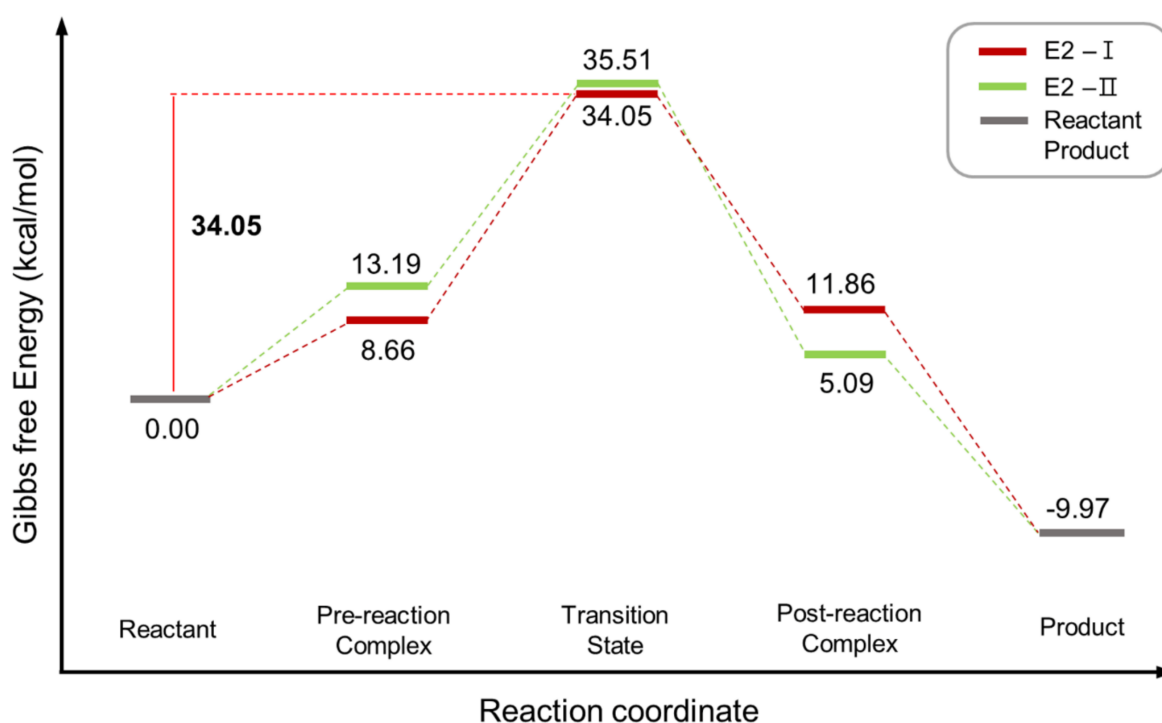


Figure 4. Calculated energetics of the E2 elimination of 1 in CH_3CN .

3. Computational Details

The M06-2X/6-311G** method [45,46] was employed as implemented in Gaussian16 [47], which proved to be very instructive for treating non-covalent interactions [48]. We adopted the cluster/continuum approximation, including the effects of the solvent continuum by the SMD-PCM method [49]. The reference for the zero of the free energy is taken as the 'free' reactant, for which the substrate and TBMA- ^{18}F are separated from each other in the

solution phase. We carried out an extensive (but not exhaustive) search for stationary states over the potential energy surface of the system. Pre-reaction and post-reaction complexes were obtained by verifying that all harmonic frequencies are real. Transition states were obtained by ascertaining the imaginary frequency of the reaction coordinate, and also by performing the intrinsic reaction coordinate analysis.

4. Conclusions

We have presented the quantum chemical analysis to account for the activation of [^{18}F]fluoride by tri-(*tert*-butanol)-methylammonium. The role of the –OHs in TBMA⁺ as a bifunctional organocatalyst has been manifested: the hydroxyl groups function as a bidentate ‘anchor’ to position the nucleophile [^{18}F]F[−] in a configuration suitable for the nucleophilic attack through hydrogen bonding. The elucidation of the underlying mechanism of the present S_N2 processes would help to drive the development of this technique forward, using better ammonium counter-cations (for example, those with other alcohol moieties containing –OHs, such as –CH₂OH, instead of –*t*-BuOH) and schemes (for example, using a less bulky leaving group such as a mesylate, to have more beneficial interactions between the counter-cation and leaving group) for more efficient ^{18}F -fluorination. The application of the present methodology to the nucleophilic radiofluorination of a variety of radiotracers would be highly desirable.

Supplementary Materials: Figure S1: Pre- and post-reaction complexes and the transition states of ^{18}F -fluorination using TBMA- ^{18}F in CH₃CN; Figure S2: Pre- and post-reaction complexes and the transition states of E2 reactions using TBMA- ^{18}F in CH₃CN.

Author Contributions: Conceptualization, S.L. and S.S.S.; methodology, Y.-H.O.; software, Y.-H.O.; formal analysis, S.L., S.S.S. and Y.-H.O.; investigation, Y.-H.O.; resources, S.L. and S.S.S.; writing—original draft preparation, Y.-H.O.; writing—review and editing, S.L. and S.S.S.; visualization, Y.-H.O.; project administration, S.L. and S.S.S.; funding acquisition, S.L. and S.S.S. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by National Research of Korea (NRF-2019R1F1A1057609).

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

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