Origin of Difference in the Reactivity of Aliphatic and Aromatic Guanidine-containing Pharmaceuticals Toward [^{18}F]Fluorination: Coulombic Forces and Hydrogen Bonding

Sung-Sik Lee,[†] Keun Sam Jang,[‡,*] Byung Chul Lee,[§,*] Young-Ho Oh,[†] Sung Wook Park,[†] Dong Woo Kim,[†] Gi Hyung Jang,[†] and Sungyul Lee[†,*]

[†]*Department of Applied Chemistry, Kyung Hee University, Gyeonggi-do 17140, Republic of Korea. *E-mail: sylee@khu.ac.kr*
[‡]*Division of Nuclear Medicine, Department of Radiology, University of Michigan Medical School, Ann Arbor, Michigan, 48109, USA. *E-mail: ksjang0704@gmail.com*
[§]*Department of Nuclear Medicine, Seoul National University Bundang Hospital, Seoul National University College of Medicine, Gyeonggi-do 13620, Republic of Korea. *E-mail: leebc@snu.ac.kr*
Received June 7, 2019, Accepted July 3, 2019, Published online August 13, 2019

Quantum chemical analysis is presented to elucidate the origin of difference in the reactivity of aliphatic *vs*. aromatic guanidine-containing pharmaceuticals toward [^{18}F]fluorination. We focus on the position (near to or far away from the site of reaction) of F^- nucleophile in pre-reaction complexes, as determined by intricate interplay of the Coulombic forces between the ionic species and hydrogen bonding with the –Boc protected guanidine. In [^{18}F]fluorination of aliphatic guanidine compounds, the freely moving nucleophile F^- is positioned close to the site of fluorination irrespective of the length of side chain, in agreement with the observed similar reaction yields for $–CH_2OMs$ and $–CH_2CH_2CH_2OMs$ side chains. As for the effects of positions of –Boc protection, we predict that the effects would to be contrary to the corresponding aromatic case, with the *N*, *N*″-bis-Boc protected guanidine compound being much more reactive than the *N*, *N*′-bis-Boc protected guanidine compound.

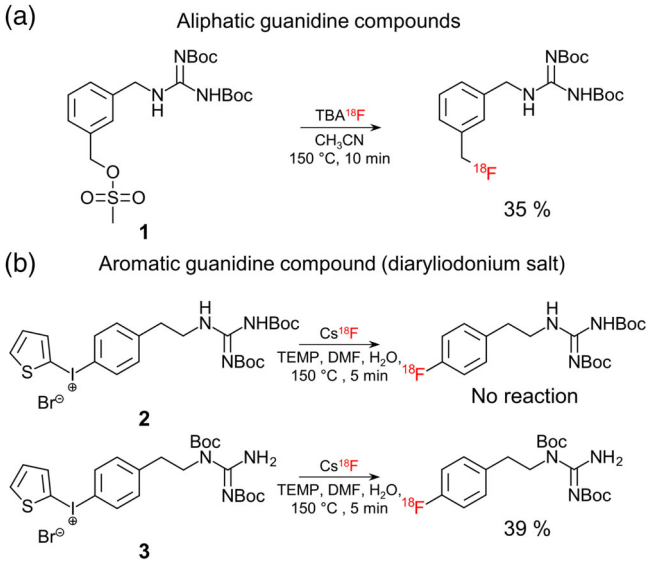
Keywords: Guanidine, Density functional, Radiopharmaceutical, Fluorination

Introduction

Guanidine units are gaining much importance in various biologically active substances and as drug targeting molecules in medicinal chemistry.[1] Radiopharmaceuticals containing guanidine units as in arginine-containing peptides are widely used positron emission tomography (PET)[2–4] and single photon emission computed tomography (SPECT),[5–7] both *in vitro* and *in vivo* studies.[8–13] As a typical guanidine—containing radiopharmaceutical, ^{18}F-labeled guanidine compounds based on MIBG structure such as *m*-[^{18}F]fluorobenzylguanidine ([^{18}F]MFBG), *p*-[^{18}F]fluorobenzylguanidine ([^{18}F]PFBG), and 4-[^{18}F]fluoro-*m*-iodobenzylguanindine ([^{18}F]4F-FIBG) proved to be potential compounds as a neuroendocrine tumor imaging agents for pheochromocytoma and neuroblastoma.[2–4]

Recently, we carried out[14] a series of synthetic approaches toward facile production of guanidine-containing [^{18}F]radiopharmaceuticals by employing various scheme of protecting the guanidine diaryliodonium salts by –Boc, in which we found that the reactivity depended highly on the degrees and positions of –Boc protection. Specifically, [^{18}F]fluorination of the *N*, *N*′-bis-Boc protected guanidine diaryliodonium salt (see Scheme 1) did not proceed at all, whereas the fully (*N*, *N*′, *N*″, *N*″-tetrakis-)-Boc protected diaryliodonium salt exhibited reasonable (with the yield of approximately 30% at 120 °C in 5 min) reactivity for [^{18}F]fluorination. The observed inactivity of *N*, *N*′-bis-Boc protected guanidine diaryliodonium salt is in high contrast with the ready [^{18}F]fluorination of the corresponding aliphatic guanidine mesylate precursor (**1** in Scheme 1) that gave approximately 35% yield in 10 min described previously.[3] It seems that the roles of the guanidine group in these two reactions are very different, probably because of the difference in the nature of interactions between the guanidine group, the nucleophile and the counter-cation (tetrabutylammonium (TBA^+) and Cs^+ in aliphatic and aromatic [^{18}F]fluorination, respectively).

Here we present a mechanistic study by quantum chemical methods on the origin of these interesting observations, focusing on the position of the nucleophile F^-. We show that F^- is more or less free from the influence of the guanidine unit in high contrast with the corresponding reactions of aromatic guanidine compounds. Therefore, the nucleophile F^- may approach the site of reaction (electropositive C atom) with $R_{C\text{-}F}$ distances that are favorable for [^{18}F]fluorination, irrespective of the –Boc protection scheme. We also give discussions for the effects of the length of the side chain on which [^{18}F]fluorination occurs, showing that the position of F^- is similar for $–CH_2OMs$ and –



Scheme 1. Comparison of aliphatic and aromatic [^{18}F]fluorination of –Boc protected salts. (b) from Ref. 3,14.

$CH_2CH_2CH_2OMs$ side chains, in agreement with the experimentally observed similar reaction yields.

Computational Details. We employed the CAM-B3LYP/6-311G** method,[15,16] including the effects of the solvent (acetonitrile) continuum by the COSMO-PCM[17,18] method (dielectric constant = 35.68) as implemented in TeraChem 1.94Beta programs.[19,20] We modeled the -Moc(methoxycarbonyl) and the TEA^+(tetraethylammonium) for –Boc and TBA^+, respectively, to save computational cost.

Results and Discussion

Figure 1 depicts the pre-reaction complexes in aliphatic fluorination of **1** and in aromatic fluorination of **2**. For aliphatic fluorination, two pre-reaction complexes ((MeG-A-01)$_{Pre}$ and (MeG-A-02)$_{Pre}$) are obtained. The most notable difference between them is the orientation of the guanidine plane with respect to the phenyl ring: The guanidine plane is nearly parallel to the phenyl ring in (MeG-A-02)$_{Pre}$, whereas it is almost orthogonal in (MeG-A-01)$_{Pre}$. In the global minimum Gibbs free energy (MeG-A-01)$_{Pre}$ for aliphatic fluorination, intramolecular hydrogen bonds are formed between the guanidine –NH groups and carbonyl O atom in –Moc ($R_N\cdots_H$ = 1.811, 1.923 Å) in approximately six-membered ring. It can be seen that the nucleophile F^- in this pre-reaction complex is situated somewhat far from the guanidine unit, weakly influenced by the bulky counter-cation TEA^+. Thus, F^- seems to be quite free to move around, being finally located nearby the site of reaction (electropositive carbon atom) within a reasonable distance to initiate the reaction ($R_C\cdots_F$ = 3.065 Å) with the resulting yield of approximately 35%. In (MeG-A-02)$_{Pre}$, whose Gibbs free energy $G_{150\ °C}$ is 1.41 kcal/mol above that for (MeG-A-01)$_{Pre}$, the two guanidine –NH groups form

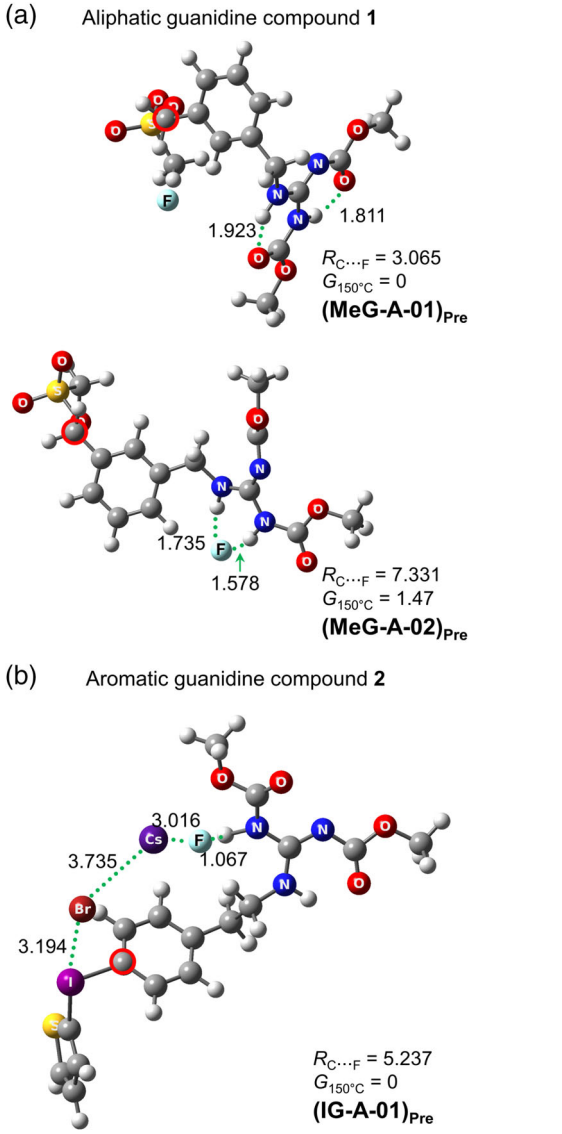
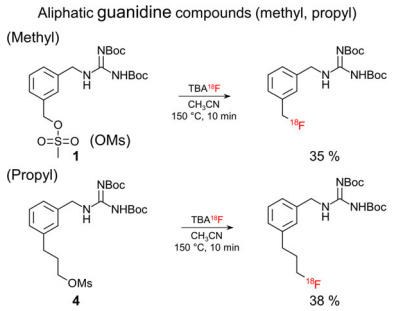


Figure 1. Pre-reaction complexes (a) in aliphatic fluorination of **1** and (b) in aromatic fluorination of **2**. Gibbs free energy in kcal/Mol, and bond lengths in Å. (the TEA^+ is not shown to clarity).

hydrogen bonds with F^-. Because of these hydrogen bonds and the Coulombic influence by TEA^+, F^- is located far away from the reaction center ($R_C\cdots_F$ = 7.331 Å). Thus, this pre-reaction complex can be considered as highly unfavorable toward fluorination, and thus the experimentally observed reasonable yield (approximately 35%) in [^{18}F] fluorination of **1** is attributed to proceeding from the global minimum Gibbs free energy structure (MeG-A-01)$_{Pre}$, in which the nucleophile F^- is brought to near the site of fluorination.

Figure 1(b) shows the lowest Gibbs free energy pre-reaction complex (IG-A-01)$_{Pre}$ in aromatic fluorination of **2** described in our earlier work.[14] In this structure, the nucleophile F^- is influenced by the Coulombic force by the counter-cation Cs^+ and hydrogen bond with the Guanidine–NH group, far away from the site of fluorination, which is



Scheme 2. Experimentally observed effects of chain length on the reaction yield of aliphatic fluorination at *meta* position.[3]

in line with the observed zero reaction yield.[14] Thus, it seems that the difference in reactivity of aliphatic *vs*. aromatic [^{18}F]fluorination (35% *vs*. 0) may be easily understood just by comparing the structures of (MeG-A-01)$_{Pre}$ and (IG-A-01)$_{Pre}$, focusing on the location of the nucleophile F^-. It would be useful to note that this location of F^- is determined by intricate influence of the counter-cation (TEA^+) in aliphatic fluorination of **1**, and by Cs^+, the guanidine –NH group, and the ionic species Br^- and the iodonium in aromatic fluorination of **2**.

Scheme 2 illustrates the experimentally observed effects of length of side chain that is at *meta* position with respect to the guanidine group. Comparing the reaction yields of aliphatic fluorination of the $-CH_2OMs$ *vs*. $-CH_2CH_2CH_2OMs$ side chain indicates that the chain length exerts essentially insignificant influence on the yield of [^{18}F]fluorination (35 *vs*. 38%).[3] It seems that the nucleophile F^- is located near the end of the aliphatic chain irrespective of the chain length, giving very small difference in yield. Figure 2 presents the two pre-reaction complexes that may be feasible for [^{18}F] fluorination of aliphatic guanidine compound containing the side chain $-CH_2CH_2CH_2OMs$. (PrG-A-01)$_{Pre}$ is the global minimum free energy structure in which F^- is close enough to the site of reaction ($R_{C\cdots F}$ = 3.278 Å) probably because of the flexibility of propyl carbon chain. In (PrG-A-02)$_{Pre}$, whose Gibbs free energy is a bit (1.20 kcal/mol) higher than that of (PrG-A-01)$_{Pre}$, the $R_{C\cdots F}$ distance (3.173 Å) is also favorable for [^{18}F]fluorination. However, this pre-reaction complex would contribute much less to reaction because it is less feasible on thermodynamic ground (higher Gibbs free energy) than (PrG-A-01)$_{Pre}$.

Another observed feature in aliphatic *vs*. aromatic [^{18}F] fluorination is the effects of the positions of –Boc protection. It was revealed in our previous work[14] that aromatic [^{18}F]fluorination of **2** did not proceed at all, whereas the *N*, *N*″-bis-Boc protected guanidine compound **3** (see Scheme 1) exhibited good reactivity (with 39% yield in 5 min at 150 °C). Detailed quantum chemical analysis[14] described in showed that the origin of this intriguing observation is the results of Coulombic interactions among Cs^+, F^-, I^+, and Br^- to position F^- near at or far from the site of fluorination in the pre-reaction complexes for [^{18}F]fluorination of **2** and **3**, respectively. To examine the effects of the position

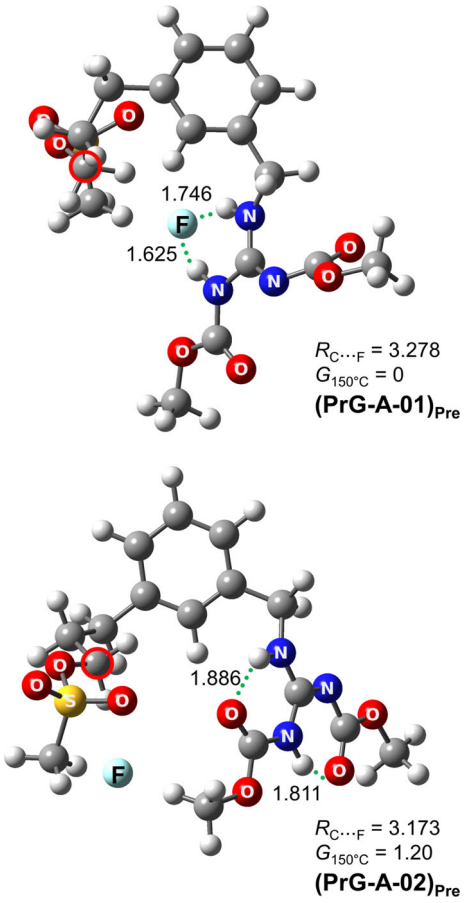


Figure 2. Pre-reaction complexes in aliphatic compound containing $-CH_2CH_2CH_2OMs$ side chain. Gibbs free energy in kcal/Mol, and bond lengths in Å. (the TEA^+ is not shown to clarity).

of –Boc protection on aliphatic [^{18}F]fluorination, we obtained the pre-reaction complexes for aliphatic guanidine compounds protected by *N*, *N*″-bis-Boc for both methyl and propyl side chain.

Figure 3 shows that the C—F distances in the lowest Gibbs free energy pre-reaction complexes for aliphatic [^{18}F]fluorination of *N*, *N*″-bis-Boc protected guanidine compounds for both methyl propyl side chain are slightly larger than that of the compound protected by *N*, *N*′-bis-Boc (3.938 and 4.008 Å, respectively), The origin of this larger C—F distances is that the –NH group forming hydrogen bond with F^- is farther away than in the compound protected by *N*, *N*′-bis-Boc protected compound. In addition, the $-NH_2$ group forms hydrogen bond not only with F^- ($R_{H\cdots F}$ = 1.513 Å in (MeG-*B*-01)$_{Pre}$, 1.479 Å in (PrG-B-01)$_{Pre}$, but also with –Boc in approximate six-membered ring. Consequently, the nucleophilicity of F^- in [^{18}F]fluorination of *N*, *N*″-bis-Boc protected guanidine compounds would be smaller than that of the compound protected by *N*, *N*′-bis-Boc lacking interactions between –NH in guanidine and F^-. We predict that in aliphatic [^{18}F]fluorination, the effects of positions of –Boc protection seem to be in

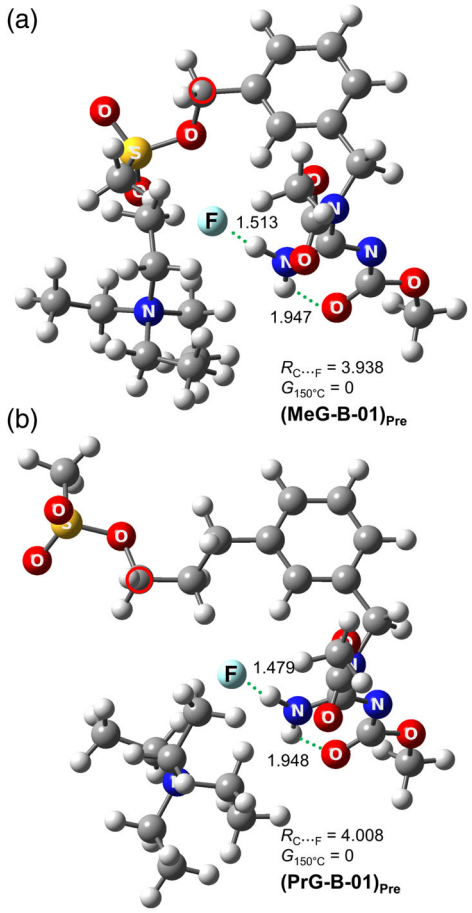


Figure 3. Lowest Gibbs free energy pre-reaction complexes in aliphatic fluorination of guanidine compounds protected by *N*, *N*″-bis-Boc with (a) –CH_2OMs and with (b) –$CH_2CH_2CH_2$OMs side chain. Gibbs free energy in kcal/Mol, and bond lengths in Å.

reverse, that in contrast with the corresponding aromatic case, in which the *N*, *N*″-bis-Boc protected guanidine compound **3** in Scheme 1 exhibits much larger reactivity (with larger [^{18}F]fluorination yield) than the *N*, *N*′-bis-Boc protected guanidine compound **2**.

Conclusion

We carried out quantum chemical analysis for aliphatic guanidine fluorination in comparison with the corresponding aromatic guanidine fluorination, focusing on the position of F^- in pre-reaction complexes. For [^{18}F]fluorination of aliphatic guanidine compounds, the freely moving nucleophile F^- positions itself close to the site of fluorination. It is predicted that the effects of positions of –Boc protection seem to be contrary to the corresponding aromatic case, with the *N*, *N*″-bis-Boc protected guanidine compound being more reactive than the *N*, *N*′-bis-Boc protected guanidine compound. For –CH_2OMs and –$CH_2CH_2CH_2$OMs side chains on which the [^{18}F]fluorination occurs, we also showed that the effects of the side chain would be minimal, giving similar positions of F^-, in agreement with the experimentally observed very similar yields.

Acknowledgments. We thank the National Research Foundation of Korea (NRF-2016R1D1A1B03931188) for financial support.

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