Heterocyclic Letters
Vol. 8| No.3|587-592|May-July|2018
ISSN : (print) 2231–3087 / (online) 2230-9632
CODEN: HLEEAI
http://heteroletters.org

THEORETICAL AND EXPERIMENTAL STUDY OF SOLVENT EFFECTS ON THE PRODUCING OF POWERFUL FLUOROPHORES 3,8-DISUBSTITUTED-3*H*-IMIDAZO[4,5-*A*]ACRIDINE-11-CARBONITRILES

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Abstract- 3-Alkyl-8-substituted-3*H*-imidazo[4,5-*a*]acridine-11-carbonitriles show very interesting fluorescence properties with high quantum yields. In this paper, the effect of solvent polarity on the producing of these powerful fluorophores has been fully investigated *via* DFT (Density Functional Theory) study by using the B3LYP hybrid functional and the 6-311++G(d,p) basis set and Polarized Continuum Model (PCM). Based on theoretical calculations, polar solvents increase the activation energy for the rate determining step while all species are more stable in solution phase. In experimental studies, 3*H*-imidazo[4,5-*a*]acridine was obtained from the reaction of 1-methyl-5-nitrobenzimidazoles with 4-methylbenzyl cyanide in basic media and various solvents at rt. Experimental observations are in good agreement with theoretical results when the reaction is carried out in the less polar solvent.

Keywords: DFT study; Solvent effect; Imidazo[4,5-*a*]acridine; Polarized Continuum Model

1. Introduction

Great progress has been made during the last decade in theoretical treatments of solvent effects by various quantum-chemical methods and computational strategies. Polarity of solvents cause stability of all the species in the reactions, obviously solvent with a great dipole moment can polarize and lead to greater stability of species. Usually transition states have much more dipole moment than reactants, then as a result of decreasing barrier energy in a polar solvent comparing the gas phase, but if the reactant becomes much more stable than transition state in a polar solvent, the activation energy increased.

On the other hand, it is demonstrated that imidazoacridine derivatives considerably noted for the synthesis of drugs for treatment of many disease [i–iii] and other aspects of industrial organic material's usage, in a large number of cases [IV–VIII]. Among the imidazoacridines, substituted-3*H*-imidazo[4,5-*a*]acridines are an important class of heterocyclic pharmaceuticals and powerful fluorophores. They exhibit interesting biological properties, such as antibacterial [iv] and antiviral [x] activities. Moreover, the interactions of 3*H*-imidazo[4,5-*a*]acridines with Human Serum Albumin (HSA) have been recently studied by

fluorescence spectroscopy. [xi,xii] In some case, 3*H*-imidazo[4,5-*a*]acridines with a suitable functionalization have a higher quantum yields compared to Fluorescein. [xiii-xv]

In our earlier study, we have gained the most reasonable mechanism in formation of 3,8-disubstituted-3*H*-imidazo[4,5-*a*]acridine-11-carbonitriles by the Density Functional Theory (DFT) methods.[xvi] This reaction is one pot synthesis and occurs usually in protic solvents apparently *via* protonation of the negatively charged oxygen of nitro group of the δ^H -adducts and elimination of water in the first step.

In this paper, the effect of polarity of solvents on the reaction mechanism in the formation of 3,8-disubstituted-3*H*-imidazo[4,5-*a*]acridine-11-carbonitriles has been theoretically and experimentally investigated.

2. Materials and methods

Melting point was recorded on an Electrothermal type-9100. Compound **3a** [xiv] was obtained according to the published method (m.p. 308–309 °C), lit. [xiv] 307–309 °C). Other reagents were commercially available.

All calculations have been performed with the Gaussian 03 [xvii] employing DFT [xviii], B3LYP hybrid functional [xix–xxi] and the 6-311++G (d, p) basis set.

At first, geometries of all species and related transition states optimized in solution and gas phase then frequencies were calculated.

In addition, the optimized geometries were revised for having just one imaginary frequency for transition states and other species have no imaginary frequencies.

The self-consistent reaction field method, the sophisticated Polarized Continuum Model (PCM) was used for all calculations in solvents. [xxii]

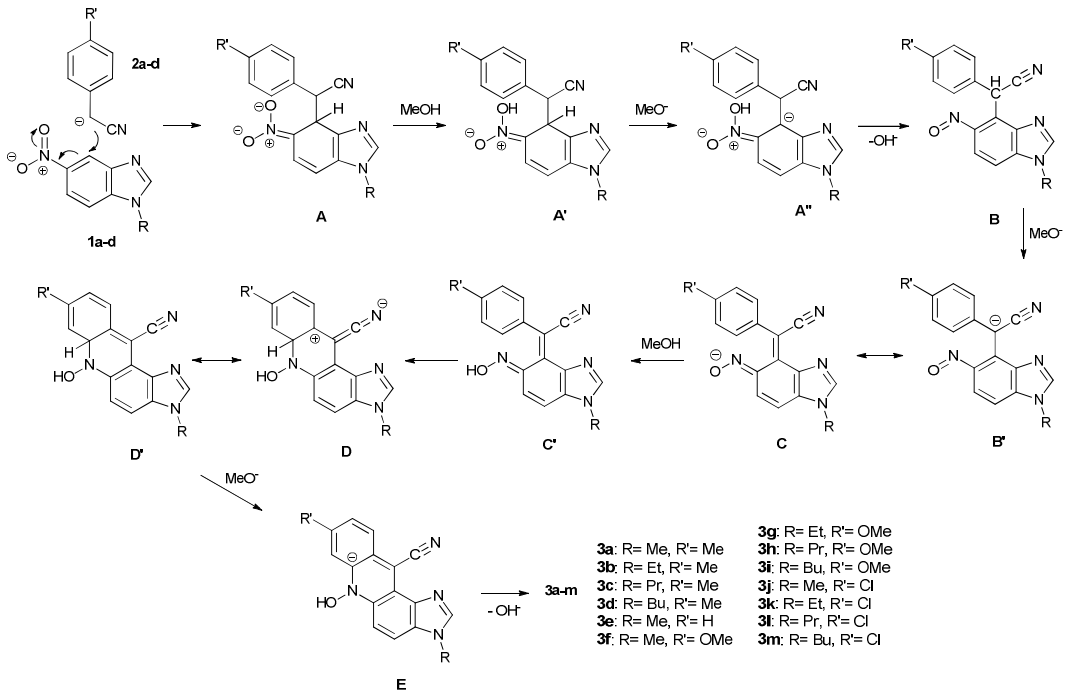
In the gas phase and PCM model, sum of electronic and zero point energies (E) and sum of electronic and thermal Free Energies (G) extracted from the frequency calculations for all species and transition states.

For all step activation's energy were calculated with using of $E_a = E_{TS} - E_R$, which E_{TS} and E_R, are energies related to transition state and reactant respectively.

All calculations were performed at room temperature and 1atm. pressure for obtaining the exact conditional with the experimental results. [xiii–xv]

3. Results and discussion

As depicted in Scheme 1, the most plausible reaction mechanism to explain the formation of fluorophores **3a–m** involves the attack of the anions **2a–d** on compounds **1a–d** and the preparation of intermediates **A** and **A'** followed by dehydration of **A''** and the formation of intermediate **B** in basic media. Finally, intramolecular electrophilic aromatic substitution of **C'** to **D** led to the formation of the compounds **3a–m.** [xvi]



Scheme 1. The most probable mechanism for the preparation of **3a–m.**

In this paper the role of solvent polarity in the formation of fluorophores **3a**–**m** is theoretically and experimentally investigated.

In theoretical investigations, we performed DFT calculations at the B3LYP/6-311++G(d,p) level and obtained the optimized geometries of the all species and related transition states of compound **3a** (R and R'=Me) involved in rate determining step (RDS) of the reaction mechanism in the gas phase and PCM model.

Since the dehydration process (conversion of A' to B) needs to protic solvent theoretical investigation has been done in protic solvents in PCM model and gas phase. [xxiii]

Some useful information about thermodynamic and kinetic of the reaction such as activation energies (Kj/mol) in various solvents were collected in Table 1.

By comparing the activation energy for the rate determining step (reaction C'→D) can be concluded that when the polarity of solvent increases, the activation energy increases too, because of the stability of reactants which are much more stable than transition state (Table 1).

Also, Free Gibbs Energy for rate determining step in various solvents in Table 1 reveals that Free Gibbs Energy of reaction in the gas phase is more negative compared to solvents.

Table1: Activation energy, ZPE* and Free Gibbs energy of RDS in various protic solvents ($kJ.mol^{-1}$)

Solvent	C'	D	TS C'→ D	E_{act} (C'→ D)	ΔG (C'→ D)	Dipole moment (D)
H_2O	-950.362366	-950.366226	-950.340266	57.97	-0.28	1.85
MeOH	-950.364315	-950.36543	-950.339531	57.54	-3.16	1.70
EtOH	-950.360934	-950.365024	-950.339145	57.15	-5.80	1.69
1-propanol	-950.360505	-950.364663	-950.338811	56.90	-5.93	1.68
2-propanol	-950.360244	-950.364530	-950.338686	56.55	-1.69	1.66

* Sum of electronic and Zero Point Energy

Optimized structures of transition states related to the determining step of proper mechanism (reaction C'→ D in Scheme 1) in some solvents with various polarity and gas phase are shown in Figure 1.

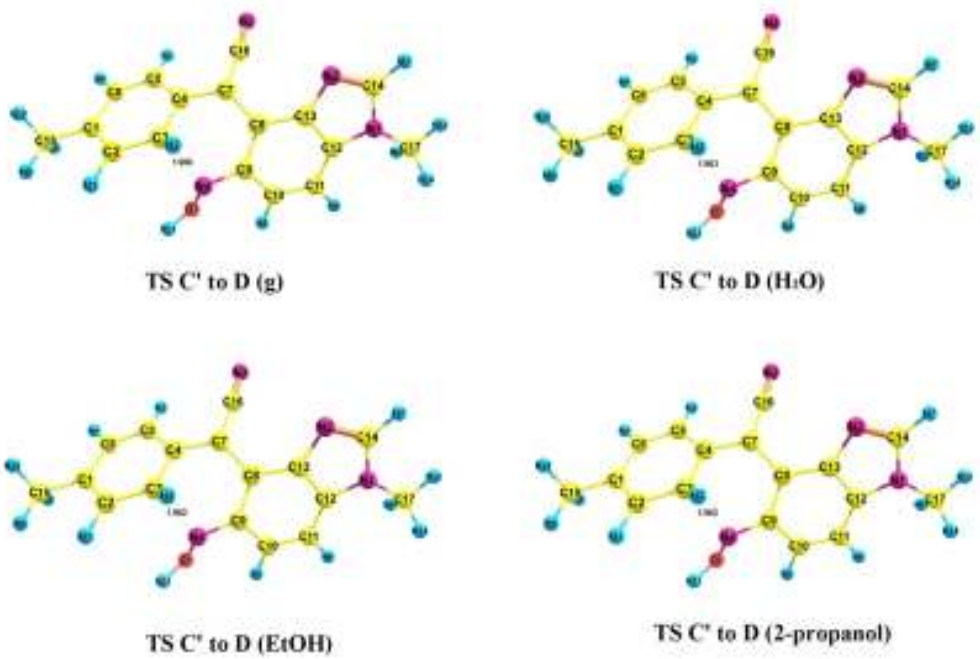


Fig. 1: Optimized structures of transition states in the gas phase and some solvents

In experimental studies, compound **3a** was obtained from the reaction of 1-methyl-5-nitrobenzimidazoles (**1a**) with 4-methylbenzyl cyanide (**2a**) in basic media and various solvents at rt (Scheme 1). Although, difference in calculated E_{act} of the rate determining step in various solvents is not very high, experimental results are impressive. Observations show that the time of the reaction decreases when the polarity of the solvent decreases. Moreover,

the percent yield of the reaction increases with decreasing the solvent polarity (Table 2). These results are in agreement with theoretical studies.

Table 2. Experimental results of the formation of **3a** in some solvents.

Solvents	H_2O	MeOH	EtOH	1-propanol	2-propanol	H_2O + MeOH (50:50)	MeOH + 1-propanol (50:50)	EtOH + 1-propanol (40:60)	EtOH + 2-propanol (40:60)
Yield (%)		61	65	-*	-*	30	60	70	76
Time (h)		24	20	-	-	72	24	15	12

* Since KOH is not very soluble in 1-propanol and 2-propanol, yield of the reaction in these solvents is trace

4. Conclusion

3,8-Disubstituted-3*H*-imidazo[4,5-*a*]acridine-11-carbonitriles show very interesting optical properties. In some case, they have higher quantum yields compared to well-known fluorescent dyes such as Fluorescein. Computational DFT Study in the solution and gas phase of the reaction confirms that the activation energy for the rate determining step of the reaction increases when the polarity of solvent increases, because of the stability of reactants which is much more stable than transition state. Furthermore, Free Gibbs Energy for rate determining step in various solvents show that reaction in all solvent has negative Free Gibbs Energy, but in the gas phase has much more negative value. Also, experimental results are in agreement with theoretical studies and show that the time of the reaction decreases with decreasing the solvent polarity. In addition, yield of the reaction increases when the polarity of the solvent reduces.

The results of the study can lead to the synthesis of new fluorophores based on acridine chromophore in high yields.

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Received on April 17, 2018.