

H-Bonding Controls the Regio-selectivities on the Acid-catalyzed Reaction of Fluorenone with Phenol Derivatives

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Electrophilic substitution reaction is the most widely used procedure for introducing functional groups to the aromatic ring. Activated electrophiles containing carbonyl functions such as aldehydes and acyl halides are added smoothly to phenol and its derivatives under catalytic condition. However, it is rare the reaction of carbonyl compounds like ketones with aromatic rings to form a carbon-carbon bond, and to be considered unusual due to the unfavorable equilibrium.¹ A recent paper reported this unusual carbonyl functionalization (Scheme 1),^{2,3} where fluorenone under acidic condition is reacted with activated aromatic compounds (phenols) to produce spiro[fluorene-9,9'-xanthene](SFX) and related compounds. The overall reaction is highly regio-selective. Those remarkable features of this reaction prompt us to study the usefulness of the reaction and identify the regio-control elements in the process.

We understand the reaction path involves an electrophilic attack of C9 of fluorene-9-one to phenol in the presence of proton. Regarding the ortho- vs. para- selectivity, we have considered the electrophilic attack of fluorene-9-one to phenol and its derivatives in the presence of proton. To understand the reaction path in detail, we have investigated the optimized chemical species involved in the reaction as shown in Scheme 2.

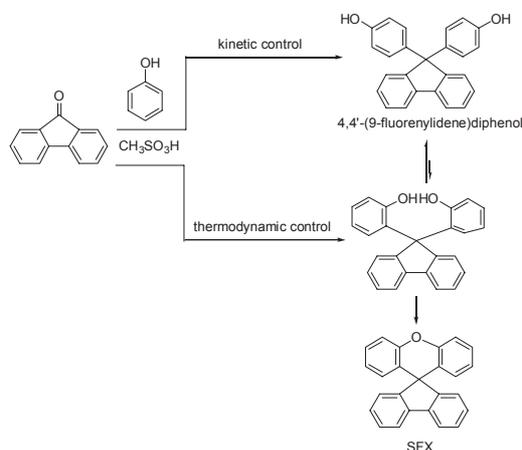
All *ab initio* calculations have been carried out using the Gaussian 98 program.⁴ The structures of the intermediates and transition states were then fully optimized using the density functional theory B3LYP/6-31G(d).⁵ Harmonic vibrational frequencies calculated at the same level were used for the characterization of stationary points. The number of imaginary fre-

quencies (0 or 1) indicates whether a minimum or a transition state has been located.

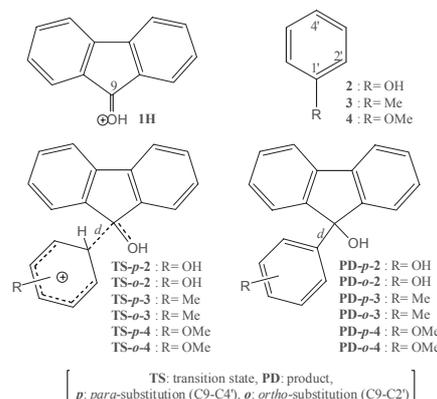
Table 1 shows optimized energies of phenol and its derivatives as well as transition states and products of the reaction in ortho- and para-approach.⁶ For the reaction with phenol, the activation energies are predicted by 10.38 kcal/mol for para-attack and 9.79 kcal/mol for ortho-attack, respectively. According to the relative TS energies for reaction of phenol to fluorenone, the ortho-approach is slightly favorable path than para-approach of phenol by 0.59 kcal/mole (entry 1 & 2 in Table 1). According to Mulliken charge density,⁶ one may anticipate the ortho-approach may be electronically favorable over para-approach. In contrast, the reaction of toluene to fluorenone is predicted by opposite fashion. The para-attack appears more favorable than the ortho-approach by 2.99 kcal/mole (entry 3 & 4 in Table 1). The difference of energy is substantially large. One may attribute the disfavorable ortho-approach to a possible steric effect of methyl group.

Figure 1 illustrates two stable TSs for each reaction of phenol and toluene, respectively. It is noted the distance of O9...H1' show 2.123 Å in the optimized transition state **TS-*o*-OH**, which is called up hydrogen bonding⁷ between phenol and fluorenone. The energy difference in products is substantial. Energetically **PD-*o*-OH** is more stable than **PD-*p*-OH** by 5.85 kcal/mol, which obviously attributes to an intra-molecular hydrogen bonding. In the optimized structure **PD-*o*-OH**, the distance of O9...H1' shows 1.761 Å, which is shorter than the distance in **TS-*o*-OH**.⁸

As the hydrogen bonding is regarded to be an important factor for the preference of ortho-approach for the reaction of phenol,



Scheme 1



Scheme 2

Table 1. The calculation results for the optimized transition states and products

no	compounds	B3LYP/6-31G*//B3LYP/6-31G*			MP2/6-31G*//B3LYP/6-31G*	
		E_{tot}^a	E_{act}^b (E_{rel}^c)	d^d	E_{tot}^a	E_{rel}^c
1	TS- <i>p</i> -OH	-883.2347805	10.383 (0.595)	1.858	-880.4719719	1.215
2	TS- <i>o</i> -OH	-883.2357293	9.788 (0.000)	1.946	-880.4739076	0.000
3	TS- <i>p</i> -Me	-847.3269977	16.368 (0.000)	1.732	-844.5986273	0.000
4	TS- <i>o</i> -Me	-847.3222300	19.360 (2.992)	1.725	-844.5961797	1.536
5	TS- <i>p</i> -OMe	-922.5449320	8.063 (0.000)	1.905	-919.6310809	0.000
6	TS- <i>o</i> -OMe ^f	-922.5406961	10.721 (2.658)	1.72	-919.6277173	2.111
7	PD- <i>p</i> -OH	-882.8935280	(5.846)	1.532	-880.1440208	6.696
8	PD- <i>o</i> -OH	-882.9028435	(0.000)	1.530	-880.1546911	0.000
9	PD- <i>p</i> -Me	-846.9954227	(0.000)	1.533	-844.2816833	0.000
10	PD- <i>o</i> -Me	-846.9890322	(4.010)	1.537	-844.2775869	2.570
11	PD- <i>p</i> -OMe	-922.2000558	(0.000)	1.532	-919.2988029	0.000
12	PD- <i>o</i> -OMe	-922.1930199	(4.415)	1.539	-919.2936513	3.233

^a E_{tot} , total energy (a.u.) at b3lyp/6-31G*//b3lyp/6-31G* and mp2/6-31G*//b3lyp/6-31G*. ^b E_{act} , activation energies (kcal/mol) are based upon the data from b3lyp/6-31G*//b3lyp/6-31G* method, which are derived from $E_{tot}(\mathbf{1H} + \mathbf{2})$, $E_{tot}(\mathbf{1H} + \mathbf{3})$ and $E_{tot}(\mathbf{1H} + \mathbf{4})$, where the total energies (a.u.) are -575.7864605 for **1H**, -307.4648665 for **2**, -271.5666211 for **3** and -346.7713204 for **4**. ^c E_{rel} , relative energies (kcal/mol) show relative stability between TS-*o* vs. TS-*p* or PD-*o* vs. PD-*p*. ^dThe distance (Å) d shows length of C9-C2' (for ortho-attack) and C9-C4' (for para-attack) in TS or PD. ^eDistance of O9-H1' in TS-*o*-OH and PD-*o*-OH. ^fThe optimized TS-*o*-OMe is deduced from scanning with increment of $d(\text{C9-C2}')$ by 0.01 Å.

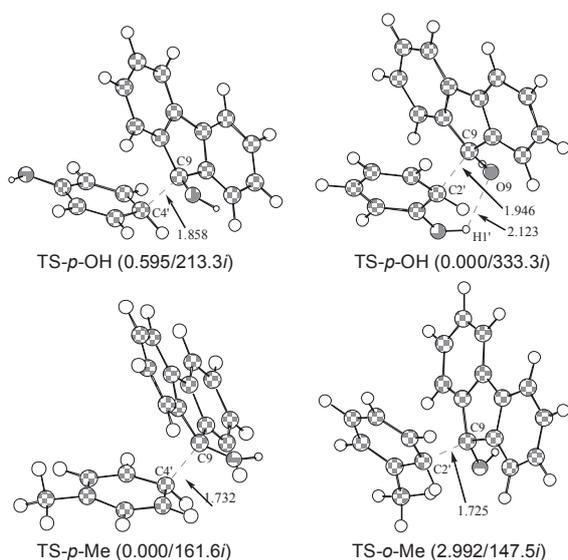


Figure 1. Geometries of four TSs, TS-*p*-OH, TS-*o*-OH, TS-*p*-Me and TS-*o*-Me, optimized at the B3LYP/6-31G(d). The values in parenthesis are relative energy values (kcal/mol) calculated at the B3LYP/6-31G(d)//B3LYP/6-31G(d) levels and the imaginary frequency.

the para-approach might be a dominant path without a hydrogen bonding in ortho-approach. For the reaction with anisole, the optimized energy of TS-*p*-OMe shows lower than TS-*o*-OMe by 2.66 kcal/mol, which is similar to toluene reaction system (see entry 3-6 in Table 1). According to the relative stability of products from the toluene and anisole, the preference of para-substitution is predicted by 4.01 and 4.40 kcal/mole, respectively (entry 9-12 in Table 1), which is contrary to the phenol system as discussed above. Such the trend between ortho- and para-substitution is in accord with mp2/6-31G* energies at the optimized geometries with B3LYP/6-31G* as shown in Table 1. The above calculation results all agree with our prospect. We conclude the para-approach would be preferred energetically without a possible hydrogen bonding for the transition states as well as the products.

For parallel experimental studies to verify, we have performed the reaction of anisole to fluorenone, where the hydrogen

bonding is not available.⁹ The reaction at 140 °C in the presence of methanesulfonic acid gave only the para-adduct 9,9-bis-(4-methoxy-phenyl)-9*H*-fluorene (32% yields in 24 h). In the case of the reaction of phenol with fluorenone, two products are obtained in 88% yields corresponding to *via* para- and ortho-adduct. The product ratio of spiro[fluorene-9,9'-xanthene] (SFX) to 4,4'-(9-fluorenylidene)diphenol increases with reaction time (23:77 at 3 h, 49:51 at 6 h, and 60:40 at 24 h). It suggests the ortho-adduct is thermodynamically more stable than para-adduct. All of experimental results are well explained by the prediction from *ab initio* calculation studies of transition states and products. During the reaction, a possible H-bonding between phenol and fluorenone is clearly involved as well as the electron density on C-2 of phenol. Moreover the hydrogen-bonding decisively reveals in the ortho-product. Thus a relative stability of PD-*o*-OH attributes to intramolecular hydrogen-bonding.

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- For the atomic charge of phenol derivatives (B3LYP/6-31G*), ortho-position show larger than para-position: the Mulliken atomic charges of ortho/para center show -0.194/-0.135 for phenol, -0.182/-0.133 for toluene, -0.196/-0.134 for anisole.
- For a review on hydrogen bond, see: Steiner, T. *Angew. Chem. Int. Ed.* **2002**, *41*, 48.
- It is noted the compound shows energetically more stabilized by increasing hydrogen bonding character. Between two optimized intermediates ortho- and para-substitution intermediate of phenol reaction, the energy difference is 6.42 kcal/mol, where the distance of OH...O for intermediate of ortho-approach shows 1.626 Å.
- Experimentally, it turns out the reaction of toluene to fluorenone has not been worked in various reaction conditions. Theoretically, the activation energy of the reaction of toluene to fluorenone is shown higher than that of the reaction of phenol or anisole. As shown in Table 1, they are predicted 16.37 and 19.36 kcal/mole for para-approach and ortho-approach, respectively.