Theoretical Study on the Chemical Reactivity in the Armchair Single-walled Carbon Nanotube: Proton and Methyl Group Transfer

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(Received 19 September 2016, Accepted 28 November 2016)

Proton transfer (PT) and methyl group transfer (MGT) occurring in small biomimetic systems, Formamide-Formamidic acid (FA-FI), and N-formyl-N-methylformamide-(E)-methyl N-formylformimidate (NMFA-NMFI) are investigated in the gas phase and in single-walled carbon nanotubes by using the density functional theory and the ONIOM approach. It is shown that PT reaction is disfavoured in single-walled CNT (5,5) because it increases the energy barrier, while confinement in CNT (6,6) decreases the energy barrier of MGT.

Keywords: Carbon nanotube, Proton transfer, Methyl group transfer, ONIOM and DFT

INTRODUCTION

Carbon nanotubes (CNTs), prepared experimentally in 1991 [1], have applications in several fields because of their optical, electronic, and mechanical properties, including their potential biocompatibility in pharmaceutical research for creating polyvalent drug delivery systems [2-8].

The nanotechnology approach based on drug administration control, has played a key role, particularly for the targeted delivery of drugs for several diseases such as tuberculosis, malaria, cancer and AIDS [9-16].

CNTs are, in fact, listed among the most powerful drug carriers because of their non-reactivity with transport drugs and also biocompatibility.

CNTs have been functionalized to increase their solubility in blood, and then they have been used as efficient delivery systems, especially for carboplatin [16-19]. The therapeutic agent and some ferromagnetic materials are placed inside. Hilder and Hill modelled the acceptance condition for the anti-cancer drug cisplatin inside a CNT based on the CNT diameter [20,21].

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Single-walled carbon nanotubes (SWCNTs) are new molecular-scale wires with useful properties for various potential applications, which include miniature biological devices [22].

We consider the possibility that proton transfer (PT) and methyl group transfer (MGT) occur inside the SWNTs with different diameters. We have investigated, with the help of theoretical methods, small-sized molecular models presenting such transfers. The examples illustrated here compare the effects of confinement on the molecules with their unconfined state (isolated state).

In biochemistry, PT, Proton Coupled Electron Transfer PCET [23-28] and MGT reactions are important processes and the mechanism of their enzymatic catalysis is of great interest. For example, the Formamide (FA)-Formamidic acid (FI) tautomeration (Fig. 1) has been used to model the tautomerization of DNA nucleobases-in particular, the tautomerization of guanine and uracil.

MGT reactions play an important role because they encompass homogeneous as well as heterogeneous catalysis and organic synthesis [29,30]. It has been specifically formulated to enhance the methylation pathways involved in homocysteine metabolism [31-34]. Several mechanisms
have been proposed to describe MGT for DNA repair and other biological systems [35-38].

The aim of this work is to present a quantum chemical investigation of the confinement effects on the mechanisms of PT and MGT reactions in SWCNT. We applied the density functional theory (DFT) [39] to localize the stationary points for reactants, transition states (TSs), and products on the potential energy surface (PES). We considered small-sized molecular models in which PT and MGT can take place in steps or through a concerted mechanism [40]. We focus on the following reactions:

- FA which leads to FI, confined within armchair (5,5) SWNTs.
- NMFA which leads to NMFI, confined within armchair (5,5) and (6,6) SWNTs.

We have used the two layers of ONIOM calculations—this approach allows us to study the essential parts of the molecular systems at a higher level of theory, while the other less important part is studied at a computationally lower level [41], in order to explore the influence of the CNT confinement on PT and MGT reactions.

**COMPUTATIONAL METHODS**

The geometries of all structures in the gas phase were fully optimized by using the Gaussian 09 program package [42] at the DFT level, with the use of the hybrid functional B3LYP with the 6-31G (d) basis sets [43]. For the molecules confined in carbon nanotubes, full geometry optimizations were carried out with the two-layered ONIOM approach [41,44]. Vibrational frequency calculations have been carried out to determine the zero point energy (ZPE) corrections and the nature of the stationary points.

Small basis sets stabilize the complex more than the separate components because of the basis set superposition error (BSSE) [45,46]. The latter is due to the fact that the wave function of the monomer is expanded in much less basis function than the wave function of the complex. One solution for BSSE is the use of extremely large basis sets. This is, however, hardly feasible for most of the biochemically interesting systems. The second approach, employed in this work is the counterpoise method (CP) [47] which is an approximate method for estimating the size of the BSSE. The counterpoise interaction energy correction can, in most simple cases be calculated by:

\[ E_{int} = E(AB, r_c) - E(A, r_c) - E(B, r_c) + E(AB) - E(A) - E(B) \]

The notation AB indicates that the complexes, as the way
Fig. 2. FA and FI geometries isolated molecule and encapsulated molecule in CNT (5,5).
for the separate components, are calculated in the same absolute basis. The label \( r_c \) indicates the geometry of the product complex AB, while \( r_i \) indicates the geometry of the separate reactants.

To estimate solvation effect, the optimized geometries were carried out by the polarizable continuum model (IEF-PCM) [42-44] at the B3LYP/6-31G (d) level with different dielectric constants that correspond to dichloromethane (\( CH_2Cl_2 \), \( \varepsilon_r = 8.9 \)) and tetrachloromethane (\( CCl_4 \), \( \varepsilon_r = 2.2 \)) [40].

The CNT is placed into the lower layer and treated by the universal field force (UFF) [48]. It has been demonstrated that the combination of the density functional theory (DFT) and the UFF molecular mechanics is an appropriate method for modelling those reactions that do not lead to covalent interactions with SWCNT [49-51]. Each transition state (TS) exhibits one imaginary frequency. As for the armchair (5,5) and (6,6) SWCNTs, hydrogen atoms were added to saturate the valences of the ending carbons to avoid dangling bonds.

**RESULTS AND DISCUSSION**

**Geometries of PT Reaction**

Formamide tautomerization has been theoretically studied by Ai-ping Fu et al., who employed the MP2 and B3LYP methods with different basis sets [52]. Here we will consider the PT reaction inside CNTs. The length of the molecular tube segment used consists of seven rows of benzenoid units, namely \( C_{28}H_{30} \) for CNT (5,5). FA and FI structures in the isolated and confined CNTs are illustrated in Fig. 2, where bond lengths are in angstroms (Å) and bond angles are in degrees.

It can be seen that the C-N bond length in FA@CNT (5,5) diminishes by 0.05 Å compared with the isolated FA. The NCO and O=C=H, bond angles are narrowed to 117.4° and 120.7°, respectively. An increase of about 3.7° in the NCO angle is observed for the Fl@CNT (5,5) molecule.

The geometrical parameters of the TS for the PT reaction are reported in Fig. 3. N-H and O-H distances in the TS are decreased to 1.33 and 1.30 Å, respectively by the confinement in CNT (5,5). The C-N bond length is shorter by 0.04 Å. The O=C=H angle of TS@CNT (5,5) is decreased to about 13.8°. It is clear that the structure of the TS is slightly affected by the confinement of CNT (5,5).

**Energetic of PT Reaction**

We estimate the encapsulation energy by the following formula [53]:

\[
E_{\text{encaps}} = E_{\text{isomer@CNT}} - (E_{\text{isomer}} + E_{\text{CNT}})
\]

The negative value of \( E_{\text{encaps}} \) indicates that the encapsulation is an exothermic process [54] (see Table 1).

Our calculated energy barrier for the isolated FA is 44.6 kcal mol\(^{-1}\), with the inclusion of ZPE corrections at the B3LYP/6-31G* level of theory. For FA@CNT (5,5), the TS is 51.4 kcal mol\(^{-1}\) above the energy of the equilibrium geometry (see Table 2). The activation energy of the PT reaction for the encapsulated FA is about 6.8 kcal mol\(^{-1}\) higher than the isolated one, suggesting that the PT reaction of FA may be controlled by the encapsulation within CNT (5,5). Figure 4 shows the relative energy of the PT reaction for both the isolated and confined systems. The energy difference between Fl@CNT (5,5) and FA@CNT (5,5) is about 1.87 kcal mol\(^{-1}\) higher than the difference between the isolated FA and Fl. These results are in line with the widely accepted view that CNT encapsulations can significantly affect the energies of chemical reactions [55].

**Geometries of the Methyl Group Transfer Reaction**

Large numbers of studies have shown that methyl transfer proceeds via a simple MGT transition state [56,57]. The intramolecular methyl transfer is found to proceed either through a methyl inversion mechanism or a methyl retention mechanism. In NMFA, only the methyl retention mechanism has been located.

We have first studied the insertion of NMFA and NMFI into CNT (5,5) and CNT (6,6). The computed encapsulation energies are reported in Table 3. The encapsulation of NMFA in CNT (5,5) is a highly endothermic process and thus we will not further consider this system. The geometrical parameters of the different isomers for the MGT isolated and encapsulated inside CNT (6,6) are reported in Figs. 5 and 6.

It can be seen that confined minimum energy geometries are somewhat different from those of the isolated system. The \( C_2-N_3, C_N-N_3 \) and \( C_6-N_3 \) bond lengths of the confined

NMFA@ (6,6) are shorter than those of the isolated NMFA. In fact, they are shorter by 0.01, 0.02 and 0.03 Å, respectively. The C$_6$N$_3$C$_4$ bond angle is compressed from an equilibrium value of 5°, while the C$_2$N$_3$C$_6$ and C$_2$N$_3$C$_4$ bond angles are increased by about 4.4 and 0.7°, respectively.

The geometrical analysis of NMFI@CNT (6,6) does not show a big change in going from the isolated state to the confined one. The C$_6$-O$_1$ bond length is compressed by 0.01 Å. The bond angles of C$_6$O$_1$C$_6$ and O$_1$C$_2$N$_3$ are increased by 1.0 and 2.1°, respectively, while the C$_2$N$_3$C$_4$ angle is compressed by 4°.

The MGT transition state adopts two different forms TS1 (syn) and TS2 (anti) as confirmed by IRC calculations [40]. The TS1 is the lowest energy transition state leading to NMFI formation. Force constant calculations confirmed that TS1 has one imaginary frequency (see Table 4). The geometrical parameters of the two transition states of different complexes are presented in Fig. 5. No significant

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**Table 1.** Isomers, Encapsulation and BSSE Energies of PT Reaction Calculated at ONIOM (B3LYP/6-31G*: UFF) Level of Theory

<table>
<thead>
<tr>
<th>Isomer@CNT(6,6)</th>
<th>E$_{encaps}$/ (Kcal mol$^{-1}$)$^a$</th>
<th>BSSE energy/(Kcal mol$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FA</td>
<td>-167.394813</td>
<td>-50.67</td>
</tr>
<tr>
<td>FI</td>
<td>-167.368819</td>
<td>-48.34</td>
</tr>
</tbody>
</table>

$^a$E$_{encaps}$ = E$_{isomer@CNT}$ - (E$_{isomer}$ + E$_{CNT}$); E$_{FA(isolate)}$ = -169.888843; E$_{NMFA(isolate)}$ = -169.866563 a.u. by B3LYP/6-31G*levels; E$_{CNT(5,5)}$ = 2.57478 a.u. by UFF.
**Table 2.** Relative Energies for the Isomers of PT Reaction

<table>
<thead>
<tr>
<th>Isomer</th>
<th>Relative energy (Kcal mol⁻¹)</th>
<th>Imaginary frequency (cm⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FA</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>FI</td>
<td>13.60&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>TS</td>
<td>44.60&lt;sup&gt;a&lt;/sup&gt;</td>
<td>-1937 cm⁻¹</td>
</tr>
<tr>
<td>FA@CNT (5,5)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>FI@CNT (5,5)</td>
<td>15.61&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>TS @CNT (5,5)</td>
<td>51.47&lt;sup&gt;b&lt;/sup&gt;</td>
<td>-1936 cm⁻¹</td>
</tr>
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</table>

<sup>a</sup>Relative energy calculated at B3LYP/6-31G* levels. <sup>b</sup>Relative energy calculated at ONIOM (B3LYP/6-31G*: UFF) levels.

**Fig. 4.** A schematic view of the PT reaction in the isolate molecule and encapsulate molecule in CNT (5,5).

**Table 3.** Isomers, Encapsulation and BSSE Energies of MGT Reaction Calculated at ONIOM (B3LYP/6-31G*: UFF) Level of Theory

<table>
<thead>
<tr>
<th>Isomer</th>
<th>E_{isomer}@CNT(6,6) (a.u.)</th>
<th>E_{isomer}@CNT(5,5) (a.u.)</th>
<th>E_{encaps} (Kcal mol⁻¹)</th>
<th>BSSE energy (Kcal mol⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NMFA</td>
<td>-320.041918</td>
<td>-319.814718</td>
<td>90.40&lt;sup&gt;a&lt;/sup&gt;</td>
<td>5.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>-17.79&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>NMFI</td>
<td>-319.982077</td>
<td>-319.974636</td>
<td>-29.26&lt;sup&gt;a&lt;/sup&gt;</td>
<td>5.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.5&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
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</table>

<sup>a</sup>E_{encaps} in CNT(5,5);<sup>b</sup>E_{encaps} in CNT (6,6). E_{CNT(5,5)} = 2.57478 a.u.; E_{CNT(6,6)} = 2.52 a.u. at UFF levels.
Fig. 5. The optimized structures of NMFA, NMFI in the isolated molecule and encapsulated molecule in CNT (6,6) systems.
Fig. 6. Molecular structures of the transition states TS1 and TS2 for MGT reaction of the isolated molecule and encapsulated molecule in CNT@ (6,6).
change is observed in the structures of TS1 while passing from the isolated molecules to the confined CNT (6,6).

As an example of C$_6$-O$_1$ and C$_6$-N$_3$, the distances of the confined molecules are shorter by about 0.01 and 0.02 Å, respectively, than those of the isolated molecules; the O$_1$C$_6$N$_3$ and O$_1$C$_2$N$_3$ bond angles increased by about 0.7, 1.6 degrees, respectively, and the C$_6$N$_3$C$_4$ bond angle is compressed by 5.2°. The same also holds for TS2 the C$_6$-O$_1$ and C$_6$-N$_3$ distances of the confined molecules are shorter by about 0.06 and 0.1 Å, respectively. For the isolated

<table>
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<th>Relative energy (Kcal mol$^{-1}$)</th>
<th>Imaginary frequency (cm$^{-1}$)</th>
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<tbody>
<tr>
<td>NMFA</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>NMFI</td>
<td>19.28$^a$</td>
<td></td>
</tr>
<tr>
<td>(TS 1)</td>
<td>67.96$^a$</td>
<td>- 584.3003</td>
</tr>
<tr>
<td>(TS 2)</td>
<td>101.12$^a$</td>
<td>- 685.2514</td>
</tr>
<tr>
<td>NMFA@CNT (6,6)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>NMFI@CNT (6,6)</td>
<td>34.52$^b$</td>
<td></td>
</tr>
<tr>
<td>(TS 1) @CNT (6,6)</td>
<td>63.0$^b$</td>
<td>- 548.9849</td>
</tr>
<tr>
<td>(TS 2) @CNT (6,6)</td>
<td>94.53$^b$</td>
<td>- 689.4142</td>
</tr>
</tbody>
</table>

$^a$Relative energy at B3LYP/6-31G* levels. $^b$Relative energy calculated at ONIOM (B3LYP/6-31G*: UFF) levels.

**Table 4.** Relative Energies for the Isomers of MGT Reaction

**Fig. 7.** A schematic view for energetic of MGT in the gas phase, in different solvents (CH$_2$Cl$_2$, CCl$_4$) and in CNT (6,6).
species, the O₃C₆N₃ and O₃C₇N₇ angles increase about 2.0 and 2.1°, respectively. The C₆N₆C₄ bond angle changes from 117° to 113.3°.

**Energetic of the Methyl Group Transfer Reaction**

The encapsulation of NMFA into CNT (6,6) and NMFI into CNT (5,5) are exothermic processes (Table 3). The activation energy of TS1@CNT (6,6) is about 63 Kcal mol⁻¹ compared to the NMFA@CNT (6,6) energy (see Fig. 7). In comparison with the isolated state, the activation energy of the MGT reaction is lower by 4.9 Kcal mol⁻¹ (TS1) with respect to TS1@CNT (6,6) while the energy barriers are lower by about 28.5 Kcal mol⁻¹ with respect to NMFA@CNT (6,6). The encapsulation effects are significantly higher than the solvent effects. Our results have shown small changes in the energy barriers when the reaction occurs in CH₂Cl₂ and CCl₄ solvent [40].

The MGT reaction is notably affected by the confinement CNT (6,6) in view of geometries and energy. The confinement CNT (6,6) has an influence on the structures and energy barriers, and the activation energies obviously decrease slightly.

The most interesting result in this work is the important change for the internal energy variation of MGT reaction inside the CNT (6,6), which could mean that the regeneration of the DNA would be better in CNT.

In all our calculations, the BSSE is less than 7 Kcal mol⁻¹ (See Tables 1 and 3), which could mean that it does not affect on the final results and related discussion.

**REFERENCES**


[54] Wang, L.; Yi, C.; Zou, H.; Xu, J.; Xu, W., On the

