

# Superacid mediated hydroxyalkylation reaction of 1,2,3-indanetrione: a theoretical study

Daniel Romero Nieto<sup>a</sup>, Mikhail G. Zolotukhin<sup>a</sup>, Lioudmila Fomina<sup>a</sup> and Serguei Fomine<sup>a\*</sup>



Energies of mono- and multiprotonation for 1,2,3-indanetrione and ninhydrin in triflic acid (TFSA) media were estimated at PBE0/aug-cc-pvtz//6-31+G\*\* level of theory. The reactivity of formed intermediates in the reaction of aromatic electrophilic substitution has been studied at the same level of theory. It appears that the basicity of carbonyl groups in 1,2,3-indanetrione is extremely low due to mutual influences of carbonyl groups. Carbonyl 2 is the least basic but the most reactive in accordance with experiment. Calculations demonstrated that monoprotated intermediates are the principal reactive species in the reaction of hydroxyalkylation of 1,2,3-indanetrione in TFSA. A new isomerization mechanism of 2,2-diaryl-1,3-indanediones to 3-(diarylmethylene)isobenzofuranones in TFSA media has been proposed. Copyright © 2010 John Wiley & Sons, Ltd.

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**Keywords:** hydroxyalkylation; PBE0; protonation; superacid

## INTRODUCTION

It has recently been established that catalyzed polyhydroxyalkylation reactions of aldehydes and ketones afford linear, high-molecular weight polymers with nonactivated aromatic hydrocarbons and provide an important synthetic tool for the synthesis of triarylmethanes, diarylmethylbenzaldehydes, and anthracene derivatives.<sup>[1–3]</sup>

It appears that the nature of reactive species participating in the reaction of superacid mediated hydroxyalkylation depends strongly on the nature of the carbonyl component. Thus, calculations suggested that in the case of triflic acid (TFSA) catalyzed polyhydroxyalkylation of aldehydes and ketones containing electron-withdrawing groups, monocationic species are the principal reaction intermediates.<sup>[4,5]</sup> On the other hand, the existence of diprotonated carbonyl molecules in superacids has been proven experimentally.<sup>[6,7]</sup> Thus, dications have been detected by low-temperature NMR<sup>[6]</sup> in TFSA catalyzed condensation of 3-pyridinecarboxaldehyde with deactivated aromatic compounds. The results provided a demonstration for the reactivity of dicationic electrophiles and suggested that protonation of an adjacent base site activates electrophilic functional group such as a carboxonium ion.

Calculations have also validated the existence of diprotonated reactive intermediates in TFSA solutions of 4-heterocyclohexanones where both the carbonyl oxygen and heteroatom are protonated.<sup>[8]</sup> This is also the case for polycarboxylic compounds. Thus, in the case of isatin polyhydroxyalkylation the calculations admit the participation of diprotonated species, although not as principal reactive intermediates.<sup>[9]</sup> On the other hand, acids stronger than TFSA such as 'magic acid' (a mixture of fluoro sulfonic acid (FSO<sub>3</sub>H) and SbF<sub>5</sub>) are capable of multiprotonation of polycarboxylic molecules when the basicity of carbonyl groups

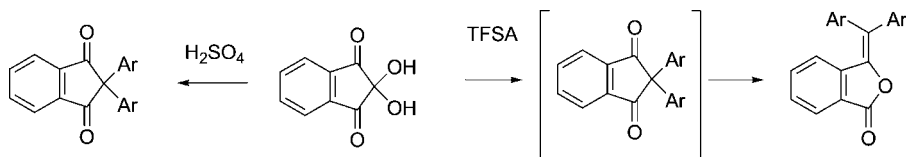
is enhanced by polar effects such as in squaric, croconic, and rhodizonic acids.<sup>[10]</sup>

Another interesting example of polycarboxylic molecule is 1,2,3-indanetrione (**1**) forming stable hydrate known as ninhydrin. Ninhydrin reacts with aromatic compounds in acid solutions to give condensation products in high yields. Ninhydrin produces 2,2-diaryl-1,3-indanediones in H<sub>2</sub>SO<sub>4</sub>, while in TFSA ninhydrin reacts with arenes to give 3-(diarylmethylene)isobenzofuranones (Scheme 1).<sup>[11]</sup> Although there have been published computational studies on the reactions of tricarbonylic compounds with nucleophiles (water),<sup>[12]</sup> no computational studies on 1,2,3-indanetrione have been done.

These reactions can be considered as an example of a 'click reaction'<sup>[13]</sup> due to high yields and easy product isolation and, therefore, 1,2,3-indanetrione or ninhydrin could be a valuable potential monomer for the polyhydroxyalkylation reactions to produce high-molecular weight polymers. The goal of this study is to explore protonation energetic of 1,2,3-indanetrione and the reactivity of protonated intermediates toward biphenyl, a common monomer for the polymer synthesis by superacid mediated polyhydroxyalkylation reaction as well as transformation mechanism of 2,2-diaryl-1,3-indanediones to 3-(diarylmethylene)isobenzofuranones taking place in TFSA.

\* Correspondence to: S. Fomine, Instituto de Investigaciones en Materiales, Universidad Nacional Autónoma de México, Apartado Postal 70-360, CU, Coyoacan, Mexico DF 04510, México.  
E-mail: fomine@servidor.unam.mx

a D. R. Nieto, M. G. Zolotukhin, L. Fomina, S. Fomine  
Instituto de Investigaciones en Materiales, Universidad Nacional Autónoma de México, Apartado Postal 70-360, CU, Coyoacan, Mexico DF 04510, México



**Scheme 1.** Reaction of ninhydrin with aromatics in different media

## COMPUTATIONAL DETAILS

All calculations were carried out using the Jaguar 7.5 suite of programs.<sup>[14]</sup> Model selection was based on its ability to reproduce experimentally determined  $pK_a$ s of different acids, since exact  $pK_a$  determination implies accurate calculation of the free Gibbs energies of solvated ionic species.

This model is described in detail in Reference<sup>[5]</sup> and average error in  $pK_a$  determination is about 1  $pK_a$  unit corresponding to 1.4 kcal/mol in  $\Delta G$  of the protonation reaction.

The free Gibbs energy in solution was calculated as a sum of two terms according to this model;  $E_s$  and  $\Delta G_c$  where  $E_s$  is the total electronic energy in solution calculated at the PBE0/aug-cc-pvtz level using PBE0/6-31+G\*\* solution-phase optimized geometry.  $E_s$  is a sum of total solute energy, total solvent energy, and solute cavity energy.  $\Delta G_c$  is the free Gibbs energy correction calculated as the difference between the total electronic energy and the free Gibbs energy in the gas phase estimated at the PBE0/6-31+G\*\* level using PBE0/6-31+G\*\* optimized geometry. Solution-phase optimizations were carried out with the Poisson-Boltzmann solver<sup>[15,16]</sup> implemented in the Jaguar v 7.5 suite of programs using dielectric constant and the solvent probe radius for TFSA of 77.4 and 2.60 Å, respectively. For sulfuric acid, the probe radius was of 2.19 Å and dielectric constant of 101.0 was applied.

The direct method for  $pK_a$  calculation is usually limited to systems in which the solvent model was parameterized for, and the good agreement with experiment does not normally hold for large test sets of molecules.<sup>[17,18]</sup> However, taking into account very good agreement of calculated TFSA acidity with experiment<sup>[5]</sup> this model is most likely to be an adequate tool for systems under investigation.

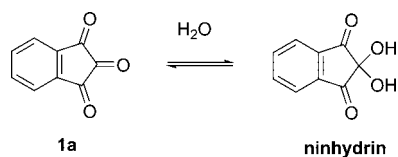
Additional calculations were carried out to test whether adopted model is able to predict experimentally observed diprotonation of squaric acid (3,4-dihydroxy-3-cyclobutene-1,2-dione) in magic acid.<sup>[10]</sup> Dielectric constant of 120 for  $\text{FSO}_3\text{H}$  was used<sup>[19]</sup> with probe radius of 2.21 Å. A complex of  $\text{FSO}_3\text{H}$  and two molecules of  $\text{SbF}_5$  was considered as a proton donor of magic acid. Calculations show that diprotonation of squaric acid is exergonic process with  $\Delta G$  of  $-9.0$  kcal/mol in accordance with experimental data. On the other hand, TFSA was found to be much weaker acid compared to magic acid with  $\Delta G$  of diprotonation of  $+10.5$  kcal/mol.

## RESULTS AND DISCUSSION

Table 1 shows the free Gibbs protonation energies of 1,2,3-indanetrione (**1**) in TFSA solution. Molecule **1** has two different heteroatomic protonation sites: 1 and 2 carbonyl oxygens. The previous theoretical works demonstrated that C-protonation in carbonyl containing aromatics requires more energy compared to O-protonation;<sup>[5]</sup> therefore C-protonation has not been considered. As seen from Table 1, the basicity of all carbonyl

**Table 1.** The free Gibbs protonation energies ( $\Delta G_p$ ) (kcal/mol) of 1,2,3-indanetrione in TFSA solution

Protonation reaction	$\Delta G_p$
	14.2
	5.2
	4.9
	11.3
	14.0
	23.9
	35.5

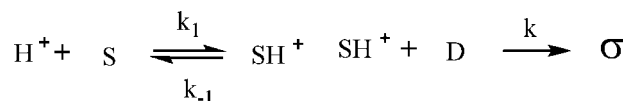


**Scheme 2.** Reaction of 1,2,3-indanetrione with water

oxygen is very low due to the electron-withdrawing character of adjacent carbonyl groups. Even monoprotection energies are positive in TFSA, carbonyl 2 being the least basic. The protonation energy of carbonyl 2 (14.2 kcal/mol) is more positive than that of 2,2,2-trifluoroacetophenone (7.8 kcal/mol)<sup>[5]</sup> while the protonation energy of carbonyl 1 is less positive (5.2 kcal/mol). Therefore, even in the TFSA solution only a very small fraction of **1** is protonated and the first protonation site is carbonyl 1. The calculations also demonstrated that in the TFSA solution the equilibrium shown in Scheme 2 is displaced to the left.  $\Delta G$  of this reaction is positive (2.91 kcal/mol) demonstrating that ninhydrin exists mostly in the form of **1** in the TFSA solution due to the strong affinity of TFSA to water. As seen from Table 1, the protonation energy of carbonyl oxygen 1 is close to that of 1,2,3-indanetrione **1**. The protonation of the hydroxyl group of ninhydrin molecule results in **2a** formation after the elimination of water molecule. This process is 2.7 kcal/mol less endergonic compared to direct protonation of carbonyl 2 of **1**. Therefore, in the TFSA solution **1** must be predominant species. As can be expected, second and third protonations require more energy than the first one. The basicity of carbonyl 2 is so low that the generation of monocation **2a** is more endergonic process than that of dication **3b**, which is the most stable diprotonated intermediate of **1**. Diprotonated molecule **3a** is almost 9 kcal/mol less stable than **3b** due to electrostatic repulsion between two closely located positive charges. The formation of triprotonated state **4a** requires even more energy as seen from Table 1. It is well recognized that carbonyl 2 is the reactive site for the nucleophilic attack in **1**<sup>[20]</sup> not carbonyl 1 which is protonated first.

Since the formation of  $\sigma$ -complex is the rate-determining step in the aromatic electrophilic substitution reactions<sup>[21]</sup>, the reaction paths for the nucleophilic attacks at carbonyls 1 and 2 for different protonated species have been studied. The intermediate **4a** has not been considered as possible reactive intermediate in the reaction of aromatic electrophilic substitution due to highly positive energy of third protonation (Table 1).

Assuming that protonation is remarkably faster than the  $\sigma$ -complex formation, the kinetic scheme of the reaction can be described as a system of two reactions where the concentration of protonated species remains constant.



where  $[\text{S}]$  is the equilibrium concentration of molecules to be protonated,  $[\text{SH}^+]$  is the corresponding concentration of mono or diprotonated species,  $[\text{D}]$  is the concentration of biphenyl, and  $[\sigma]$  is the concentration of  $\sigma$  complexes. The overall reaction rate for the  $[\sigma]$ -complex formation ( $V_\sigma$ ) can be then expressed as

$$V_\sigma = k_K [\text{S}] [\text{H}^+] [\text{D}] \quad (1)$$

where  $K = k_1/k_{-1}$  is the equilibrium constant. Since  $K = \exp(-\Delta G/RT)$  and  $k = A \exp(-G_a/RT)$ , where  $\Delta G$  is the free Gibbs protonation energy

**Table 2.** The free Gibbs activation ( $G_a$ ) and reaction ( $\Delta G$ ) energies of  $\sigma$ -complexes formation

Reaction	$G_a$	$\Delta G$	$G_a + \Delta G_p^a$
<b>2b</b> + biphenyl = <b>5a</b>	24.0	19.8	29.2
<b>3a</b> + biphenyl = <b>6a</b>	9.4	8.8	38.5
<b>3b</b> + biphenyl = <b>7a</b>	23.5	10.3	42.7
<b>2a</b> + biphenyl = <b>8a</b>	1.0	1.0	15.2
<b>3a</b> + biphenyl = <b>9a</b>	0	-6.7	29.1
<b>8a</b> + biphenyl = <b>10a</b>	21.5	8.3	21.5
<b>8b</b> + biphenyl = <b>10b</b>	28.5	17.9	35.4

<sup>a</sup> Sum of free Gibbs activation energies ( $G_a$ ) and the protonation energies required for generation of the corresponding protonated species.

and  $G_a$  is the free Gibbs activation energy, for the  $\sigma$ -complex formation Eqn (1) can be rewritten in a form:

$$V_\sigma = A[\exp(-(\Delta G + G_a)/RT)] [\text{S}] [\text{H}^+] [\text{D}] \quad (2)$$

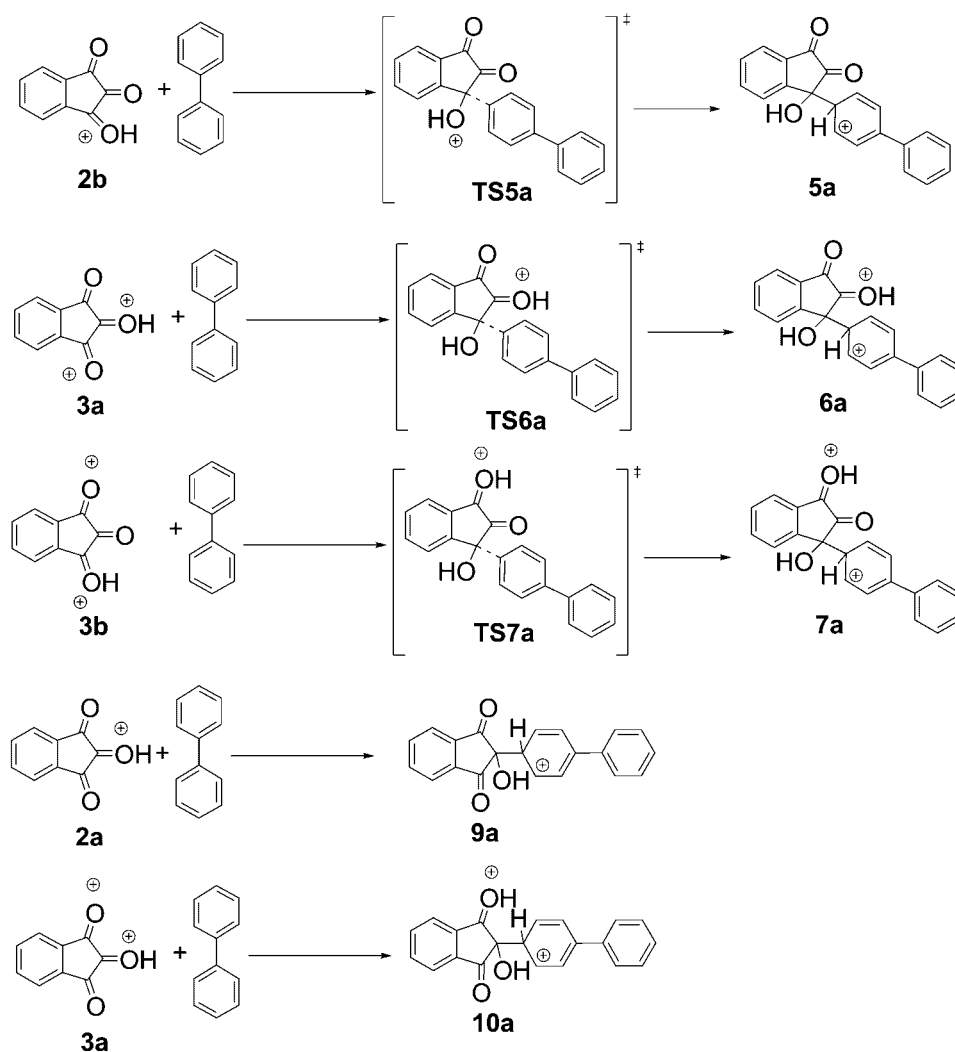
where the expression  $A \exp(-(\Delta G + G_a)/RT)$  has a form of a rate constant ( $k_{\text{eff}}$ ) while the sum of the free Gibbs protonation and the activation energy is the effective activation energy ( $G_{a, \text{eff}}$ ). Therefore, protonation energy must be summed to the activation energy for the correct reactivity comparison between different protonated species.

Table 2 lists the free Gibbs activation and reaction energies for  $\sigma$ -complex formation shown in Scheme 3.

As can be seen from Table 2, carbonyl 2 is the most reactive site in accordance with the experiment showing  $G_{a, \text{eff}}$  of 15.2 kcal/mol and thus validating the computational model. It is interesting to note that although diprotonated intermediate **3a** is more reactive compared to monoprotated one **2a** (lower  $G_a$ ), the effective activation energy is smaller for **2a** due to less positive protonation energy. Although carbonyl 1 is far more basic compared to carbonyl 2 and, therefore, it is easier to be protonated,  $G_{a, \text{eff}}$  is higher for carbonyl 1 due to high  $G_a$ . Therefore, the calculations demonstrate that monoprotated intermediate **2a** is the most reactive species in TFSA solution.

Second reaction step is shown in Scheme 4: Since cation **10a** has two carbonyl groups it can also be protonated to generate dication **10b**. Unlike **1**, the formation of dication from **10a** is relatively easy process requiring only 6.9 kcal/mol in the TFSA solution. This fact can be rationalized in terms of additional stabilization of positive charge by biphenyl group. Thus, according to calculations, in cation **10a** 95% of positive charge is concentrated at biphenyl group and in dication **10b** the biphenyl group has a charge of 1.46. As seen from Table 2, the calculated free Gibbs activation energies for **10a**  $\rightarrow$  **11a** transformation are lower compared to these for the **10b**  $\rightarrow$  **11b** process. This is quite unusual since **10b** is a dication and, therefore, is more reactive compared to **10a**. We believe that this effect can be explained by the withdrawing of the electron density from biphenyl substituent, and, thus decreasing the susceptibility of carbonyl 2 to nucleophilic attack.

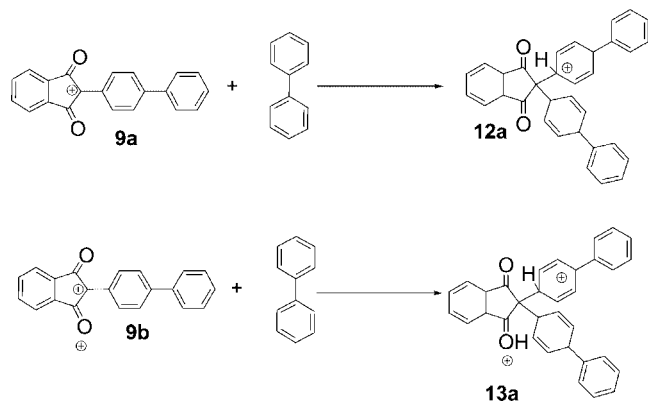
Figure 1 depicts lowest unoccupied molecular orbital (LUMO) distribution in **10a** and **10b**. As seen, LUMO amplitude is remarkably higher on carbon atom of carbonyl 2 of **10a** compared to that at **10b**, in accordance with higher activation energy calculated for **10b** intermediate. Therefore, according to



**Scheme 3.** First step of hydroxyalkylation of 1,2,3-indanetrione

calculations, intermediate **10a** and not **10b** is the reaction intermediate. After deprotonation of  $\sigma$ -complex **11a** the final product **12** is formed (Scheme 4).

It is noteworthy that ninhydrin produces 2,2-diaryl-1,3-indanediones during the reaction of hydroxyalkylation in  $\text{H}_2\text{SO}_4$  media, while 2,2-diaryl-1,3-indanediones are not stable in the presence of TFSA isomerizing to 3-(diarylmethylene)isobenzofuranones (Scheme 5).



**Scheme 4.** Second step of hydroxyalkylation of 1,2,3-indanetrione

It has been suggested<sup>[11]</sup> that the difference between sulfuric and TFSA is due to the ability of TFSA to generate diprotonated reactive intermediate **DP**, which is then transformed into isomerization product **I** (Scheme 5). Our calculations reveal, however, that diprotonation intermediates do not play important roles in the reaction of hydroxyalkylation of 1,2,3-indanetrione in TFSA media due to extremely high energies of their formation (Table 3). Therefore, we have been searching for an alternative explanation for the different behavior of 2,2-diaryl-1,3-indanediones in TFSA and  $\text{H}_2\text{SO}_4$  media. Scheme 6 shows the isomerization process of 2,2-di(biphenyl)-1,3-indanedione **12** to 3-(di(biphenyl)methylene)isobenzofuranone **13** and the corresponding reaction for monoprotated intermediates (**12a** and **13a**). As seen from Table 3, the isomerization of **12** into **13** is an endergonic process in either TFSA or sulfuric acid. However, the same reaction becomes exergonic when protonated species of **12a** and **13a** are involved. Therefore, isomerization is thermodynamically viable only when protonated species are involved. According to calculations, the driving force of the isomerization reaction is the difference in solvation energies between **12a** and **13a**. Carbonyl group of **12** is a rather weak base since even in TFSA the free Gibbs protonation energy is positive (2.7 kcal/mol, Table 3) whereas this value is remarkably more positive (8.7 kcal/mol) in

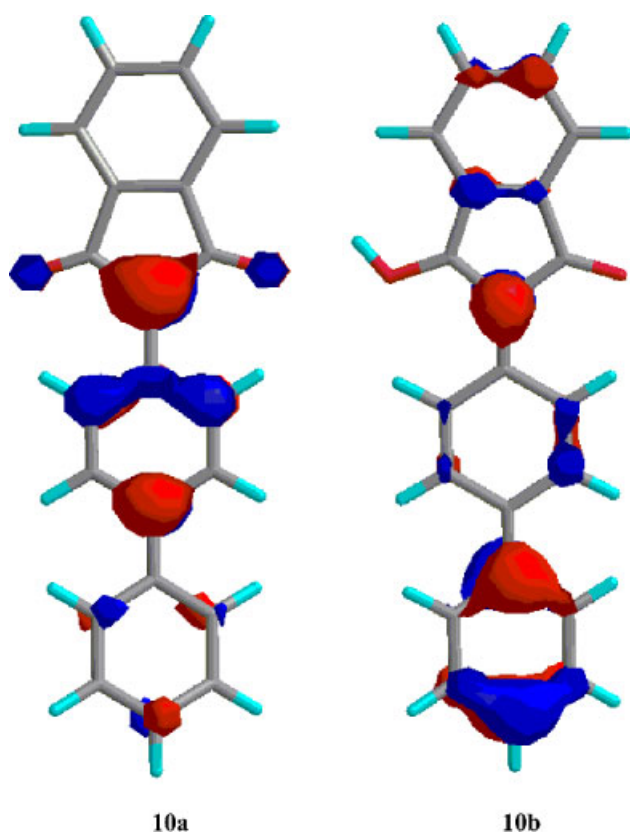


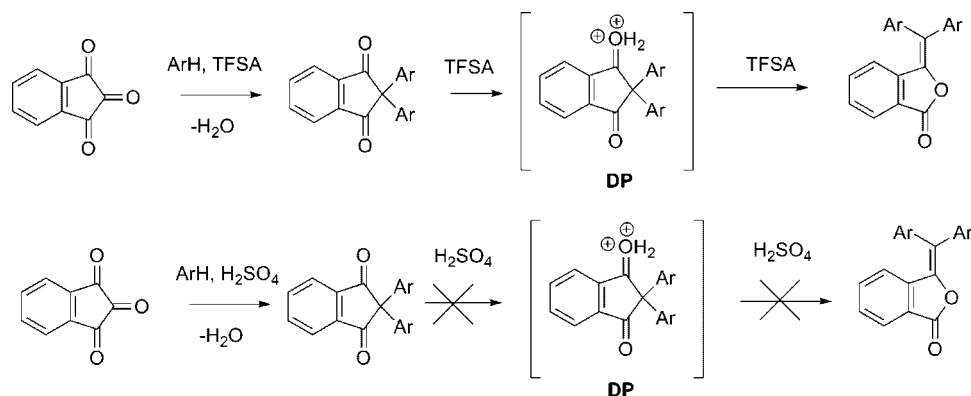
Figure 1. LUMO distribution in **10a** and **10b**.

sulfuric acid implying lower equilibrium concentration of **12a** in sulfuric acid. It is noteworthy that at this point the difference between the behavior of **12** in TFSA and sulfuric acid can be explained without involving diprotonated intermediate **12b**. Thus, in order for isomerization to occur, **12a** must be generated first from neutral **12**. Due to higher acidity of TFSA compared to sulfuric acid, the equilibrium concentration of **12a** is significantly higher in TFSA. On the other hand, the calculations show (Table 3) that the free Gibbs energy required for protonation of already protonated **12a** to form diprotonated intermediate **12b** exceeds 60 kcal/mol in H<sub>2</sub>SO<sub>4</sub> and even in TFSA reaches 48.5 kcal/mol. The free Gibbs activation energy required to produce

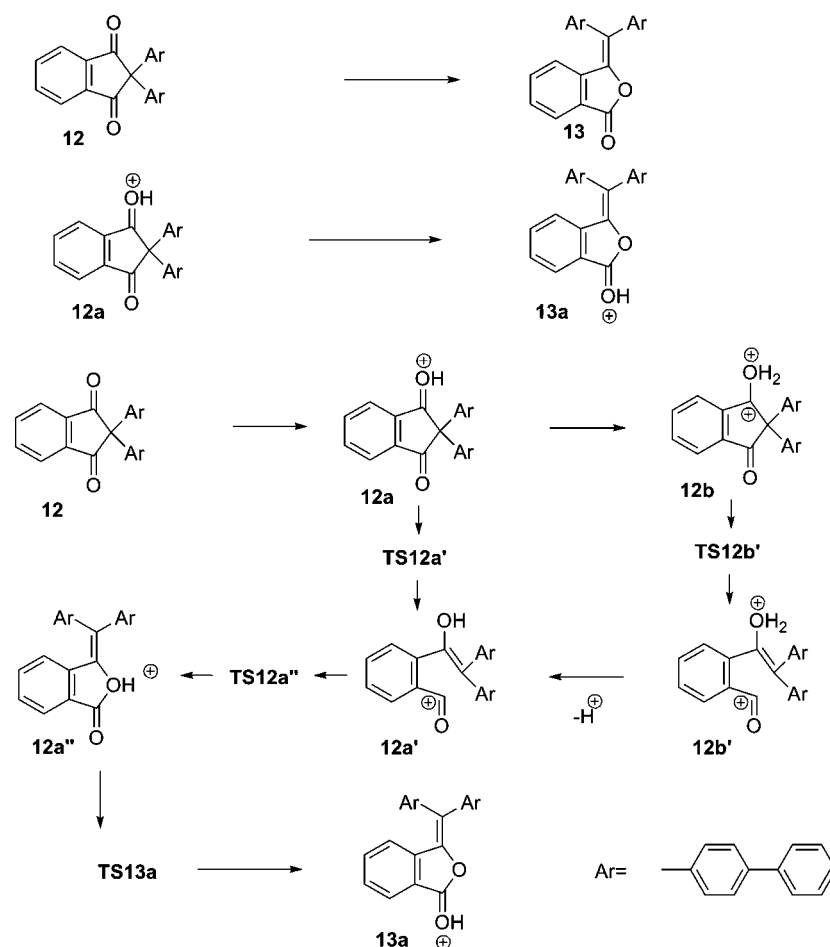
**Table 3.** Calculated free Gibbs reaction energies and free Gibbs activation energies (in brackets) in different media in kcal/mol

Reaction	TFSA	H <sub>2</sub> SO <sub>4</sub>
<b>12</b> → <b>13</b>	12.8	12.9
<b>12a</b> → <b>13a</b>	−9.8	−6.7
<b>12</b> → <b>12a</b>	2.7	8.7
<b>12a</b> → <b>12b</b>	48.5	62.0
<b>12b</b> → <b>12b'</b>	−8.5 (7.2)	—
<b>12b'</b> → <b>12a'</b>	−22.4	—
<b>12a</b> → <b>12a'</b>	17.2 (21.6)	—
<b>12a'</b> → <b>12a''</b>	0.8 (5.6)	—
<b>12a''</b> → <b>13a</b>	−27.8 (26.7)	—

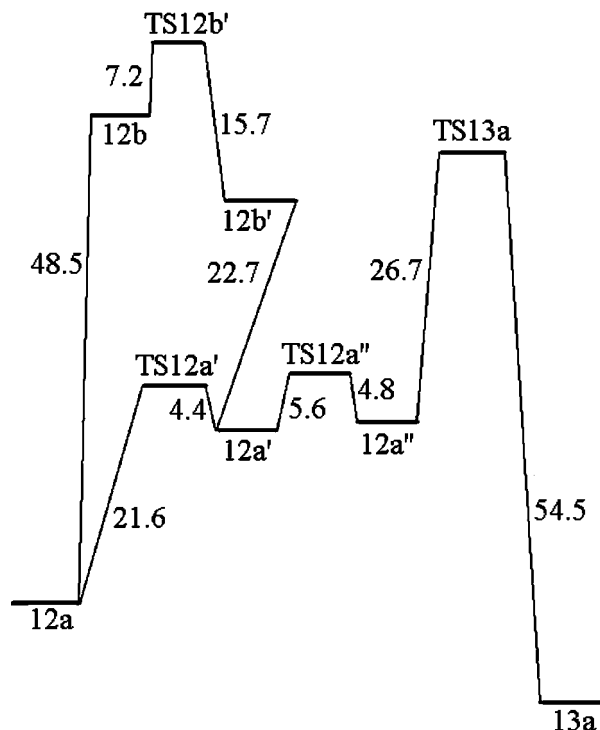
diprotonated intermediate **12b'** from **12b** is of 7.2 kcal/mol, significantly lower compared to similar reaction for monoprotinated intermediates **12a** → **12a'** (21.6 kcal/mol, Table 3) demonstrating higher reactivity of diprotonated molecule **12b** compared to monoprotinated **12a**. However, as seen from the reaction energy profile (Fig. 2), diprotonated transition state **TS12b'** lies 34.0 kcal/mol above the corresponding monoprotinated transition state **TS12a'**. Therefore, it is highly improbable that the reaction mechanism involves the formation of diprotonated intermediate **12b**. Thus, the difference in the reactivity of 2,2-diaryl-1,3-indanedione toward aromatic hydrocarbons in TFSA and H<sub>2</sub>SO<sub>4</sub> can simply be related to the fact that the equilibrium concentration of **12a** is significantly higher in TFSA compared to H<sub>2</sub>SO<sub>4</sub> resulting in fast isomerization of **12a** to **13a** in TFSA. A possible mechanism of this transformation is shown in Scheme 6. Thus, the calculated free Gibbs activation and reaction energies for **12a** → **12a'** process are of 21.6 and 17.2 kcal/mol, respectively (Table 3), which is significantly lower compared to the energy required only for protonation of **12a** to **12b**. The next step is the formation of intermediate **12a''** which is only slightly endergonic (0.8 kcal/mol), with the free Gibbs activation energy of 5.6 kcal/mol. The last step is the transformation of **12a''** to **13a**. This is an exergonic process with the free Gibbs activation energy of 26.7 kcal/mol. The energy profile shown in Fig. 2 demonstrates that the transformation of **12a** to **13a** requires less energy than only second protonation of **12a** according to the mechanism involving only monoprotinated intermediates. Although diprotonated



**Scheme 5.** Participation of diprotonated intermediates (DP) in isomerization of 2,2-diaryl-1,3-indanediones to 3-(diarylmethylene)isobenzofuranones according to Klumpp<sup>[11]</sup>



**Scheme 6.** Two possible mechanisms of isomerization of **12a** to **13a** involving monoprotonated and diprotonated intermediates



**Figure 2.** The free Gibbs energy profile of **12a** → **13a** isomerization involving mono- and diprotonated intermediates

intermediate **12b** is indeed much more reactive compared to **12a** as seen from the reaction energy profile (Fig. 2), the reaction path involving only monoprotonated intermediates is more energetically favorable when energy required for second protonation is taken into account. Therefore, the hypothesis of participation of diprotonated intermediate **12b** in the isomerization process of **12** to **13** seems to be erroneous. Different behavior of 2,2-di(biphenyl)-1,3-indanediones in TFSA and H<sub>2</sub>SO<sub>4</sub> can be explained by the low basicity of carbonyl groups in these diketones and monoprotonated species are the principal reaction intermediates.

While 4-heterocyclohexanones<sup>[8]</sup> form diprotonated species in TFSA media this is not apparently the case for 1,2,3-indanetrione. Strong electron-withdrawing effect of three closely situated carbonyl groups decreases their basicity compared to carbonyl group of 4-heterocyclohexanones. Separation of two protonation centers (carbonyl group and a heteroatom) by dimethylene bridge in 4-heterocyclohexanones increases their basicity, thus favoring diprotonation.

## CONCLUSIONS

Mutual influence of carbonyl groups in 1,2,3-indanetrione reduces their basicity to such an extent that TFSA is only capable of monoprotonated species generation. Even though carbonyl 1 is easier to protonate compared to carbonyl 2,

carbonyl 2 is the most reactive in the reaction of aromatic electrophilic substitution due to extremely low activation energy of  $\sigma$ -complex formation. Calculations show that only mono-protonated species participate in the process of the formation of 2,2-di(biphenyl)-1,3-indanedione from 1,2,3-indanetrione and biphenyl in TFSA media. The calculation suggested that the difference in the behavior of 2,2-diaryl-1,3-indanediones in TFSA and H<sub>2</sub>SO<sub>4</sub> media can be explained without involving diprotonated intermediates. The transformation of 2,2-diaryl-1,3-indanediones to 3-(diarylmethylene)isobenzofuranone is thermodynamically possible only for protonated species. Only TFSA is capable of protonation of 2,2-diaryl-1,3-indanediones due to very low basicity of carbonyl groups making possible the isomerization.

## SUPPORTING INFORMATION

Complete sets of coordinates of optimized structures and the free Gibbs energies in TFSA and H<sub>2</sub>SO<sub>4</sub> solutions are given in the Supporting Information.

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