Superelectrophilic Activation of *N*-Substituted Isatins: Implications for Polymer Synthesis, a Theoretical Study

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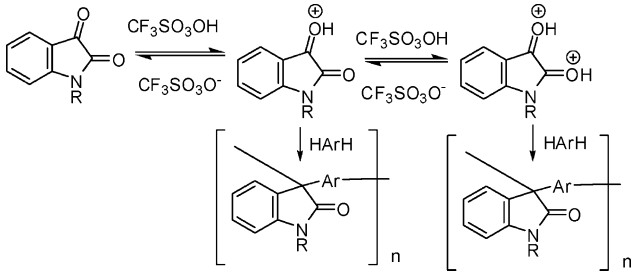
The stability and reactivity of mono- and multi-protonatred *N*-substituted isatin derivatives were studied at PBE0/aug-cc-pvtz//PBE0/6-31+G** level of theory in triflic acid (TFSA) solution. Calculations showed that the monocationic intermediates are the principal reactive species in the reaction of hydroxyalkylation of isatin derivatives in TFSA media. Electron-withdrawing substituents on the nitrogen atom increase the reactivity of isatin-containing electrophiles towards aromatic hydrocarbons, in accordance with their expected electronic influence. Steric factors also play an important role in the reactivity of isatin-containing electrophiles, especially in the second reaction step, due to their more sterically hindered reactive center.



Introduction

The concept of superelectrophilic activation was first advanced by Olah in order to explain the reactivities of some electrophiles in superacid solution.[1] Superelectrophilic activation may occur when a cationic electrophile reacts with a Brönsted or Lewis acid to give a dicationic superelectrophile. Superelectrophilic activation has been proposed in the Friedel–Crafts-type reactions of 1,2-dicarbonyl groups,[2] aldehydes,[3] nitriles,[4] ketones and other systems.[5]

Recently, it has been discovered that catalyzed polyhydroxyalkylation reactions of aldehydes and ketones, containing electron-withdrawing substituents adjacent or relatively close to the place where the carbocation is formed, afford linear, high molecular weight polymers with nonactivated aromatic hydrocarbons.[6,7] It has been shown that the reactivity enhancement of carbonyl compounds bearing electron-withdrawing groups is due to stabilization of their lowest unoccupied molecular orbital (LUMO).[8]

In the case of triflic acid (TFSA)-catalyzed polyhydroxyalkylation of aldehydes and ketones, the increase of reactivity observed for diprotonated species is not sufficient to compensate for the high Gibbs energy needed to form these species and monocationic species are the principal reaction intermediates.[9] On the other hand, the existence of diprotonated carbonyl molecules in superacids has been proven experimentally[10] when an alternative site for second protonation was available (heteroatom or electron-rich double bond). Thus, the TFSA-catalyzed condensation of 3-pyridinecarboxaldehyde with deactivated aromatic compounds, in which the dication was observed by low-temperature NMR, have been

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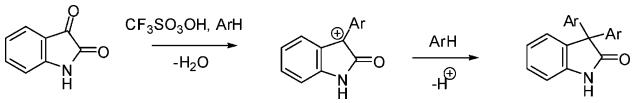


Scheme 1. Scheme of TSFA-mediated polycondensation of isatin with aromatic nucleophiles.

reported.[11] The results provided a demonstration of the reactivity of dicationic electrophiles and suggested that protonation of a strong, adjacent base site activate an electrophilic functional group, such as a carboxonium ion. Calculations also validate the existence of diprotonated reactive intermediates in TFSA solutions of 4-heterocyclohexanones, where both carbonyl oxygen and heteroatom are protonated.[12]

One of the promising monomers for superelectrophilic polymerization is isatin. It was first shown in 1998 that isatin reacts smoothly with aromatics resulting in 3,3-diaryloxindoles[2b] (Scheme 1). First linear[13] and then hyperbranched[14] polymers were obtained using the polyhydroxyalkylation reaction of isatin and its derivatives. A convenient A(2) + B(3) approach to hyperbranched poly(arylene oxindole)s was developed.[15] Very recently, synthesis of isatin-based hyperbranched poly(arylene oxindole)s, with a degree of branching of 100%, for the construction of nanocontainers has been reported, demonstrating the high synthetic potential of isatin monomers in superacid catalyzed polyhydroxyalkylation.[16]

This reaction takes place only in superacid media ($pK_a < -11.5$), which is considered to be indirect evidence for the reactive dicationic species in this process.[2b] Indeed, isatin has multiple protonation sites, making it a suitable substrate for diprotonation. On the other hand, isatin can be considered to be a carbonyl-molecule-bearing electron-withdrawing group. It has been shown[9] that, in this case, monoprotonated intermediates are the reactive species in hydroxyalkylation reactions in TFSA. Therefore, the aim of this paper is to study the protonation process of isatin in superacid media and to propose reactive species participating in the hydroxyalkylation of isatin to get deeper insight into the mechanism of its polymerization.

Computational Details

All calculations were carried out using the Jaguar 7.5 suite of programs.[17] The model selection was based on its ability to reproduce the experimentally determined pK_a values of different acids, since exact pK_a determination implies accurate calculation of the Gibbs free energies (ΔG) of solvated ionic species. This model is described in detail in Reference [9]. The average error in pK_a determination was about 1 pK_a unit, corresponding to about 1.4 kcal · mol^{-1} in the ΔG of the protonation reaction.

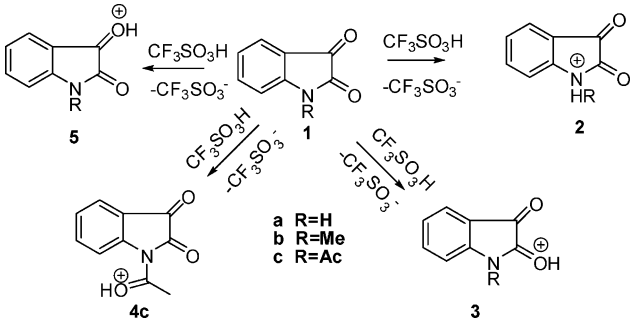
The Gibbs energy in solution was calculated, according to the model, as the sum of two terms: E_s, and ΔG_c where E_s is the total electronic energy in solution, calculated at the PBE0/aug-cc-pvtz level using PBE0/6-31+G** solution-phase optimized geometry, and ΔG_c is the free Gibbs energy correction, calculated as the difference between the total electronic energy and the Gibbs free 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,[18,19] implemented in the Jaguar v7.5 suite of programs using a dielectric constant and a solvent probe radii for TFSA of 77.4 and 2.60 Å, respectively. Calculations of the electron affinity (EA) of isatin-containing electrophiles were carried out at the PBE0/aug-cc-pvtz//PBE0/6-31+G** level of theory in TFSA solution.

Results and Discussion

Monoprotonation

Three different isatin derivatives were studied; isatin (**1a**), *N*-methyisatin (**1b**) and *N*-acetylisatin (**1c**) to monitor the electronic effect of substituents on the reactivity of isatin derivatives. Isatin molecules have three heteroatoms and, therefore, three possible protonation sites. **1c** has additional protonation site – the oxygen atom of the acetyl group. Scheme 2 and Table 1 show the monoprotonation reactions in TFSA and the corresponding Gibbs free energies of the protonation reactions.

In all cases, in particular **1c** – where the effect of acetyl group reduces even further the nitrogen basicity – the nitrogen atom is the less favored protonation site. This situation is common for many amides, in which carbonyl rather than nitrogen is the first protonation site,[20] due to delocalization by resonance of the nitrogen lone pair over the carbonyl group. In fact, amide carbonyl is the most favored protonation site for all studied isatin derivatives except for **1c**, where the –I effect of the acetyl group reduces the basicity of the amide carbonyl to such an

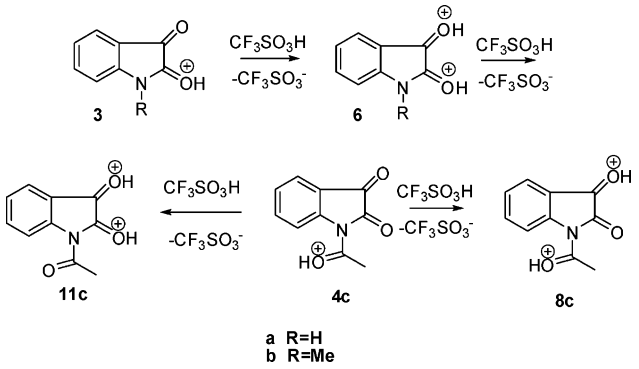


Scheme 2. The reactions of isatin monoprotonation in TFSA.

Table 1. Calculated the free Gibbs energies of protonation (ΔG_p) of different molecules in TFSA.

Reaction	ΔG_p
	kcal · mol^{-1}
First Protonation	
1a → **2a**	8.51
1b → **2b**	11.81
1c → **2c**	20.11
1a → **3a**	−0.70
1b → **3b**	−1.55
1c → **3c**	5.94
1c → **4c**	−0.85
1a → **5a**	1.79
1b → **5b**	2.01
1c → **5c**	3.18
15a → **16a**	8.84
15b → **16b**	5.29
15c → **16c**	15.61
15c → **17c**	2.23
Second Protonation	
3a → **6a**	13.88
3b → **6b**	13.87
4c → **8c**	8.54
4c → **11c**	20.47

extent that the acetyl carbonyl becomes the most favored protonation site. However, in order to generate the electrophile for hydroxyalkylation, the ketone carbonyl of isatin must be protonated. As seen from Table 1, the protonation of ketone carbonyl in isatin derivatives is an endergonic reaction in all cases, even when in TSFA, suggesting that diprotonated intermediates are not necessarily the reactive species in the hydroxyalkylation of isatin. Moreover, the protonation energies are barely affected by the nature of the *N*-substituent. The relatively weak basicity of the ketone carbonyl of isatin derivatives compared to acetophenone,[9] for example, is due to the –I effect of the adjacent amide carbonyl. In fact, the basicity of ketone carbonyl in isatin is close to that of 2,2,2-trifluoracetophenone,[9] where the carbonyl group is also affected by an electron-withdrawing trifluormethyl group. It has been shown[6,7] that 2,2,2-trifluoracetophenone reacts smoothly with aromatics to give high molecular weight polymers and that monoprotonated species are the principal reactive intermediate. The isatin molecule is different because of multiple protonation sites and multiprotonated species are likely to exist in TSFA solution. Therefore, second, third and fourth protonation



Scheme 3. The reactions of isatin diprotonation in TSFA.

energies were calculated and listed in the Table 1. The protonation reactions are shown in Scheme 3.

Diprotonation

Scheme 3 shows possible multiprotonated isatin intermediates. Since the protonation of ketone carbonyl is a necessary condition for aromatic electrophilic substitution to occur, the only multiprotonated intermediates considered were these for which ketone carbonyl is also protonated. The most stable monoprotonated intermediates – **5a**, **5b** and **4c** – were selected as possible intermediates for multiple protonation. All of them have negative ΔG_p and, therefore, are the predominant species in TSFA solution.

As seen from Table 1, the most stable diprotonated isatin molecule is **8c**, for which positive charges are well separated, while the least stable is **11c**, where the proximity of two protons and electron withdrawing acetyl group discourage dication stability. On the other hand, diprotonated intermediates **6a** and **6b** show very similar energies, revealing that methyl substitution of nitrogen in the isatin molecule affects the stability of protonated species very little. In all cases, the second protonations are endergonic, with ΔG being markedly more positive compared to the first protonation. Owing to the very high values of the Gibbs energy of the third and fourth protonations – much higher than those of the first and second – these reactions were excluded from the theroretically calculations.

Formation of σ-Complexes

The σ-complex formation is the rate-determining step in the reaction of aromatic electrophilic substitution.[21] Therefore, it is possible to elucidate the true reactive intermediates of the aromatic electrophilic substitution by the comparison of the free Gibbs activation energies of σ-complex formation and the corresponding protonation

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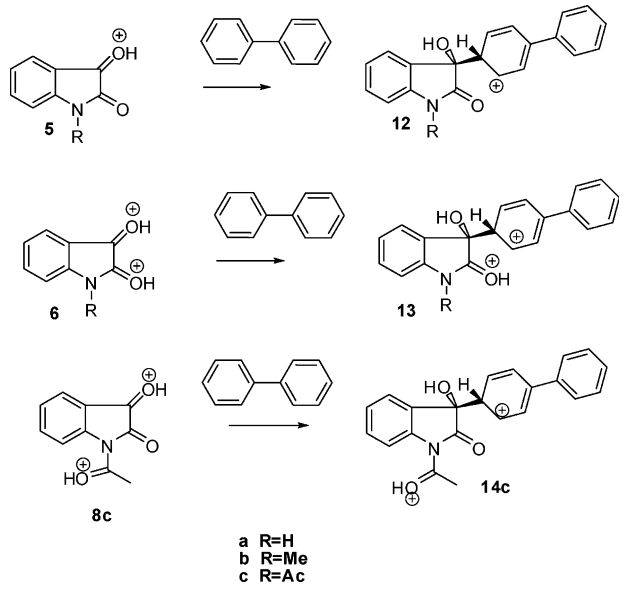


Scheme 4. The reactions of σ-complex formation between protonated isatin derivatives and biphenyl (fist step).

energies of isatin derivatives. As an example, the reaction between isatin derivatives and biphenyl was chosen, since biphenyl is a common monomer in the reactions of superelectrophilic polymerization.[6–9] Scheme 4 shows the reaction of σ-complex formation from different protonated isatin derivatives and biphenyl. Among monoprotonated isatins, the only reactive species are **5a**, **5b** and **5c**, since the protonation of the ketone carbonyl is the necessary condition for the reaction to occur.

When comparing the G_a of σ-complex formation for monoprotonated intermediates (Table 2) it is seen that the activation energy is highest for **5b** and lowest for **5c**, in accordance with the electronic effect of *N*-substituents. These differences, however, are small – not exceeding 4 kcal · mol^{-1}. The effect of second protonation is more pronounced. Thus, the decrease of G_a on protonation of the amide carbonyl is 9 kcal · mol^{-1} for diprotonated intermediate **6a**. On the other hand, the protonation of acetyl oxygen for **8c** decreases the activation energy by less than 3 kcal · mol^{-1} compared to monoprotonated **5c**. This is related to the 4.71 to 5.53 eV change of EA for the **5a** → **6a** process, while for the **5c** → **8c** process this is 4.89 to 5.26 eV (Table 3), which is due to there being a larger distance between the second protonated site and the reactive center. Intermediates **6a–c** and **8c** are the most stable diprotonated isatin derivatives for which ketone carbonyl is protonated. To estimate the relative contribution of mono- and diprotonated intermediates to the reaction mechanism, one should compare the G_a of diprotonated species with the sum of the G_a for monoprotonated isatin derivatives and the corresponding energies of second protonation, according to the Curtin-Hammett principle.[23]

Table 2. Calculated the free Gibbs activation energies of σ-complexes formation (G_a) of different molecules in TFSA.

Reaction	G_a	$\Delta G_p + G_a$ [a)]
	kcal · mol^{-1}	kcal · mol^{-1}
5a → **12a**	31.03	–
5b → **12b**	32.07	–
5c → **12c**	28.41	–
6a → **13a**	22.03	–
6b → **13b**	27.59	–
6c → **13c**	22.50	–
8c → **14c**	25.97	–
15a → **18a**	27.70	–
15b → **18b**	25.36	–
15c → **18c**	31.00	–
16a → **19a**	24.64	–
16b → **19b**	25.60	–
16c → **19c**	18.65	–
17c → **20c**	32.60	–
5a → **6a** → **13a**	–	33.42
5b → **6b** → **13b**	–	37.90
5c → **6c** → **13c**	–	40.64
5c → **4c** → **14c**	–	30.48
15a → **16a** → **19a**	–	33.48
15b → **16b** → **19b**	–	30.89
15c → **16c** → **19c**	–	34.26
15c → **17c** → **20c**	–	34.83

[a)] $\Delta G_p + G_a$ represents a sum of the Gibbs free energy of protonation and the Gibbs activation free energies of σ-complexes formation (G_a) between the corresponding protonated molecule and biphenyl.

These data are listed in Table 2. As seen, in spite of the fact that the free Gibbs activation energies of σ-complex formation for diprotonated isatin derivatives are lower compared to monoprotronated ones, the strongly positive ΔG_p of second protonation increases the energy of diprotonated transition states to such an extent that they become higher in energy compared to monoprotonated ones. This is especially pronounced for *N*-methylisatin (**1b**), for which the difference between mono- and diprotonated transition states is more than 5 kcal · mol^{-1}. In the case of **1a** and **1c**, the differences are only 2.39 and 4.51 kcal · mol^{-1}, respectively. It is noteworthy that, according to calculations, **8c** is more reactive than **6c**, even thought the ketone carbonyl is more activated in **6c**. However, the strongly positive ΔG_p for the formation of **6c** compared to **8c** increases the effective free Gibbs

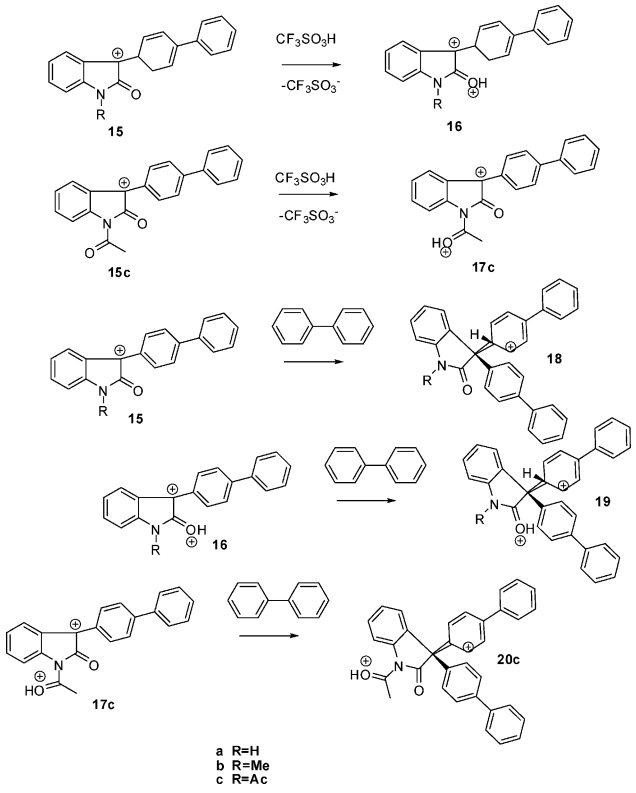
Table 3. The electron affinities (EA) of isatin-containing eletrophiles.

Molecule	EA
	eV
5a	4.71
5b	4.69
5c	4.89
6a	5.53
6b	5.51
6c	5.78
8c	5.26
15a	5.01
15b	5.00
15c	5.14
16a	5.70
16b	5.65
16c	5.85
17c	5.36

activation energy for reactions involving **6c**. Therefore, monoprotonated intermediates are the most important reaction intermediates in the hydroxyalkylation of isatin derivatives. However, at least for **1a** diprotonated intermediates, **6a** can contribute to some extent to the total reaction rate, since the energy difference between mono- and diprotonated transition states is not very high.

The formation of σ-complexes **12a–c**, **13a–c** and **14c** is the first step of the hydroxyalkylation reaction. The second and last step is the reaction of carbocations **15a–c**, formed from σ-complexes **12a–c**, **13a–c** and **14c** with biphenyl molecule to produce σ-complexes **18a–c**, **19a–c** and **20c** (Scheme 5). The formation of this type of complex has recently been discussed in detail.[9] Since cations **15a–c** have heteroatoms with lone pairs, they also can be protonated in superacid media. Their free Gibbs protonation energies in TFSA are shown in Table 1. As seen, the amide carbonyl in cations **15a–c** is much less basic, compared to the neutral molecules **1a–c**. The protonation energies are strongly affected by the nature of the substituent at the nitrogen atom. Thus, the protonation energy difference between **15b**, bearing an electron-donating methyl group, and **15c,** having an electron-withdrawing acetyl group, exceeds 10 kcal · mol^{-1}. In the case of **15c**, there is a possibility of acetyl-group protonation, giving dication **17c**. Table 2 shows the Gibbs activation free energies for the formation of **18a–c**, and their protonated forms **19a–c** and **20c**.

As seen, there is no clear correlation observed between G_a and the electronic properties of *N*-substituents for



Scheme 5. The reactions of σ-complex formation between isatin-containing mono- and dications and biphenyl (second step).

cations **15a–c**, contrary to observations of the formation of the first σ-complexes, **5a–c**. On the other hand, correlation is observed for dicationic species **16a–c**. Thus, the protonation of **15b** causes a slight increase of the Gibbs activation free energies, while the protonation of **15a** and **15c** results in a reduction in the G_a. Cation **15c** has two protonation sites: the acetyl and amide carbonyls. As could be expected, the protonation of the amide carbonyl (closest to the reaction center) causes the most pronounced reduction of the Gibbs activation free energy (Table 2, Scheme 5). As mentioned above, to estimate the relative contribution of mono- and diprotonated intermediates to the reaction mechanism, one should compare the G_a of diprotonated species with the sum of the G_a for monoprotonated isatin derivatives and the corresponding energies of second protonation, according to the Curtin-Hammett principle.[22] As Table 2 shows, in all cases monocations are the true reaction intermediates. Similar to the first reaction step, the dicationic transition states are higher in energy than monocationic ones. However, it is possible that there is some contribution from dicationic intermediates to the total reaction rate, since the difference does not exceed a few kcal · mol^{-1}.

As has been shown previously,[23] the difference between the electron affinity (EA) of the electrophile

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Table 4. Correlation coefficients (R) between calculated reactivity indexes (EA) and the Gibbs activation free energies of studied reactions.

Molecule	R
5a–17c	0.73
5a, 6a, 15a, 16a	0.90
5b, 6b, 15b, 16b	0.83
5c, 6c, 8c, 15c, 16c, 17c	0.75
5a, 5b, 5c, 6a, 6b, 6c, 8c	0.90
15a, 15b, 15c, 16a, 16b, 16c, 17c	0.60

and the ionization potential of the nucleophile is a simple, yet reliable, descriptor for the reactivity of the monomers in the superelectrophilic polymerization. For the case of the only nucleophile, EA can be considered as a descriptor of the electrophile reactivity. Table 3 and 4 show the vertical EA of electrophiles and the correlation coefficients (R) between EAs and G_a. As seen from Table 4, R is different for different groups of cations. Thus, the best correlation is observed for unsubstituded isatin derivatives and for the first step reaction step ($R = 0.90$). The worst correlation is manifested for the reaction intermediates involved in the second reaction step ($R = 0.60$) and for the intermediates derived from *N*-acetylisatin (**1c**) derivatives ($R = 0.75$). As seen, the correlation decreases with the size of substituent at the nitrogen atom, implying that the hydroxyalkylation of isatin is sensitive to steric effect. A similar conclusion can be drawn by observing the reduction of R for the second step of hydroxyalkylation; the bulky biphenyl substituent at the reaction center causes the deterioration of the correlation between the EA of the electrophile and the Gibbs activation free energy of the σ-complex formation with the biphenyl molecule.

Conclusion

The obtained results shed new light upon the possibility of monomer design for the superelectrophilic polymerization. Calculations demonstrate that monocationic intermediates are the most important reactive species in the reaction of hydroxyalkylation of isatin derivatives. The fact that this reaction takes place only in superacid media ($pK_a < -11.5$) does not contradict this conclusion, since even in TFSA the monoprotonation of ketone carbonyl is endergonic. However, due to the relatively small difference (a few kcal $\cdot$ mol^{-1}) between the energies of mono- and dicationic transition states, a small contribution from dicationic intermediates cannot be completely ruled out. Although the electronic factor is of importance (the Gibbs activation free energies for the formation of σ-complexes are generally lower for intermediates having an electron-withdrawing acetyl group at the nitrogen atom compared, to an electron-donating methyl group) steric factors play an important role too, especially for the second reaction step. According to our calculations, the increase of the acidity of the media beyond TFSA will favor the formation of diprotonated intermediates, increasing isatin reactivity in superelectrophilic polymerization.

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