Research Article

Journal of Physical Organic Chemistry

Received: 21 August 2010, Revised: 27 September 2010, Accepted: 28 September 2010, Published online in Wiley Online Library: 7 December 2010

(wileyonlinelibrary.com) DOI 10.1002/poc.1817

The mechanism of aromatic nucleophilic substitution reaction between ethanolamine and fluoro-nitrobenzenes: an investigation by kinetic measurements and DFT calculations

K.B. Jose[a], J. Cyriac[a], J. T. Moolayil[a], V.S. Sebastian[a] and M. George[a]*

We have studied the kinetics and elucidated the mechanism by DFT calculation of the reaction between ethanolamine (EOA) and 1-fluoro-2,4-dinitrobenzene (DNFB) in acetonitrile and toluene. To determine the contribution of the nitro group, the activation energy of the reaction between ethanolamine and 1-fluoro-2-nitrobenzene (MNFB) vs. DNFB was determined in acetonitrile and calculated by DFT method. Kinetic measurements reveal that the reaction is faster in acetonitrile than in toluene. The reaction follows overall second-order kinetics: first order with respect to both EOA and DNFB which is similar to the results reported for reaction between other primary amines and 1-substituted-2,4-dinitrobenzenes. The calculations by using DFT methods reveal that the mechanism of the reaction involves the formation and decomposition of a Meisenheimer complex (MC). DFT calculations also reveal that the activation energy of the reaction is highest in vacuum and decreases with increasing polarity of the solvent reaching a minimum in acetonitrile. In addition, activation energies obtained by both DFT calculations and experiments show that the reactivity of MNFB is less than that of DNFB showing the effect of the 4-nitro group. Copyright © 2010 John Wiley & Sons, Ltd.

Supporting information may be found in the online version of this paper.

Keywords: activation energy; aromatic nucleophilic substitution; DFT calculation; Meisenheimer complex; solvent effects

INTRODUCTION

Aromatic nucleophilic susbstitution reactions involving primary amines are an important class of organic synthetic reactions and continue to inspire studies of kinetics and mechanisms.[1–10] Studies have revealed that the displacement of the substituent at 1- position is faster when the aromatic ring contains electron-withdrawing substituents at *ortho* and *para* positions.[2,3] Mechanisms involving the formation and decomposition of Meisenheimer complexes (MC) have been proposed for S_NAr reactions on the basis of kinetic studies[4,5] and summarized recently.[9,10] Amine catalysis for the decomposition of MC has been suggested on the basis of kinetic measurements.[5] The effect of electron-withdrawing substituents and solvents on the rate of the displacement of fluorine, chlorine or phenoxy groups at the 1-position by primary and secondary amines. Most reports on kinetic measurements concur that the reaction is overall second order: first order with respect to both substrate and amine; and the rate-determining step is the formation of the MC.

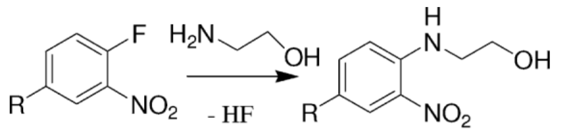
Molecular orbital calculations using Density Functional Theory (DFT) is being increasingly used for deducing and understanding mechanisms of organic reaction in the molecular level.[11] The mechanisms of few aromatic nucleophilic substitution reactions have been investigated by performing theoretical calculations by other methods.[10,12] For example, the mechanism of nucleophilic displacement of chloride from 1-chloro-2,4-dinitrobenzene by thiomethoxide ion (CH_3-S-) was investigated by both Hartree-Fock and MP2 using 6–31+G** basis set.[13] The mechanism involves the formation and decomposition of MC between thiomethoxide ion and 1-chloro-2,4-dinitrobenzene. The rate-determining step is the formation of the MC and the calculated energy barrier for its decomposition to products is very small. The results of the study have been utilized for the theoretical modeling of the enzyme catalyzed displacement of chloride ion by DFT (B3LYP/6-311+G**) and PM3 semi-empirical methods.[14]

Other examples are the nucleophilic displacement of halide by another halide ion[15] and fluoride by ammonia, explored by DFT calculations.[16] DFT Calculations, at B3LYP/6-31G* level of theory, have been utilized to calculate the energy profile of the reaction between ammonia and polyfluorobenzene to arrive at the relative energies of the transition states for the formation and decomposition of the MC, indicated as the rate-determining step. The effect of solvent on the aromatic nucleophilic substitution reaction between azide ion and 4-fluoronitrobenzene has been investigated using DFT calculations.[17] However, the mechanism of displacement of aromatic halides by primary amines has not been explored theoretically. In addition, the preferred method for the synthesis of *N*-(2-nitroaryl)aminoethanol involves either the displacement of halide using ethanolamine[18,19] or the Smiles rearrangement of 2-(nitrophenoxy)ethylamine.[20]

---

* *Correspondence to: M. George, Department of Chemistry, Sacred Heart College, Thevara, Kochi 682013, India.*
E-mail: georgem_mathai@yahoo.co.in

a *K. Jose, J. Cyriac, J. T. Moolayil, V. Sebastian, M. George*
Department of Chemistry, Sacred Heart College, Thevara, Kochi 682013, India



1. R=NO_2
2. R=H

3. N-(2,4-dinitrophenyl)ethanol
4. N-(2-nitrophenyl)ethanol

Scheme 1. The reactions under study.

We report the investigation of the displacement of fluoride from 1-fluoro-2,4-dinitrobenzene (DNFB) or 1-fluoro-2-nitrobenzene (MNFB) by ethanolamine (EOA) a primary amine by kinetic measurements. We employed molecular modeling by DFT methods to confirm the mechanism of these reactions (Scheme 1). The kinetic measurements were conducted in acetonitrile and toluene to study the effect of solvent polarity on the rate of reaction. Furthermore, the effect of solvent on the activation energy of the reaction has been explored by applying solvation models (SM8 model, Spartan v. 8) to calculate the activation energies required for the displacement of fluorine in various solvents having different dielectric constants.

EXPERIMENTAL

Synthesis of the products

Products **3** and **4** (Scheme 1) were synthesized by reaction between 1-fluoro-2,4-dinitrobenzene and 1-fluoro-2-nitrobenzene, respectively, with excess of ethanolamine in acetonitrile at room temperature.[18] The structures of the purified products were confirmed by IR, NMR, and mass spectral data (Supporting Information). The UV/VIS spectra were recorded to determine the λ_{max} of the products.

Kinetic measurements

The progress of reactions was monitored by measuring the increase in the absorbance of the reaction mixture (at intervals of 10 s) at the λ_{max} of the product, *N*-2,4-dinitrophenyl -2-aminoethanol. Absorbance was measured by using Shimadzu, UV 1800 double beam UV/VIS spectrometer equipped with (thermoelectrically controlled) thermo-stated cell holder and UVProbe software. To start a kinetic run, a stock solution of DNFB in acetonitrile was added into a thermostated cell containing the solution of the primary amine such that the cell contained a total of 3 ml of the reaction mixture. In the reference beam, a cell containing pure solvent was kept (acetonitrile or toluene was used as solvent). All kinetic runs were carried out under pseudo-first-order conditions with the substrate concentration of the order of 10^{-5} M. For each kinetic run a time course graph is obtained by plotting the absorbance against time, for a set convenient time by using the UVProbe software and a kinetic 'point-pick' report which gives the absorbance at any time, '*t*' was generated. By assuming 100% conversion, the absorbance at completion of reactions (A_α) was determined by plotting a calibration graph between the absorbance of the isolated product at its λ_{max} and molar concentration for a series of standard solutions. The absorbance at any time (A_t) was obtained by subtracting the initial absorbance from the measured value. Pseudo-first-order rate constants (k_{obs}) were obtained by a linear least-squares fit of the experimental data, absorbance vs. time (Supporting Information).

Molecular modeling

All DFT calculations both in vacuum and in solution phase (in ethanol, toluene, diethylether, and acetonitrile) were carried out using Spartan 08 software package.[21] Geometry optimizations were carried out at B3LYP/6-31G* and B3LYP/6-311G* (vacuum) levels of theory to determine the energies of the reactants, products, transitions states, and intermediates. For the calculations of the solvation models (SM8)[22] geometry optimizations were performed using the B3LYP/6-31G* method. The relative energies (relative enthalpies of formation/reaction) of the intermediates, transition states, and products were computed relative to the total energies of the reactants.

RESULTS AND DISCUSSIONS

Kinetic studies

The reactions of ethanolamine with DNFB, and MNFB yield products **3** and **4** formed by the displacement of fluorine in quantitative yields at room temperature (Scheme 1). From the UV/VIS spectra, the λ_{max} of **3** and **4** were determined in acetonitrile to be 351 nm (345 nm in toluene) and 428.5 nm, respectively.

The rate of reaction of ethanolamine with DNFB in acetonitrile at 313K was studied at several amine concentrations. In all runs the DNFB concentration was much less than that of amine to maintain pseudo-first-order kinetics. The observed rate constant k_Y increased linearly with increase in the initial concentration of ethanolamine used, Table 1. The second-order rate constants, k_A obtained from the relation $k_A = k_Y/[EOA]$, were practically constant, indicating, first-order dependence of the rate on the [EOA]. The first-order dependence of rate on the [EOA] is further confirmed by the log k_Y vs. log [EOA] plots, which are linear with slopes of almost unity (linear regression method gives $r = 0.99027$ and slope = 1.086). The study of the kinetics of reaction between EOA and DNFB was repeated in toluene at 303K at several amine concentrations, where again low concentrations of DNFB were maintained to preserve pseudo first-order rate conditions. The rate of reaction was likewise first-order on [EOA] and less than that in acetonitrile (Table 2).

When the progress of the reaction was studied with different initial concentrations of the DNFB, keeping the [EOA] constant, in acetonitrile at 313K under pseudo first-order conditions, plots of log absorbance versus time were found to be linear which indicates first-order dependence of rate on the [DNFB]. This was

Table 1. The observed rate constants at various concentrations of EOA

S. No.	[EOA]/10^{-3} M	$k_\psi/10^{-2}$ S^{-1}	$k_A = k_\psi/[EOA]$ mol^{-1} L s^{-1}
1	2.26	1.05	4.65
2	3.40	1.43	4.22
3	4.53	1.72	3.79
4	5.10	2.04	4.00
5	7.94	3.30	4.16

[DNFB] = 2.671×10^{-5} M; Temperature = 313K; Solvent: acetonitrile.

Table 2. The observed rate constants at various concentrations of ethanolamine

S. No.	[EOA]/10^{-3} M	$k_\psi/10^{-5}$ S^{-1}	$k_A = k_\psi$/[EOA] × 10^{-3} mol^{-1} L s^{-1}
1	2.74	1.99	7.28
2	5.48	4.19	7.64
3	8.23	6.12	7.44
4	10.97	8.84	8.57
5	13.71	12.59	9.18

[DNFB] = 4.055 × 10^{-5} M; Temperature = 303 K; Solvent: toluene.

Table 3. Second-order rate constants, k_A, obtained by dividing the pseudo-first-order rate constant by the [EOA] for the nucleophilic displacement of fluorine from DNFB and MNFB with EOA

Trial No.	DNFB in acetonitrile [DNFB] = 2.671 × 10^{-3} M Temp = 313 K k_A (L mol^{-1} s^{-1})	DNFB in toluene [DNFB] = 4.052 × 10^{-5} M Temp = 303 K k_A (L mol^{-1} s^{-1})	MNFB in acetonitrile [MNFB] = 1.615 × 10^{-3} M Temp = 313 K k_A (L mol^{-1} s^{-1})
1	4.65(2.26 × 10^{-3})	7.28 × 10^{-3}(2.74 × 10^{-3})	1.96 × 10^{-4}(0.0487)
2	4.22(3.40 × 10^{-3})	7.64 × 10^{-3}(5.48 × 10^{-3})	2.08 × 10^{-4}(0.122)
3	3.79(4.53 × 10^{-3})	7.44 × 10^{-3}(8.23 × 10^{-3})	2.28 × 10^{-4}(0.146)
4	4.00(5.10 × 10^{-3})	8.05 × 10^{-3}(10.97 × 10^{-3})	2.46 × 10^{-4}(0.195)

Values in parenthesis represent molar concentrations of EOA.

Table 4. Rate constants for the reaction of EOA with DNFB and MNFB at various temperatures (pseudo-first-order w.r.t halide)

Temp (K)	DNFB in acetonitrile [DNFB] = 2.6696 × 10^{-5} M [EOA] = 4.5343 × 10^{-3} s^{-1}	DNFB in toluene [DNFB] = 4.0552 × 10^{-5} [EOA] = 0.2272 × 10^{-3} s^{-1}	MNFB in acetonitrile [DNFB] = 1.6148 × 10^{-3} [EOA] = 0.1218 s^{-1}
293	1.09 × 10^{-2}	4.67 × 10^{-5}	4.77 × 10^{-6}
298	1.26 × 10^{-2}	5.75 × 10^{-5}	8.49 × 10^{-6}
303	1.41 × 10^{-2}	6.12 × 10^{-5}	11.98 × 10^{-6}
308	1.61 × 10^{-2}	7.86 × 10^{-5}	16.33 × 10^{-6}
313	1.72 × 10^{-2}	—	26.55 × 10^{-6}

further confirmed from the observation that, the pseudo-first-order rate constants k_Ψ, were independent of the initial concentration of DNFB (Table 3). Furthermore, the reaction was found to be first order with respect to DNFB in toluene; the rate constant of the reaction is less than that in acetonitrile. Since the reaction is first order both in the concentration of the DNFB and the amine, the reaction has an overall order of 2. The Arrhenius activation energies determined by studying the variation of rate with temperature (ln second-order rate vs. 1/*T*) are 17.8 kJ/mol in acetonitrile and 24.4 kJ/mol in toluene (Table 4).

The rate of reaction of MNFB with ethanolamine in acetonitrile was similarly determined at different ethanolamine concentrations (Supporting Information). Pseudo-first-order constants were observed and the second-order rate constants calculated show constancy within experimental limits. The reaction follows an overall second-order kinetics showing first order with respect to MNFB and ethanolamine (Table 3). The Arrhenius activation energy was determined at 62.4 kJ/mol (Table 4).

Comparison of rates and activation energies

In summary, second-order rate coefficients, k_A, determined from experimental pseudo-first-order rate coefficients, k_Ψ, are listed in Table 3. Comparison of the rate constants, k_A, reveals that rate of the reaction between ethanolamine and DNFB in acetonitrile is much greater than corresponding rate in toluene medium with corresponding activation energies of 17.8 and 24.4 kJ/mol, respectively. The kinetic data indicate a general tendency for a decrease in k_A values with the less polar nature of toluene. In addition, the rate of reaction of ethanolamine with MNFB in acetonitrile is much lower than that of DNFB with

Table 5. The relative energies of the reactants, products, intermediates, and transition states for the reaction between DNFB and EOA, in vacuum by DFT calculations (kJ/mol)

Species	B3LYP 6_31G*	B3LYP 6_311G*
DNFB + 2EOA	0	0
DNFB + EOA complex	−18.28	−21.34
TS1	35.16	35.33
MC	29.23	30.12
P1 + P2 Product complex	−168.86	−178.78
Product (P1 + P2)	−73.17	−88.43
P1+ HF	5.82	−11.03
Anion + (EOA + H)	361.57	350.66

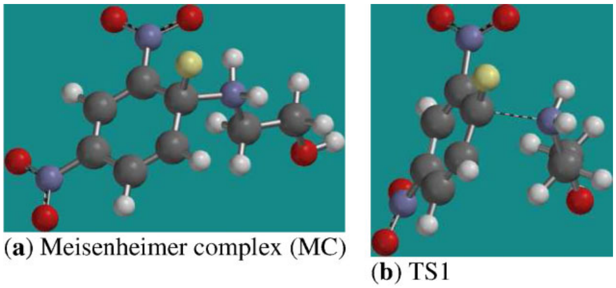


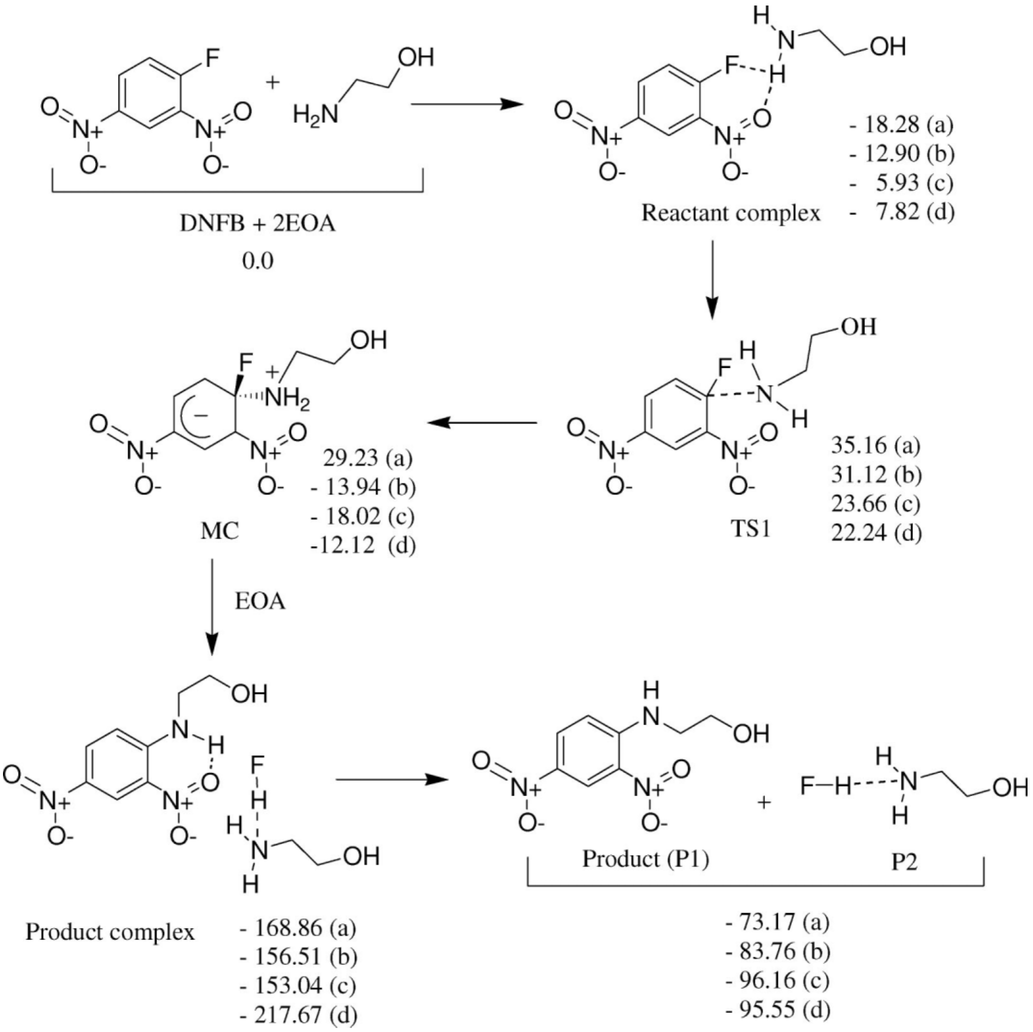
Figure 1. (a) MC; C—F bond length = 1.441 Å; C—N bond length = 1.572 Å; FCN bond angle = 95.76°; (b) TS1; C—F bond length = 1.390 Å; C—N bond length = 1.812 Å; FCN bond angle = 91.99°

corresponding activation energy of 62.4 kJ/mol, which indicates that the absence of the nitro group at the 4-position greatly slows the rate of the reaction.

Theoretical calculations

DFT calculations were performed in vacuum and in various solvents to explore possible mechanisms for the displacement of fluorine from 1-fluoro-2,4-dinitrobenzene by ethanolamine (Experimental). Usually, S_NAr reaction involves two steps: the first step is the formation of a MC and second is the decomposition of MC. The total energies of the reactants, intermediates, transition states, and products calculated by DFT methods are given in Table 5. The possible formation of a complex between the reactants ethanolamine (EOA) and 1-fluoro-2,4-dinitrobenzene (DNFB-EOA complex), an ion–dipole complex held together by electrostatic attraction was explored (Scheme 2). The lowest energy structure obtained for the electrostatic complex of the reactants, DNFB-EOA complex, is 18.3 kJ/mol (gas-phase, GP) more stable than the reactants; in the complex the hydrogen atom of the amino group of the primary amine interacts (H-bonding) with the F atom and the oxygen atom of the nitro group. The attack of the primary amine at the C1 position leads to the formation of the MC, a zwitterionic intermediate, which is 29.2 kJ/mol less stable than the reactants (Fig. 1a). We note that the MC is more stable than reactants for solution phases (Scheme 2). The relative energy of the transition state (TS1), Fig. 1b, for the formation of MC is 35.2 kJ/mol (GP) which indicate that the MC forms a shallow potential well. Kinetic data reveal the rate-determining step of the reaction is the formation of the MC.

To understand the stochiometry of the reaction and decomposition pathway of the MC, three possible product



Scheme 2. Mechanism of reaction of EOA and DNFB based on DFT calculations (B3LYP/6-31G*). Energies (relative to DNFB + 2EOA) are given in kJ/mol: (a) in vacuum, (b) in toluene, (c) in ethanol, and (d) in acetonitrile

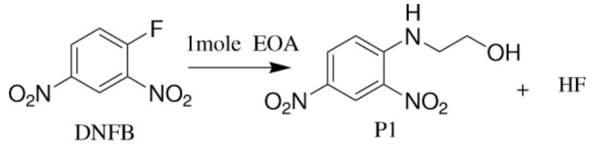
Table 6. The relative energies of the reactants, products, intermediates, and transition states for the reaction between DNFB and EOA, in acetonitrile, ethanol, and toluene obtained by DFT calculations (B3LYP/6-31G*) (kJ/mol)

Species	Acetonitrile	Ethanol	Toluene
DNFB + 2EOA	0	0	0
DNFB + EOA complex	−7.82	−5.93	−12.90
TS1	22.24	23.66	31.12
MC	−12.12	−18.02	−13.94
P1 + P2 product complex	−217.67	−153.04	−156.51
Product (P1 + P2)	−95.55	−96.16	−83.76

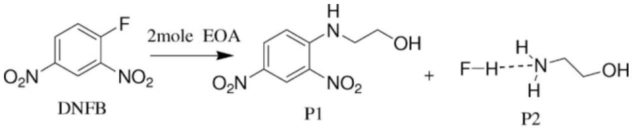
Table 7. Activation energies for the reaction of DNFB with ethanol amine in vacuum and in various solvents (kJ/mol)

Method	Vacuum	Toluene	Diethyl ether	Ethanol	Acetonitrile	DMF
MO calculation, B3LYP/6-31G*	35.16	31.12	28.89	23.66	22.22	21.92
Experimental value	—	24.36	—	—	17.82	

combinations were considered: (1) *N*-(2,4-dinitrophenyl)amino ethanol (P1) and HF (Eqn (1)), (2) *N*-(2,4-dinitrophenyl)amino ethanol (P1), fluoride ion and protonated ethanolamine (EOA + H), (3) *N*-(2,4-dinitrophenyl)amino ethanol (P1) and an HF hydrogen-bonded complex with EOA (P2), (Eqn (2)). For the first combination, relative energies of the products are near thermoneutral (Table 5). For the second combination, the sum of the relative energies of the products is much higher than the sum of the energies of the reactants and hence it does not represent the probable combination of products. The relative energies of the third combination of products show that the reaction is substantially exothermic (Table 5). In addition, deprotonation of the MC by ethanolamine was considered but the relative energies of the incipient anion and protonated ethanolamine are very endothermic (Table 5). Hence, the stochiometric equation for the reaction may be written as given in Eqn (2).



Eqn (1)



Eqn (2)

Since the overall order of the reaction is 2; the formation of the MC must be rate determining and the decomposition of the MC must be faster than formation. No transition state could be located for the unimolecular dissociation of MC to form a mixture of HF and P1, but in the presence of EOA the decomposition takes place without a forward barrier to form a product complex in which P1 is electro-statically bound to HF and ethanolamine, which is much lower in energy than products (Scheme 2). The relative energy of the product complex is calculated as −168.86 kJ/mol while the relative energy of the sum of the products (P1 + P2) is −73.17 kJ/mol (Table 5). Therefore, DFT calculations in vacuum indicate that the reaction involves two steps: the first is the slow formation of an MC and followed by its decomposition catalyzed by ethanolamine (Scheme 2).

To understand the effect of solvent polarity on the activation energy of the reaction, the total energies of the transition states and intermediates in acetonitrile, ethanol, and toluene were estimated by repeating the DFT calculations using B3LYP/6-31G* method, using solvation models (Experimental). The relative energies of the transition states (TS1) for the formation of the MC and that of MC are found to be lower in acetonitrile, ethanol, and toluene compared to that in vacuum (Scheme 2, Table 6). In addition, the relative energies of the MC in all three solvents are found to be lower than the sum of the energies of the reactants, hence exothermic. Moreover, the relative energies of

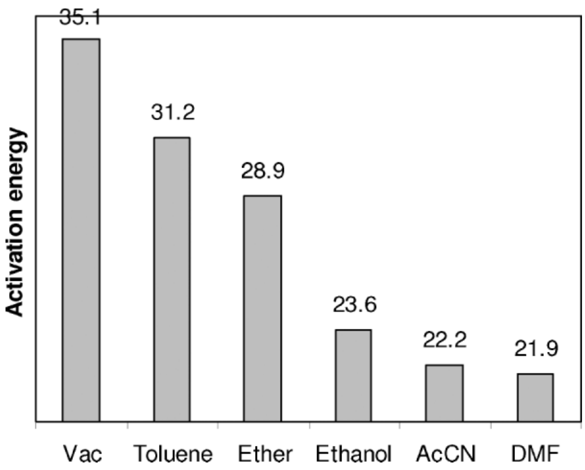


Figure 2. Variation of activation energy in solvents

Table 8. The relative energies of the reactants, products, intermediates, and transition states for the reaction between MNFB and EOA, in vacuum, and in acetonitrile by MO calculations (kJ/mol)

Species	(Vacuum) B3LYP 6-311G*	(Acetonitrile) B3LYP 6-31G*
MNFB + 2EOA	0	0
MNFB + EA complex	−17.57	−8.82
TS1	67.10	59.66
MC	63.71	42.23
P1 + P2 complex	−196.61	−190.50
Product (P1 + P2)	−73.06	−69.30

the transition state (TS1) decrease when the medium of the reaction is varied from toluene to acetonitrile, indicating the effect of solvent polarity on the activation energy of the reaction, hence increasing reaction rate. This is in agreement with the experimental observation that the reaction is faster in acetonitrile than in toluene at the same temperature, Table 4, as well as solvent effects reported.[1,6] Furthermore, the energies of the transition states were calculated in two more solvents, diethylether and dimethylformamide (DMF). In diethylether, a solvent having dielectric constant in between that of toluene and ethanol, the energy of the transition state for the formation of MC is calculated at 28.9 kJ/mol which is between that for toluene and ethanol. However, in DMF, a solvent more polar than acetonitrile, the calculated activation energy is close to that of acetonitrile, 21.9 kJ/mol (Table 7, Fig. 2). Moreover, measured activation energies for the reaction in toluene and acetonitrile are 5–6 kJ/mol lower than that calculated by DFT methods. Nevertheless, the overall similarity between the experimental and calculated activation energies of the reaction indicate that the mechanism predicted by theory is suitable for describing the reaction of EOA with DNFB.

DFT calculations were repeated for the reaction of MNFB and ethanolamine in vacuum and in acetonitrile medium. The relative energy of the transition state for the formation of MC was found to be 67.1 in vacuum (Table 8) and 59.7 kJ/mol in acetonitrile, (experimental = 62.4 kJ/mol). These results are higher than those for reaction of EOA with DNFB. Furthermore, the relative energy of the MC in acetonitrile is less than that in vacuum. Therefore, ethanolamine reacts with MNFB by a mechanism similar to that for its reaction with DNFB (Scheme 2). The calculated higher activation energy of the reaction of MNFB with EOA can be attributed to the absence of the nitro group at 4-position.

CONCLUSIONS

The rate constants and activation energy values for the reaction between ethanolamine and 1-fluoro-2,4-dinitrobenzene were determined by both kinetic measurements and DFT calculations. The experiments were conducted in acetonitrile and toluene whereas the calculations were performed in vacuum, toluene, acetonitrile, and other solvents. The results of both experiment and DFT calculations show that activation energy decreases with increase in solvent polarity. By comparison, the higher activation energy determined by both kinetic measurements and DFT calculations indicate that MNFB is less reactive than DNFB towards EOA in acetonitrile. This study illustrates that the mechanism of reaction of ethanolamine with fluoronitrobenzenes involves the formation of MC and its decomposition is catalyzed by a second molecule of ethanolamine.

Acknowledgements

The authors thank Principal, S. H. College, Thevara for providing infrastructure facilities. The authors also thank Daryl Giblin, Scientist, Washington University in St. Louis, USA for useful discussions.

REFERENCES

[1] C. E. S. Alvaro, A. D. Ayala, N. S. Nudelman, *J. Phys. Org. Chem.* **2010**, DOI: 10.1002/poc.1712

[2] F. Terrier, in *Nucleophilic Aromatic Displacement* (Ed.: H. Feuer), VCH, New York, **1991**.

[3] C. Isanbor, A. I. Babatunde, *J. Phys. Org. Chem.* **2009**, *22*, 1078.

[4] M. R. Crampton, T. A. Emokpae, C. Isanbor, A. S. Batsanov, J. A. K. Howard, R. Mondal, *Eur. J. Org. Chem.* **2006**, *2006*(5), 1222.

[5] M. R. Crampton, C. Isanbor, T. A. Emokpae, *Eur. J. Org. Chem.* **2007**, *2009*(8), 1378.

[6] M. R. Crampton, in *Nucleophilic Aromatic Substitution* (Ed.: A. C. Knipe C), John Wiley & Sons, Chichester, UK, **2004**.

[7] A. H. Yangjeh, Y. J. Tarzanag, A. R. Banaei, *Int. J. Chem. Kinet.* **2009**, *41*, 153.

[8] N.S. Nudelman, M. Savini, C.E.S. Alvaro, V. Nicotra, J. Yankelevich, *Chem. Soc. Perkin Trans.* **1999**, *2*, 1627.

[9] C. Isanbor, T. A. Emokpae, *Int. J. Chem. Kinet.* **2008**, *40*, 125.

[10] T. Giroldo, L. A. Xavier, J. M. Riveros, *Angew. Chem. Int. Ed.* **2004**, *43*, 3588.

[11] N. Celebi-Olcum, A. Sanyal, V. Aviyente, *J. Org. Chem.* **2009**, *74*, 2328.

[12] W. Danikiewicz, T. Bienkowski, D. Kozłowska, M. Zimnicka, *J Am. Soc. Mass Spectrom.* **2007**, *18*, 1351.

[13] Y. J. Zheng, R. L. Ornstein, *J. Am. Chem. Soc.* **1997**, *119*, 648.

[14] Y. J. Zheng, T. C. Bruice, *J. Am. Chem. Soc.* **1997**, *119*, 3868.

[15] M. N. Glukhovtsev, R. D. Bach, S. Laiter, *J. Org. Chem.* **1997**, *62*, 4036.

[16] K. Tanaka, M. Deguchi, S. Iwata, *J. Chem. Res. (S)* **1999**, 528. : DOI: 10.1039/a902901j

[17] O. Acevedo, W. L. Jorgensen, *Org. Lett.* **2004**, *6*(17), 2881.

[18] W. S. Li, N. Zhang, L. M. Sayre, *Tetrahedron* **2001**, *57*, 4507.

[19] J. Dudash, Jr., Y. Zhang, J. B. Moore, R. Look, Y. Liang, M. P. Beavers, B. R. Conway, P. J. Rybczynski, K. T. Demarest, *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4790.

[20] G. G. Wubbels, A. M. Halverson, J. D. Oxman, V. H. D. Bruyn, *J. Org. Chem.* **1985**, *50*, 4499.

[21] Y. Shao, L. F. Molnar, Y. Jung, J. Kussmann, C. Ochsenfeld, S. T. Brown, A. T. B. Gilbert, L. V. Slipchenko, S. V. Levchenko, D. P. O'Neill, R. A. DiStasio, Jr., R. C. Lochan, T. Wang, G. J. O. Beran, N. A. Besley, J. M. Herbert, C. Y. Lin, T. Van Voorhis, S. H. Chien, A. Sodt, R. P. Steele, V. A. Rassolov, P. E. Maslen, P. P. Korambath, R. D. Adamson, B. Austin, J. Baker, E. F. C. Byrd, H. Dachsel, R. J. Doerksen, A. Dreuw, B. D. Dunietz, A. D. Dutoi, T. R. Furlani, S. R. Gwaltney, A. Heyden, S. Hirata, C.-P. Hsu, G. Kedziora, R. Z. Khalliulin, P. Klunzinger, A. M. Lee, M. S. Lee, W. Z. Liang, I. Lotan, N. Nair, B. Peters, E. I. Proynov, P. A. Pieniazek, Y. M. Rhee, J. Ritchie, E. Rosta, C. D. Sherrill, A. C. Simmonett, J. E. Subotnik, H. L. Woodcock, III, W. Zhang, A. T. Bell, A. K. Chakraborty, D. M. Chipman, F. J. Keil, A. Warshel, W. J. Hehre, H. F. Schaefer, J. Kong, A. I. Krylov, P. M. W. Gill, M. Head-Gordon, *Phys. Chem. Chem. Phys.* **2006**, *8*, 3172.

[22] C. J. Cramer, D. G. Truhlar, *Acc. Chem. Res.* **2008**, *41*(6), 760–7768.