Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy 98 (2012) 378–383

Contents lists available at SciVerse ScienceDirect

Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy

journal homepage: www.elsevier.com/locate/saa

Spectroscopic and theoretical studies on the nucleophilic substitution of 2,3-dichloronaphthoquinone with *para*-substituted anilines in solid state via initial charge transfer complexation

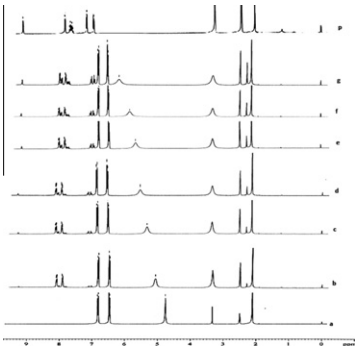
Angupillai Satheshkumar, Kuppanagounder P. Elango *

Department of Chemistry, Gandhigram Rural Institute (Deemed University), Gandhigram 624302, India

HIGHLIGHTS

- Nucleophilic substitution of DCNQ with anilines in solid state has been demonstrated.
- Driving force for the reaction is the ease with which initial EDA adduct forms between reactants.
- It is an environment friendly attempt for the preparation of aminonaphthoquinone derivatives.

GRAPHICAL ABSTRACT



ARTICLE INFO

Article history:
Received 26 April 2012
Received in revised form 11 August 2012
Accepted 21 August 2012
Available online 27 August 2012

Keywords:
EDA complex
Solid state
DCNQ
HOMO–LUMO calculations
Amino naphthoquinone
Nucleophilic substitution

ABSTRACT

Various spectroscopy techniques (UV–Vis, DRS, FT-IR, ^{1}H NMR, LC–MS) and theoretical computations have been employed to investigate the mechanism of the nucleophilic substitution reaction of 2,3-dichloronaphthoquinone (DCNQ) with *para*-substituted anilines in solid state under base- and solvent-free conditions against traditional synthetic routes. The initial formations of electron donor acceptor (EDA) adduct between DCNQ and aniline was found to be the driving force for the substitution reaction to occur in solid phase.

Introduction

Quinones are prevalent motifs in various natural products, which are associated with diverse biological activities. Among the naphthoquinones, 2-amino-1,4-naphthoquinone derivatives are interesting molecules because of their molluscicidal, cytotoxic, anti-tumor, anti-fungal and anti-bacterial activities [1,2]. The 2-amino-1,4-naphthoquinone moiety can also be found in natural products, such as echinamines A and B from the sea urchin [3–11].

Synthetic chemists continue to develop various techniques for obtaining better products with less environmental impact. The solid-state synthesis provides several advantages such as operational simplicity, neutral condition, high yield, environment friendly and economically cheap. In recent years, wide varieties of organic reactions have been studied in solid-state [12–16]. Many of the nucleophilic substitution reactions between DCNQ and anilines were performed in the presence of bases like $NaHCO_3$, K_2

* Corresponding author. Tel.: +91 451 2452371; fax: +91 451 2454466.
E-mail address: drkpelango@rediffmail.com (K.P. Elango).

1386-1425/$ - see front matter © 2012 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.saa.2012.08.056

CO_3, Et_3N, etc. in organic solvents at high temperatures (or) under microwave irradiation [17]. Different organic solvents such as ethanol [18,19], methanol [20], benzene, chloroform, dichloromethane, dimethylformamide, dimethylsulfoxide, diethyl ether, tetrahydrofuran and toluene [21] have been used to carry out nucleophilic substitution reactions of quinones.

In conventional method, DCNQ is heated with aniline in benzene at 50 °C for 30 min to give the product around 60%. Sarhana et al. [22] have reported a yield of 73% by changing the medium from non polar to polar. Recently, the nucleophilic substitution reaction of DCNQ with aniline was also carried out in aqueous medium [23]. The main objective, therefore, of the present endeavor is to investigate the nucleophilic substitution reaction of DCNQ with *para*-substituted anilines under environment friendly solid state condition against conventional methods i.e. in organic solvents in the presence of a base.

Experimental

General

The chemical reagents and solvents were purchased from Aldrich and/or Merck, India and were used as received. The UV–Vis spectra were recorded on a JASCO-V-630, Japan double beam spectrophotometer. Millisecond UV–Vis absorption spectra were recorded on an Ocean Optics (DH-2000) spectrograph in absorption mode using an optical fiber probe. The infrared spectra were recorded on a JASCO 460 Plus, Japan, FT-IR spectrometer. Fluorescence spectra were recorded on a JASCO-FP-6200, Japan, spectrofluorometer. ^{1}H NMR spectra were recorded on a Bruker NMR (300 MHz) with DMSO-d_6 as solvent. DRS were performed on a (Shimadzu UV-2550) UV–Vis spectrophotometer (DRS accessory Model: ISR-2200).

Synthesis of compound ***3a–g***

In a typical experiment, both DCNQ and given aniline (**2a–g**) were taken in 1:1.2 M ratio in a clean beaker and mixed thoroughly using a glass rod for 30 min. The color of the reaction mixture was changed from yellow to dark red within 30 min. The progress of the reaction was monitored by TLC. Then the reaction mixture was washed with excess of water and dried under vacuum to obtain the product as a dark red colored powder. The products obtained were characterized using FT-IR, ^{1}H NMR and HRMS spectral techniques (Supplementary information).

Results and discussion

As a representative case, the reaction of DCNQ (**1**) with *p*-chloroaniline (Scheme 1) has been carried out under conventional conditions reported earlier. The results obtained in different solvents, including water, at varying time intervals and in presence different bases are given in Table 1.

Table 1
Reaction of DCNQ with aniline on different condition.

Entry	Solvent	*T* (°C)	Time (h)	Yield (%)	Base
1	EtOH	40–50	4–6	73	K_2CO_3
2	H_2O	60–70	6	93	–
3	MeOH	40–50	12	78	K_2CO_3
4	CH_3CN	50–60	12	85	Et_3N

The results obtained were found to be in line with those reported earlier. According to Tandon and Maurya [23], the yield of the product is relatively higher in aqueous medium than that in non-aqueous media even though DCNQ is insoluble in water. The observed high yield, according to them, is due to the interaction of non polar (or) hydrophobic regions of the reactants [23].

Since the interaction of non-polar regions play the key role for the reaction to occur in a heterogeneous environment, we presumed that the same can be achieved in a non-conventional homogenous environment i.e. in solid phase. The reaction of DCNQ (**1**) with different *para*-substituted anilines possessing electron donating and electron withdrawing substituents (**2a–g**) has been carried out in solid phase (Scheme 2) by simply grinding the reactants in a beaker in the absence of any base. The results obtained are collected in Table 2.

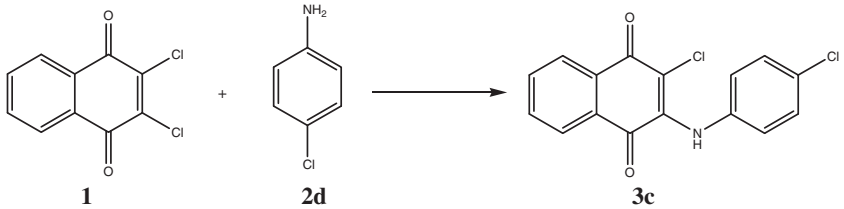
Interestingly, the yields obtained in the solid-state are comparable with that reported in aqueous and non-aqueous media but within a short period of time at room temperature (or on slight warming) and also in the absence of any base. Also, the results in Table 2 indicated that the unsubstituted aniline (**2a**) and anilines with electron donating substituents (**2b** and **c**) gave relatively higher yields at room temperature. While anilines with electron withdrawing substituents (**2d–g**) required warming of the vessel and also gave relatively lower yields. This observation indicated that the nature of the substituent present in aniline has a significant role to play even in the solid state.

Mechanism of the reaction

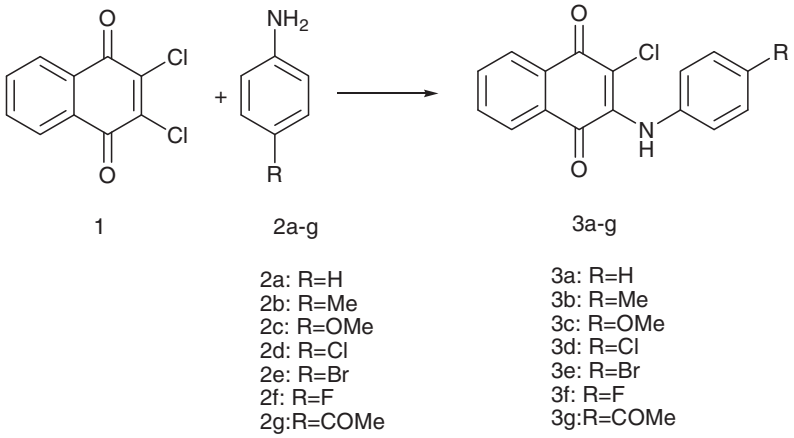
The mechanism of the nucleophilic substitution of DCNQ with anilines is a well established one [16,24]. A general scheme of the mechanism of the reaction is shown in Scheme 3. The first step is the formation of an EDA adduct between DCNQ and the nucleophile. In a subsequent step substitution takes place with the removal of chloride ion. Also it is well known that the reactivity of aniline depends on the nature of the substituent. The reactivity is higher with electron donating substituents than with electron withdrawing ones [25]. This is due to the fact that anilines with electron donating substituent readily form the EDA adduct and hence the higher reactivity.

Electronic spectral studies

In order to ascertain the mechanism of the reaction, UV–Vis spectra of the reaction mixture were recorded in ethanol. A



Scheme 1. Reaction of DCNQ (1) with *p*-chloroaniline (2c).



Scheme 2. The reaction of DCNQ (1) with different *para*-substituted anilines in solid phase.

Table 2
Reaction of DCNQ with anilines (**2a–g**) on solid state.

Entry	Quinone	Aniline	Time (min)	Temp (°C)	Product	Yield (%)
1	**1**	**2a**	30	RT	**3a**	88
2	**1**	**2b**	20	RT	**3b**	93
3	**1**	**2c**	50	RT	**3c**	90
4	**1**	**2d**	40	40	**3d**	80
5	**1**	**2e**	40	60	**3e**	82
6	**1**	**2f**	30	40	**3f**	83
7	**1**	**2g**	30	40	**3g**	81

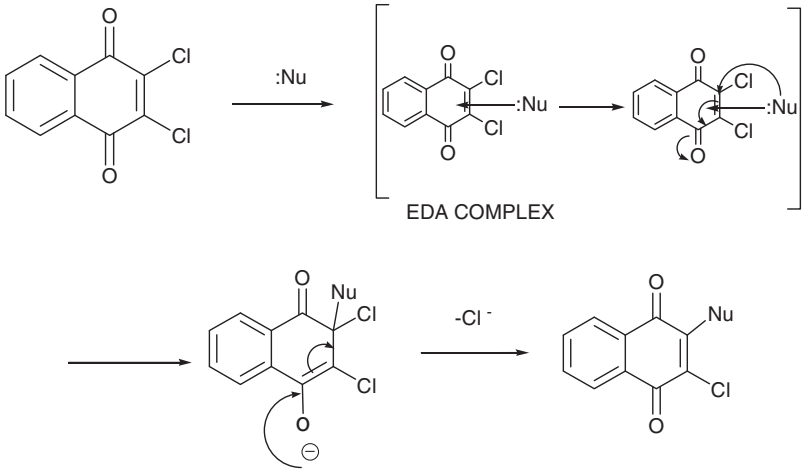
representative UV–Vis spectrum is shown in Fig. 1. The electronic spectrum of DCNQ exhibits a peak at 341 nm due to the π–π^* transition [26–28]. Immediately, on adding aniline to DCNQ, the electronic spectrum of the reaction mixture showed a new broad peak centered around 479 nm and the absorbance of which increased progressively with elapse of time indicating the formation of the product. The broadness of the peak is due to the existence of intramolecular charge transfer transition between N-atom and quinone in the product [29].

Parallel to the observation made by Neelgund and Budni [30], who reported that the formation of EDA complex between DCNQ and *n*-butylamine is an instantaneous process and also the concentration of which is very low, in the present study we could not visualize the EDA complex using conventional electronic spectroscopic technique. Hence, the nature of the intermediate formed in the interaction between aniline and DCNQ was identified using the following experiment employing millisecond absorption spectrograph in absorbance mode. Chloroform solutions of the acceptor and donor were extracted separately with water and the water extracts were mixed together. The electronic spectrum of the mixture, recorded immediately after mixing the water extracts, exhibited no absorption in the visible region. Whereas the chloroform solutions of the acceptor and donor were mixed together and the red colored solution thus obtained was extracted with water. The absorption spectrum of the aqueous extract, recorded immediately, is shown in Fig. 2. The curve C_1 is characteristic of quinone radical ion, which is converted to curve C_3 (through curve C_2) the characteristic curve of the reaction product. This spectrum remained unchanged after half an hour (curve C_4). This observation suggests the formation of a polar intermediate (the EDA complex) in the interaction between the donor and acceptor [31–33].

The diffused reflectance spectra of the reactants (**1** and **2b**) and the product (**3b**) were also recorded. A representative spectrum is shown in Fig. 3. It is evident, from the figure, that the appearance of a new broad peak (where either of the reactants are non-reflective) in the 450–650 nm region indicated the formation of the product in solid state.

^{1}H NMR spectral studies

^{1}H NMR spectra of a representative reactant (**2b**) and the reaction mixture (**1** and **2b** in 1:1 ratio) in DMSO-d_6 were recorded to



Scheme 3. The mechanism of nucleophilic substitution of DCNQ with aniline.

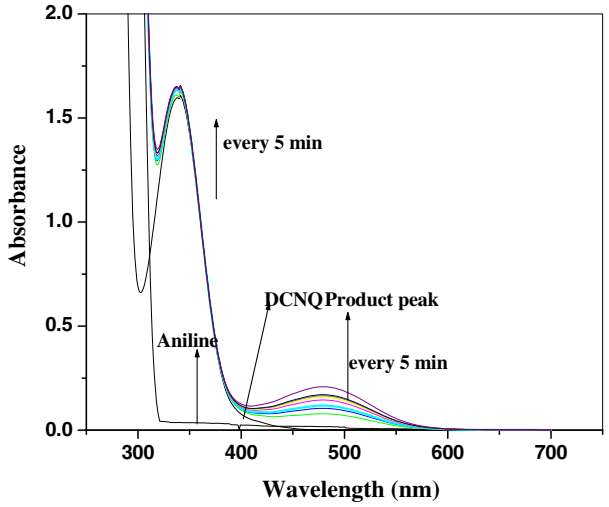


Fig. 1. Absorption spectra of DCNQ (A), Aniline (D), and CT-complexes (P) of DCNQ with Aniline in ethanol.

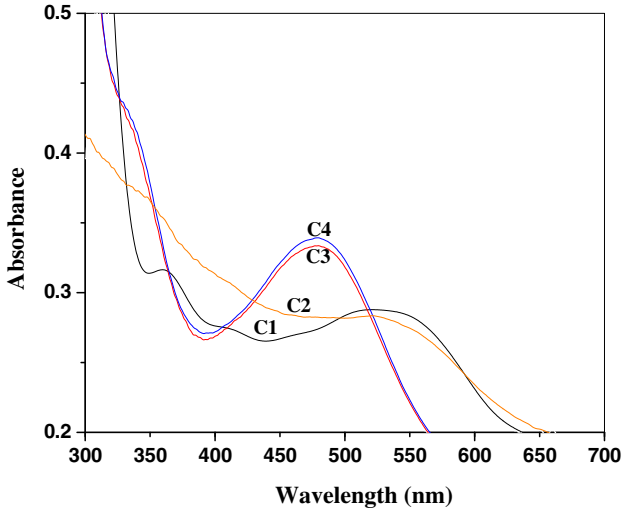


Fig. 2. Millisecond UV–Vis absorption spectra of Aniline – DCNQ EDA complex (C1) and product (C3).

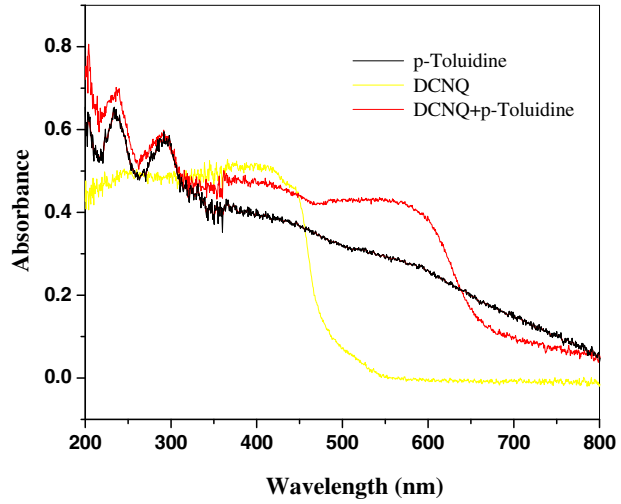


Fig. 3. UV–Vis diffuse reflectance spectra of DCNQ, *p*-toluidune and DCNQ + *p*-toluidine system.

elucidate the reaction mechanism. The signal at 4.764 ppm (Fig. 4a) corresponds to the $-NH_2$ protons of 2b. The ^1H NMR spectra of the reaction mixture recorded with elapse of time (in the NMR tube) are shown in Fig. 4b–g. The deshielding of the $-NH_2$ protons, immediately after mixing 2b and 1, may be due to the formation of an EDA adduct between them. With elapse of time the extent of deshielding was observed to increase. Concurrently, after 5 min, the new signal appeared at 9.314 ppm corresponds to the –NH proton in the product. The intensity of the signal increased with an increase in time as it is evidenced from the Fig. 4. The ^1H NMR spectrum of the product is also shown in the figure for comparison. The ^1H NMR study of the DCNQ–2a system is also shown in Fig. S2. The ^1H NMR study supported the fact that the mechanism of the reaction involves two steps: the first one being the formation of an EDA adduct between the reactants and in the second step the substitution occurs with the removal of chloride ion.

Naked-eye detection

It is interesting to note that the course of the solid state reaction can even be visualized with naked eye. A representative system is depicted in Fig. S1. A yellow colored solid DCNQ (A) on grinding with dirty white *p*-methylaniline (B) gave a brown colored solid (C) which subsequently changed to reddish-brown solid (D) within 10 min and finally to a red colored product (E) in 20 min. No further color change in color was observed after 20 min indicating completion of the reaction. The initially formed brown colored solid may be the EDA adduct which is converted into the final product.

Since the formation of an EDA adduct between DCNQ and nucleophile is the driving force for the reaction to occur, the influence of an external inert electron donor, hexamethyl benzene (HMB), on the course of the reaction is also studied in solid state. The selection of HMB is based on the fact that it is a well known electron donor in an EDA complex formation and also it is chemically inert towards DCNQ and the anilines. When colorless HMB (F) was ground with DCNQ in forms an orange colored (G) EDA adduct. On subsequent addition of *p*-methylaniline (2b) to this adduct, the desired nucleophilic substitution reaction has occurred, but very slowly. This may be due to the fact that the added nucleophile, aniline, has to replace HMB from the DCNQ–HMB EDA adduct for the reaction to occur and hence the rate of the substitution reaction is slow.

Fluorescence study

With an aim to find out the relative stabilities of the DCNQ–HMB and DCNQ-2b EDA adducts, fluorescence studies were carried out. The fluorescence spectrum of the donors HMB and **2a** were recorded at room temperature in the range of 230–730 nm upon excitation at 271 and 284 nm, respectively. It is observed that in both the cases addition of DCNQ quenched the fluorescence of the donors through EDA complexation. The experimental results indicated that the quenching efficiency, in both the cases, increased with an increase in the concentration of DCNQ at a fixed concentration of the donor (Figs. 5 and 6).

Fluorescence intensity data was analyzed according to the Stern–Volmer law [34,35]:

$$F_0/F = 1 + Ksv[Q] \quad (1)$$

where F_0 is emission intensity in the absence of quencher (Q) and F is emission intensity at quencher concentration [Q]. The linear Stern–Volmer plots (Fig. 7) indicated that only one quenching mechanism is operative and the quenching is bimolecular and dynamic.

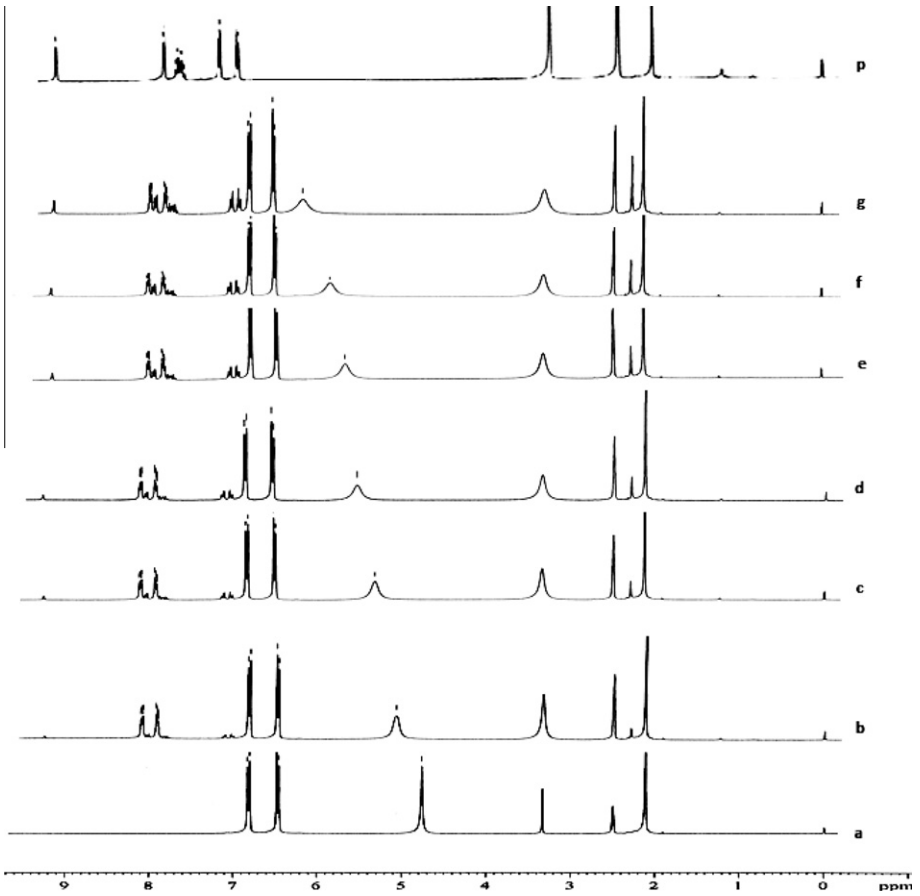


Fig. 4. The ^{1}H NMR spectra (300 MHz) of the reaction mixture of DCNQ with (2b) (1:1 M ratio) in DMSO-d_6. a-only (2b). b–g are mixture of DCNQ-(2b) after 2, 5, 7, 10, 15 and 20 min respectively and p is the pure product.

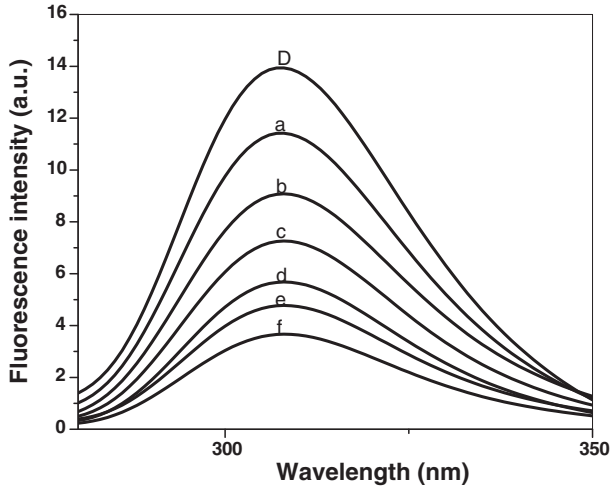


Fig. 5. Fluorescence spectra for HMB–DCNQ system in ethanol at fixed concentrations of [D] = {5 × 10^{-3} M (curved)} and variable concentration of [A] = {1.25 (a), 2.5 (b), 3.75 (c), 5.0 (d), 6.25 (e), 7.5 (f)} × 10^{-5} M at 298 K.

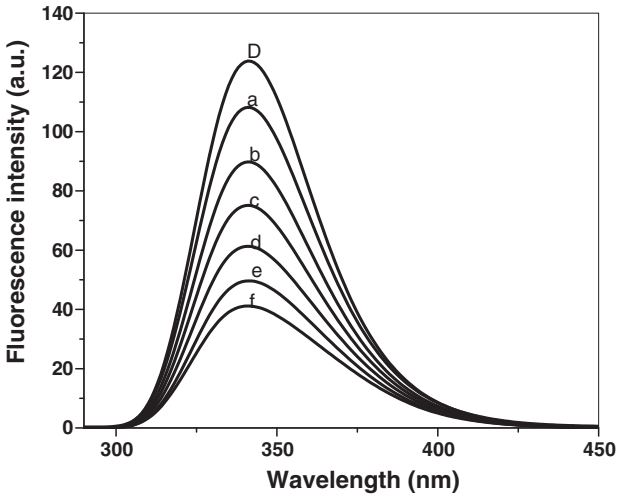


Fig. 6. Fluorescence spectra for aniline–DCNQ system in ethanol at fixed concentrations of [D] = {5 × 10^{-3} M (curved)} and variable concentration of [A] = {1.25 (a), 2.5 (b), 3.75 (c), 5.0 (d), 6.25 (e), 7.5 (f)} × 10^{-5} M at 298 K.

The binding constant values of DCNQ–HMB and DCNQ–2a EDA adducts are found to be 2.9 × 10^4 and 3.2 × 10^4 l/M, respectively. The results showed that, the binding constant for the formation of DCNQ–HMB and DCNQ–2a EDA adduct are comparable. Hence, addition of HMB to DCNQ, prior to the addition 2a, forms DCNQ–HMB EDA adduct from which HMB is to be replaced by 2a to form DCNQ–2a EDA adduct. Such a process is possible as the binding constants are comparable but it requires few seconds and hence the slow rate of the reaction, as observed in the naked eye detection section.

Theoretical calculations

To understand the effect of substituents present in the aniline moiety on the neuclephilic substitution reaction, we have performed the complete geometrical optimization of DCNQ and

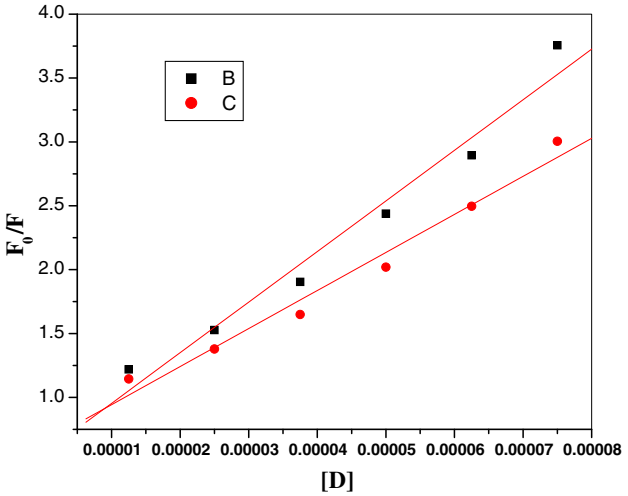


Fig. 7. Stern–Volmer plots for the fluorescence quenching of HMB (B) and aniline (C) with DCNQ at 298 K.

2a–g at the SCF level with the Gaussian program. The geometries were fully optimized in the RHF framework with 6-31G basis sets. The energy of the LUMO of DCNQ and that of the HOMO of the anilines along with ΔE (=HOMO of donor − LUMO of acceptor) for the formation of EDA adducts are depicted in Fig. S3. The results, given in the figure, indicated that the ΔE for anilines with electron donating substituents is relatively less than that for anilines with electron withdrawing substituents when compared to the unsubstituted aniline. This suggested that the formation of EDA adduct by anilines with electron donating substituents is relatively easy and consequently the substitution reaction (in solid phase) occur at room temperature. While reaction of anilines possessing electron withdrawing substituents require slight warming as expected. Also, the value of ΔE for DCNQ–HMB adduct is comparable with that for DCNQ–anilines with electron withdrawing substituents. Hence, addition of HMB prior to the nucleophile slows down the rate of the reaction rather than preventing it. If the ΔE for the DCNQ–HMB EDA adduct would have been very low than that observed, it may even prevent the substitution at DCNQ.

Conclusion

To conclude, the driving force, for the nucleophilic substitution reaction to occur at DCNQ, is the ease with which the initial EDA adduct forms between the reactants. This can easily be achieved in solid state itself against the conventional methods i.e. in the absence of any solvent and base. Such an environment friendly attempt would certainly be useful in the preparation of many biologically significant amino naphthaquinone derivatives.

Acknowledgement

The authors thank the University Grants Commission, New Delhi for its financial assistance to carry out this research work.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.saa.2012.08.056.

References

[1] M.D. Sarma, R. Ghosh, A. Patra, B. Hazra, Eur. J. Med. Chem. 43 (2008) 1878–1888.
[2] P.H. Bernardo, C.L. Chai, M. LeGuen, G.D. Smith, P. Warning, Bioorg. Med. Chem. Lett. 17 (2007) 82–85.
[3] S. Spyroudis, Molecules 5 (2000) 1291–1330.
[4] T.C. Barbosa, C.A. Camara, T.M. Silva, R.M. Martins, A.C. Pinto, M.D. Vargas, Bioorg. Med. Chem. 13 (2005) 6464–6469.
[5] Aurora Molinari, Alfonso Oliva, Claudia Ojeda, José Ma Miguel del Corra, Ma Angeles Castro, Carmen Cuevas, Arturo San Feliciano, Bioorg. Med. Chem 13 (2005) 6645–6650.
[6] O. Bakare, C.L. Ashendel, H. Peng, L.H. Zalkow, E.M. Burgess, Bioorg. Med. Chem 11 (2003) 3165–3170.
[7] C.G.T. Oliveria, F.F. Miranda, V.F. Ferreira, C.C. Freitas, R. Rabello, J.M. Carballido, L.C.D. Correa, J. Braz. Chem. Soc 12 (2001) 339–345.
[8] N.P. Mischenko, S.A. Fedoreyev, N.D. Pokhilo, V.Ph. Anuferiev, V.A. Denisenko, V.P. Glazunov, J. Nat. Prod 68 (2005) 1390–1393.
[9] P. Cai, F. Kong, M.E. Ruppen, G. Glasier, G.T. Carter, J. Nat. Prod 68 (2005) 1736–1742.
[10] V.K. Tandon, H.K. Maurya, N.P. Misshra, P.K. Shukla, Eur. J. Med. Chem. 44 (2009) 3130–3137.
[11] J. Benites, J.A. Valderrama, K. Bettega, R.C. Pedrosa, P.B. Calderon, J. Verrax, Eur. J. Med. Chem. 45 (2010) 6052–6057.
[12] M. Leibovitch, G. Olovsson, G. Sundrababu, V. Ramamurthy, J.R. Scheffer, J. Trotter, J. Am. Chem. Soc. 118 (1996) 1219–1220.
[13] G.R. Desiraju, K.V.R. Kishan, J. Am. Chem. Soc. 111 (1989) 4838–4843.
[14] K. Tanaka, F. Toda, Chem. Rev. 100 (2000) 1025–1074.
[15] Leonard R. Mac Gillivray, J. Org. Chem 73 (2008) 3311–3317.
[16] A. Ram Reddy, N.V. Krishnamurthy, B. Bhudevi, Spectrochim. Acta Part A 63 (2006) 700–708.
[17] A.T. Ricardo, C. Lorena, C. Mauricio, V. Joan, J. Braz. Chem. Soc. 20 (2009) 999–1002.
[18] V.K. Tandon, D.B. yadav, R.V. Singh, M. Vaish, A.K. Chturvedi, P.K. Shukla, Bioorg. Med. Chem. Lett 15 (2005) 3463–3466.
[19] V.K. Tandon, D.B. yadav, R.V. Singh, A.K. Chturvedi, P.K. Shukla, Bioorg. Med. Chem. Lett 15 (2005) 5324–5328.
[20] S. Yerushalmi, C. Lem, S. Bittner, Synthesis 2 (2007) 239–242.
[21] J.C. Lien, L.J. Huang, J.P. Wang, C.M. Teng, K.H. Lee, S.C. Kuo, Bioorg. Med. Chem 5 (1997) 2111–2120.
[22] E.W.A.O. Sarhana, A.M. K El-Dean, M.I. Abdel-Mmnem, Monatshefte fur Chemie 129 (1998) 205.
[23] V.K. Tandon, H.K. Maurya, Tetrahedron Lett. 50 (2009) 5896–5902.
[24] G.M. Neelgund, A.S. Kulkarni, M.L. Budni, Monatshefte fur Chemie 135 (2009) 343–355.
[25] A. Graja, R. Swietilk, M. Polomska, A. Brau, J.P. Farges, Synthetic Metals 125 (2002) 319–324.
[26] F. El-Zahraa, M.E. Hegazy, A.F. Soheirz, E.A. Hamed, S.M. Sharaf, J. Phys. Org. Chem. B (2000) 549–554.
[27] M. Aguilar-Matrtinez, G. Cuevas, M. Jimenez-Estrada, I. Gonzalez, B. Lotina-Hennsen, N. Macias-Ruvalcaba, J. Org. Chem. 64 (1999) 3684–3694.
[28] N. Macias- Ruvalcaba, G. Cuevas, I. Gonzalez, M. Aguliar-Martinez, J. Org. Chem. 67 (2002) 3673–3681.
[29] L. Elisa Leyva, I. Lopez, E. Loredo-carrillo, Margarita Rodriguez-Kessler, Antonio Monte-Rojas, J. Flu. Chem. 132 (2011) 94–101.
[30] G.M. Neelgund, M.L. Budni, Spectrochim. Acta A 61 (2005) 1729–1735.
[31] H.M.A. Salman, M.M. Abu-Krisha, H.S. El-Sheshtawy, Can. J. Anal. Sci. Spectrosc. 49 (2004) 282–289.
[32] M. Pandeeswaran, E.H. El-Mossalamy, K.P. Elango, Int. J. Chem. Kinetics (2009) 787–799.
[33] Yanlan Hui, Elaine Lay Khim Chng, Cheryl Yi Lin Chng, Hwee Ling Poh, Richard D. Webster, J. Am. Chem. Soc. 131 (2009) 1523–1534.
[34] Qin. Zhou, Timothy M. Swager, J. Am. Chem. Soc. 117 (1995) 12593–12602.
[35] Basavaraj G. Evale, S.M. Hanagodhimath, J. Lumin. 130 (2010) 1330–1337.