

Chapter 3

Solvent Effect on Stabilization Energy

3.1. Introduction:

In chapter 2, a conclusion was drawn from an analytical equation (2.19) that there occurs stabilization at zero charge transfer limit i.e., before the adduct formation. The explanation of stabilization at the zero charge transfer limit is attributed to weak non-bonding interactions (which include dipole-dipole, charge-induced dipole and London dispersion interactions) between the donor and the acceptor. Also, it was claimed that in presence of strong solvent, ΔE_{eqtm} in the adduct formation process will be less negative i.e., the adduct is less stable in presence of strong solvent. In the present chapter, first a formalism and the corresponding computational method is developed to take care of the variation of stabilization energy with solvent polarity in the process of adduct formation. This formalism is further tested on two adduct formation processes.

The 1:1 adduct formation from the two species is the simplest chemical reaction in which one of the reactants acts as an electron donor (B) while the other acts as an electron acceptor (A). There may be different types of bonding between the two species (e.g., covalent, ionic or coordinate-covalent) or there may be non-bonding interactions (e.g., electrostatic, dipole-dipole, dipole-induced dipole, dispersion etc.). When intermolecular interaction (bonding or non-bonding) takes place between the two species, it results in the formation of adduct.

In the conceptual DFT (or DFRT) the analytical expression of stabilization energy, in the process of adduct (AB) formation, was first given by Parr and Pearson.¹ However, they considered only the charge transfer components in the expression of stabilization energy. It was Nalewajski,² who first explained the importance of electrostatic effect in deriving the expression of stabilization energy. Later on, Ayers³ derived an elaborate expression of stabilization energy after inclusion of charge transfer, electrostatic, polarization and dispersion contribution.

Roy and co-workers devised Comprehensive Decomposition Analysis of Stabilization Energy (CDASE) scheme⁴ by working on Parr and Pearson's¹ expression of stabilization energy during the process of adduct formation. Although, this scheme is also confined to the charge transfer only, the advantage of this scheme is that overall expression of stabilization energy was divided into two energy components: kinetic component (representing energy-raising part) and thermodynamic component (representing energy-lowering part). Using this scheme, Roy and co-workers⁵⁻¹⁰ explained kinetics, thermodynamics and finally overall stabilization of various interacting systems. However, in all these earlier studies, the components of stabilization energy are evaluated in the gas phase only, because the expressions of CDASE scheme do not have

explicit consideration of dielectric properties of the solvent (i.e., the medium) in which the reaction is taking place. In the last chapter, the formalism of CDASE scheme was extended after including the effect of perturbation on external potential of the interacting species.¹¹ The extended formalism takes care of charge transfer, electrostatic, polarization and dispersion interactions etc. in the CDASE scheme implicitly (i.e., in terms of different parameters related to perturbation on external potential). Also, from the extended formalism of the stabilization energy it was conjectured that with the increase in solvent polarity (i.e., dielectric constant), stabilization energy becomes less negative (i.e., decreases) in the process of adduct formation. In this context, it is worth mentioning that Klopman^{12,13} argued that with increasing solvent polarity (or dielectric constant) the charges on the electron donor and acceptor will be reduced (due to solvation), thereby reducing the chances of adduct formation (i.e., decreases the stabilization energy). However, unlike the present one the approach used by Klopman was polyelectronic perturbation theory.

Some related experimental studies are also worth mentioning in this context. Nabavizadeh *et al.*¹⁴ reported that adduct formation occurs between methyltrioxorhenium (MTO) and pyridine in different solvents. They compared thermodynamic parameters (enthalpy, entropy and free energy) at standard states as well as formation constant (K_f) at different temperatures by changing the solvent, thereby highlighted the role of dielectric constant of solvent in the process of adduct formation. Recently, Miyan *et al.*¹⁵ also reported that complex formed between 1,2-dimethylimidazole and 3,5-dinitrobenzoic acid is more stable in less polar solvent due to high value of formation constant.

Sanchez-Lozano *et al.*¹⁶ reported the impact of the solvent environment on the stabilization of the complexes formed by fluorine and cyanide substituted tweezers (i.e., T-F and T-CN, respectively) with halide anions. In another study Cossi *et al.*¹⁷ investigated the complexation energies and overall activation energies of the S_N2 reaction between CH_3Cl and Cl^- ion in vacuum and in water. As per their observations, it is clear that in vacuum the reaction is more favorable than in water. Recently, Soury and Mohammadi¹⁸ reported the solvent effect on the complexation energies and hydrogen bond properties of adenine-thymine complex. As per their results properties, such as the complexation energy, solvation energy, optical gap and dipole moment of the adenine-thymine complex, are functions of dielectric constant of the solvent. They also reported that the complexation energy becomes numerically less negative with the increase in

solvent polarity. However, they have not proposed any analytical expression which relates these properties with the dielectric constant of the solvent.

Although, the extended formalism of CDASE scheme, as developed by Roy and co-workers¹¹ shows the effect of solvent polarity on the stabilization energy in the adduct formation process, there is no direct way to implement this computationally. This is because some parameters of an atom-in-a molecule need to be computed and no clear-cut prescription is available right now [to be discussed in details in section 3.2(a)]. However, this should not deter one to investigate theoretical implications of the extended formalism by some indirect method. So, in this study the effect of solvent polarity on the stabilization energy in the adduct formation process is computed by augmenting CDASE scheme based gas phase stabilization energy with a newly proposed simple definition of the ‘net desolvation energy’ (can also be defined as binding free energy).¹⁹

The present chapter is framed in the following way: In section 3.2, a brief theoretical background of the CDASE scheme is presented [Section 3.2 (a)] and simple definition of ‘net desolvation energy’ is proposed [Section 3.2 (b)]. The phenomenological justification in favour of the newly proposed definition of the ‘net desolvation energy’ is also discussed in this section. Section 3.3 covers computational techniques adopted, keeping in mind the chosen adduct formation processes. Results and discussion, on the basis of the generated data, are elaborated in section 3.4. Finally, in section 3.5 (i.e., in concluding section) the entire study is summarized with an outline of the probable future scope.

3.2. Theoretical background:

(a) Analytical form of stabilization energy to take care of solvent effect:

As in most of the adduct formation processes the donors and acceptors are of comparable size the stabilization energy during the adduct formation process is interdependent (i.e., depends on the electronic properties of both the species). This is unlike to the situation where the electron donor is an ideal one (i.e., no appreciable change in its energy or chemical potential is observed when the electrons are given to an acceptor).²⁰ Keeping this in mind Roy and co-workers⁴ re-denoted Parr and Pearson's stabilization energy expression¹ by equation (1.48).

It was further shown that the overall stabilization energy ($\Delta E_{SE(AB)}$) is decomposed into energy raising (i.e., kinetic) and energy lowering (i.e., thermodynamic) components [equations

(1.49) and (1.50)]. The corresponding charge (electron) transfer (from the donor to the acceptor) is given by equation (1.47).

It is obvious that to explain intermolecular interaction through this formalism needs calculation of global reactivity descriptors e.g., chemical potential (μ)^{1,21,22} and chemical hardness (η)¹ of both the electron donor (B) and the electron acceptor (A) species which are analytically defined as: $\mu = \left(\frac{\partial E}{\partial N}\right)_v$ and $\eta = \left(\frac{\partial^2 E}{\partial N^2}\right)_v$. The working equations for μ and η are given by equations (1.15) and (1.20a), respectively.

Here, it is to be noted that ionization potential (IP) and electron affinity (EA) are calculated through Δ SCF method [IP = $E_{N-1} - E_N$ and EA = $E_N - E_{N+1}$, where, E_N , E_{N-1} and E_{N+1} represent energy values of the neutral, cationic and anionic species, respectively, at the optimized geometry of the neutral species]. Hence, the parameters ΔN , $\Delta E_{SE(AB)}$, $\Delta E_{B(A)}$ and $\Delta E_{A(B)}$ can easily be calculated using equations (1.47) - (1.50). The advantage of CDASE scheme is that it provides authenticity of a molecule whether it acts as a donor or an acceptor by simply looking at the sign of the ΔN (positive ΔN value confirms B is a donor otherwise it is an acceptor in the adduct formation process). But the limitation of this scheme is that we can calculate interaction energies of adducts in gas phase only as there is no provision of taking the solvent effect explicitly.

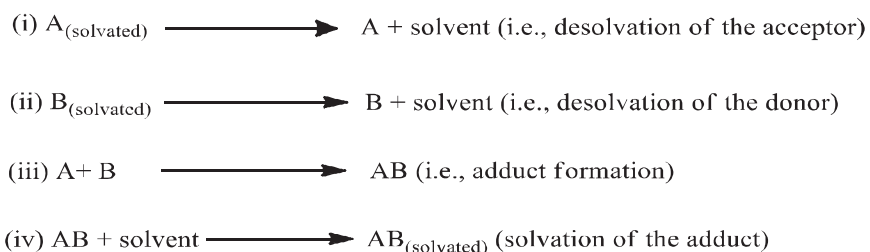
Roy and co-workers have modified the expression of stabilization energy after inclusion of first and second order effects (due to perturbing external potential of the partner of a given atom-in-a-molecule) in the individual energy components as well as overall stabilization energy.¹¹ The modified equation of stabilization energy at equilibrium (i.e., when there is no further electron exchange between the donor and the acceptor) is given by equation (2.19).

It is obvious from equation (2.19) that effects other than charge transfer (e.g., electrostatic, polarization, dispersion etc.) are taken care by different perturbation parameters (e.g., v , α , β , ΔZ). It is argued that as the solvent polarity increases (i.e., dielectric constant, ϵ increases) both the donor and the acceptor will be solvated more, reducing the extent of mutual external potential perturbation (as, both ΔZ_A and ΔZ_B values, both of which are positive quantities, will be reduced). So, net stabilization energy is expected to decrease (i.e., less negative) as the net negative contribution of the second term in the right hand side of equation (2.19) decreases. So, equation (2.19) can be considered as a formalism based on density functional reactivity theory (DFRT) to show solvent effect on stabilization energy during adduct formation process.

However, the problem of calculating ΔE_{eqm} value from equation (2.19) is that there is no straightforward way to calculate parameters, ν , α , β and ΔZ of an atom-in-a-molecule when the adduct formation takes place between two molecules. As an alternative, a slightly less rigorous and augmented approach can be adopted, as elaborated below.

(b) Working equations to take care of solvent effect in stabilization energy:

Various thermodynamic cycles have been proposed earlier²³⁻²⁵ to evaluate Gibbs free energy of solvation [$\Delta G_{(solvation)}$] or ‘solvation free energies’ in different solvents. Phenomenologically, the process of adduct formation in presence of a solvent can be assumed to have taken place through the following steps:



From, thermodynamic consideration step (i) and step (ii) are endothermic processes as energy is required to overcome the attractive interaction between either A or B and the solvent (in the process of desolvation). However, once the adduct is formed [step (iii)], its solvation is exothermic. So, the ‘net desolvation energy’ can be formulated from the equation given below,

$$\Delta E_{desolv}^{net} = (\Delta E_{A(desolv)} + \Delta E_{B(desolv)}) - \Delta E_{AB(desolv)} \quad (3.1)$$

where,

$$\Delta E_{B(desolv)} = -\Delta G_{B(solvation)} = E_{B(gas)} - E_{B(solvent)} \quad (3.2)$$

$$\Delta E_{A(desolv)} = -\Delta G_{A(solvation)} = E_{A(gas)} - E_{A(solvent)} \quad (3.3)$$

$$\Delta E_{AB(desolv)} = -\Delta G_{AB(solvation)} = E_{AB(gas)} - E_{AB(solvent)} \quad (3.4)$$

Here, $\Delta E_{B(desolv)}$, $\Delta E_{A(desolv)}$ and $\Delta E_{AB(desolv)}$ represent, respectively, the differences in the energies of the donor (B), the acceptor (A) and the adduct (AB) in the gas phase and in the corresponding solvent. $\Delta G_{X(solvation)}$ represent the corresponding Gibbs free energy of solvation (where X = A, B or AB). From equation (3.1), an analogy can be drawn that the ‘net desolvation energy’, ΔE_{desolv}^{net} , is equal to the ‘net free energy of solvation’, $\Delta G_{(solvation)}^{net}$ with negative sign²⁵ (also called the ‘binding free energy’)¹⁹ as shown below:

$$\Delta E_{desolv}^{net} = [(E_{A(gas)} + E_{B(gas)}) - E_{AB(gas)}] - [(E_{A(solvent)} + E_{B(solvent)}) - E_{AB(solvent)}]$$

$$= -B.E._{(gas)} + B.E._{(solvent)} = B.E._{(solvent)} - B.E._{(gas)} = \text{Binding free energy} \quad (3.5)$$

$$\begin{aligned} \text{Similarly, } \Delta E_{desolv}^{net} &= -(\Delta G_{A(solvation)} + \Delta G_{B(solvation)}) + \Delta G_{AB(solvation)} \\ &= -\Delta G_{(solvation)}^{net} \end{aligned} \quad (3.6)$$

Finally, the stabilization energy of the adduct formation process in the solvent can be written as,

$$\Delta E_{SE(AB)}^{solvent} = \Delta E_{desolv}^{net} + \Delta E_{SE(AB)}^{gas} \quad (3.7)$$

Here, $\Delta E_{SE(AB)}^{gas}$ is the gas phase stabilization energy as obtained from equation (1.48) and represents the energy released in step (iii) of the adduct formation process. The computational procedure related to equations (3.1) – (3.4) is described in the next section.

3.3. Computational Details:

The adduct forming pairs chosen in the present study are (i) methyltrioxorhenium (MTO) and pyridine (Figure 3.1) and (ii) (azidomethyl)benzene and methylpropiolate (Figure 3.2). Initial structures were generated using GaussView 05 program package.²⁶ Geometry optimization followed by frequency calculations for donors (B), acceptors (A) as well as adducts (AB) were performed in gas phase and in different solvents using Gaussian09 software.²⁶ Computation of $\Delta E_{SE(AB)}^{gas}$ [equation (3.7)] is done through CDASE scheme [equations (1.48) - (1.50)] and in gas phase only. Equations (3.2), (3.3) and (3.4) are used to evaluate desolvation energies of the individual species, whereas ‘net desolvation energy’ is computed through equation (3.1). Finally, stabilization energy for the adduct formation process in solvent (i.e., $\Delta E_{SE(AB)}^{solvent}$) is computed using equation (3.7).

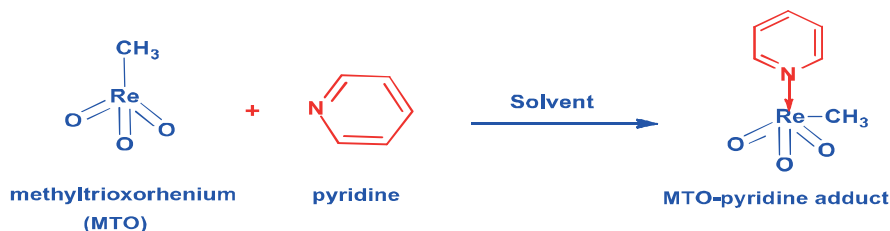


Figure 3.1. Schematic diagram representing the methyltrioxorhenium(MTO)-pyridine adduct formation process in solvent.

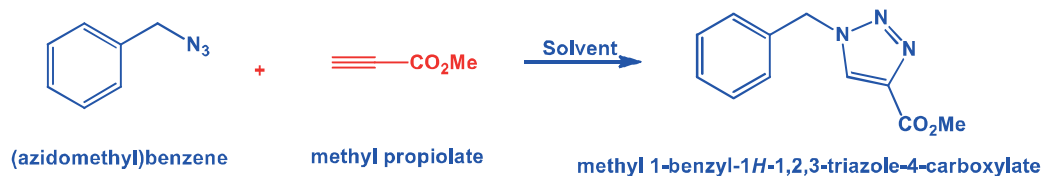


Figure 3.2. Schematic diagram representing the formation of methyl 1-benzyl-1H-1,2,3-triazole-4-carboxylate from (azidomethyl)benzene and methylpropiolate in solvent.

To prove worthiness of the equations (3.1) - (3.7), all calculations are carried out in different methods. For pair (i) the calculations are carried out at two different methods. The first one is M06-2X/Def2SVP. In this method, Def2SVP²⁷ (all-electron basis set) is used for all the atoms in methyltrioxorhenium (MTO), pyridine and methyltrioxorhenium(MTO)-pyridine adduct. The second one is M06/6-31G(d,p), LANL2DZ. In this method LANL2DZ basis set with ECP is used only for Re atom to take care of chemically inert core electrons and are effective in reducing computational expense,^{28,29} whereas 6-31G(d,p) basis set is used for pyridine and for the atoms other than Re in both methyltrioxorhenium (MTO) and methyltrioxorhenium(MTO)-pyridine adduct. However, all-electron basis sets are known to be more efficient than the mixed basis sets.²⁷

For pair (ii) the methods used are (a) M06/6-31G+(d,p) and (b) M06-2X /6-31G (d,p). It is well known that both M06 and M06-2X functionals take care of dispersion corrections reasonably well.³⁰ Effect of solvation is taken care implicitly through IEF-PCM^{31,32} model as well as through SMD³² model and are as available in Gaussian 09.²⁶ Apart from the above two models the solvation effect is also tested explicitly for pair (ii) in three different solvents and considering one solvent molecule in each case.

3.4. Results and Discussion:

It is known that the solvent effect signifies the influence of solvent on chemical reactivity or molecular associations. The solvent with high dielectric constant increases polarity of the solution to a greater extent than the solvent with low dielectric constant, the effect of which results in variation of electrostatic, polarization, dispersion etc. interactions between the solvent and the reactant. These effects are more pronounced in a solvent of high polarity than in one with low polarity and negligible in non-polar solvents (i.e., having very low dielectric constants). Now, the physical interactions among the electron donor (B), the electron acceptor (A) and the solvent in a solution can be categorized as the (i) interaction between individual reactants (i.e., A or B) with

the solvent and (ii) intermolecular interaction between the two reactants (i.e., A and B). The reactants are solvated more in a solvent having high dielectric constant (i.e., the reactants show stronger interaction towards the solvent than between themselves), which results to a less stable adduct or product. On the contrary, in a solvent with less polarity or no polarity reactants are not solvated completely, causing poor hindrance to intermolecular interaction between the reactants. This finally leads to a stable adduct or product. One way to verify the above argument is by calculating the ‘net desolvation energy’ of the adduct formation process in different solvents. The expectation is that with increasing solvent polarity (i.e., dielectric constant) the ‘net desolvation energy’ (ΔE_{desolv}^{net} , a positive quantity) will increase. So, when the ΔE_{desolv}^{net} values are added to the $\Delta E_{SE(AB)}^{gas}$, the $\Delta E_{SE(AB)}^{solvent}$ should go on decreasing (i.e., become less negative) with increasing solvent polarity [equation (3.7)]. The obtained trends of ΔE_{desolv}^{net} and $\Delta E_{SE(AB)}^{solvent}$ values of the adduct forming pairs chosen in the present investigation is discussed in the rest of this section.

(a) MTO-pyridine adduct formation in different solvents and comparison of $\Delta E_{SE(AB)}^{solvent}$ with experimentally reported formation constant (K_f):

The methyltrioxorhenium(MTO)-pyridine adduct formation process in a solvent is depicted in Figure 3.1. In this process pyridine acts as an electron donor while MTO acts as an electron acceptor. This is verified from the positive value of ΔN which comes out to be 0.22 at M06-2X/Def2SVP level of theory in gas phase by assuming pyridine to be the donor (B) and MTO to be the acceptor (A) [equation (1.47)].

Table 3.1. The $\Delta E_{A(desolv)}$, $\Delta E_{B(desolv)}$, $\Delta E_{AB(desolv)}$, ΔE_{desolv}^{net} and $\Delta E_{SE(AB)}^{solvent}$ values (in kcal mol⁻¹) in MTO-pyridine adduct formation process. In this case the donor (B) is pyridine and the acceptor (A) is methyltrioxorhenium (MTO). All the calculations are carried out at M06-2X/Def2SVP level of theory. The solvation model used here is IEF-PCM.

Entry	Medium	Dielectric constant (ε)	$\Delta E_{A(desolv)}$	$\Delta E_{B(desolv)}$	$\Delta E_{AB(desolv)}$	ΔE_{desolv}^{net}	$\Delta E_{SE(AB)}^{solvent}$
1	gas	1.00	0.00	0.00	0.00	0.00	-6.28
2	n-hexane	1.89	3.57	1.08	2.76	1.89	-4.39
3	benzene	2.27	4.60	1.35	3.51	2.44	-3.84
4	chloroform	4.70	7.33	2.18	5.52	3.99	-2.29
5	ethylacetate	6.00	7.98	2.37	6.00	4.35	-1.93

6	dichloromethane	8.90	9.34	2.62	6.63	5.33	-0.95
7	acetone	20.70	10.33	2.93	7.43	5.83	-0.45

From Table 3.1, it is observed that $\Delta E_{B(desolv)}$ [equation (3.2)], $\Delta E_{A(desolv)}$ [equation (3.3)] and $\Delta E_{AB(desolv)}$ [equation (3.4)] values, individually, are increasing with the solvent polarity (i.e., dielectric constant). However, the ‘net desolvation energy’ (ΔE_{desolv}^{net}) [equation (3.5)] follows increasing order with the increase in solvent polarity, as shown below:

gas < n-hexane < benzene < chloroform < ethylacetate < dichloromethane < acetone.

Again, stabilization energy values of the adduct formation process in different solvents ($\Delta E_{SE(AB)}^{solvent}$) [equation (3.7)] are decreasing (i.e., becoming less negative) with the increase in solvent polarity, causing the trend of stabilization as follows:

gas > n-hexane > benzene > chloroform > ethylacetate > dichloromethane > acetone.

Table 3.2 presents the same parameters as represented in Table 3.1 in M06/6-31G(d,p), LANL2DZ (for Re) method. Again, the positive value of ΔN (i.e., 0.218) computed at M06/6-31G(d,p), LANL2DZ (for Re) level of theory in gas phase claims that pyridine is donor and MTO is acceptor. Although, the values of charge transfer (ΔN), $\Delta E_{A(desolv)}$, $\Delta E_{B(desolv)}$, $\Delta E_{AB(desolv)}$, ΔE_{desolv}^{net} , and $\Delta E_{SE(AB)}^{solvent}$ are different from the previous method the trends for all these parameters remain similar.

Table 3.2. The $\Delta E_{A(desolv)}$, $\Delta E_{B(desolv)}$, $\Delta E_{AB(desolv)}$, ΔE_{desolv}^{net} , and $\Delta E_{SE(AB)}^{solvent}$ values (in kcal mol⁻¹) in MTO-pyridine adduct formation process. In this case the donor is pyridine and the acceptor is methyltrioxorhenium (MTO). All the calculations are carried out at M06/6-31G(d,p), LANL2DZ (for Re) level of theory. The solvation model used here is IEF-PCM.

Entry	Medium	Dielectric constant (ϵ)	$\Delta E_{A(desolv)}$	$\Delta E_{B(desolv)}$	$\Delta E_{AB(desolv)}$	ΔE_{desolv}^{net}	$\Delta E_{SE(AB)}^{solvent}$
1	gas	1.00	0.00	0.00	0.00	0.00	-6.12
2	n-hexane	1.89	3.04	1.05	2.54	1.55	-4.57
3	benzene	2.27	3.88	1.32	3.22	1.98	-4.14
4	chloroform	4.70	6.62	2.13	5.08	3.67	-2.45
5	ethylacetate	6.00	6.99	2.32	5.51	3.8	-2.32
6	dichloromethane	8.90	7.96	2.56	6.01	4.51	-1.61
7	acetone	20.70	9.36	2.87	6.77	5.46	-0.66

The trend of stabilization energy can be compared with the formation constant (K_f) values of the methyltrioxorhenium(MTO)-pyridine adduct obtained from experimental study in six different solvents.¹⁴ The data from Table 3.3 supports the fact that the formation constant depends on the dielectric constant of the solvent. The values of the formation constant (K_f) were found to decrease with the increase in dielectric constant of the solvent, the trend of which again is similar to the trend of $\Delta E_{SE(AB)}^{solvent}$. Thus both K_f and $\Delta E_{SE(AB)}^{solvent}$ support the claim drawn from equation (2.19).

Table 3.3. Comparison of the theoretically calculated Stabilization energy ($\Delta E_{SE(AB)}^{solvent}$) values (in kcal mol⁻¹) with experimentally observed formation constant (K_f)¹⁴ in the process of MTO-pyridine adduct formation.

Entry	Solvent	K_f (L mol ⁻¹) at 10 °C ¹⁴	$\Delta E_{SE(AB)}^{solvent}$	
			M06-2X/Def2SVP	M06/6-31G(d,p), LANL2DZ (for Re)
1	n-hexane	1236.80	-4.39	-4.57
2	benzene	1036.70	-3.84	-4.14
3	chloroform	376.30	-2.29	-2.45
4	ethylacetate	314.10	-1.93	-2.23
5	dichloromethane	247.70	-0.95	-1.61
6	acetone	151.50	-0.45	-0.66

The trend of stability of the MTO-pyridine adduct in different solvents can also be investigated by another well-known DFRT based reactivity descriptor, the global hardness (η). This is because according to the principle of maximum hardness, ‘chemical system tries to arrange itself as hard as possible’.^{33,34} Thus chemical species having lesser value of η is less stable.^{35,36} When the donor (B) and the acceptor (A) species form the adduct (AB) the energy is released which is known as ‘stabilization energy’ [$\Delta E_{SE(AB)}$] in DFRT. More the energy released, [i.e., more negative is the value of $\Delta E_{SE(AB)}$], the adduct (AB) formed will be more stable i.e., having larger hardness (η) value. As with the increase in solvent polarity $\Delta E_{SE(AB)}^{solvent}$ values decreases (i.e., becomes less negative) the adduct will be less stable decreasing the η value.

The global hardness values of the adduct in different solvents is calculated through Δ SCF method [$\eta = \left(\frac{IP-EA}{2}\right) = E_{N-1} + E_{N+1} - 2E_N$, here, E_N , E_{N+1} and E_{N-1} represent, respectively, the energy values of the neutral, anionic and cationic species, respectively, at the optimized geometry of the neutral species] as well as through Koopmans' approximation $\eta = \left(\frac{E_{LUMO}-E_{HOMO}}{2}\right)$, here, E_{LUMO} and E_{HOMO} , represent, respectively, the energies of lowest unoccupied and highest occupied molecular orbitals. The values of η , shown in Table 3.4 (a), also confirm that with increase in solvent polarity stability of the adduct is decreased. Interestingly, when η values are generated using less rigorous Koopmans' approximation here, the trend is again as per expectation [Table 3.4 (b)].

Table 3.4 (a). Hardness (η) values (in kcal mol⁻¹) of methyltrioxorhenium(MTO)-pyridine adduct in different solvents through Δ SCF method. The solvation model used here is IEF-PCM.

Entry	Medium	Hardness (η)	
		M06-2X/Def2SVP	M06/6-31G(d,p), LANL2DZ (For Re)
1	gas	111.99	109.01
2	n-hexane	90.43	84.91
3	benzene	85.34	80.04
4	chloroform	72.21	67.29
5	ethylacetate	70.82	65.78
6	dichloromethane	68.02	61.14
7	acetone	61.98	57.62

Table 3.4 (b). Hardness (η) values (in kcal mol⁻¹) of methyltrioxorhenium(MTO)-pyridine adduct in different solvents through Koopmans' approximation. The solvation model used here is IEF-PCM.

Entry	Medium	Hardness (η)	
		M06-2X/Def2SVP	M06/6-31G(d,p), LANL2DZ (For Re)
1	gas	92.77	62.72
2	n-hexane	90.44	61.10
3	benzene	89.86	60.60
4	chloroform	88.67	59.16

5	ethylacetate	88.41	58.88
6	dichloromethane	88.10	58.38
7	acetone	87.78	51.51

(b) Methyl 1-benzyl-1H-1,2,3-triazole-4-carboxylate formation in different solvents:

Figure 3.2 (section 3.3) represents the Huisgen [3+2] cycloaddition reaction³⁷ in a solvent. This is a well known reaction in organic chemistry and is commonly known as ‘click reaction’. In this reaction (azidomethyl)benzene acts as an electron donor (B) and methyl propiolate acts as an electron acceptor (A). This is verified from positive ΔN values of 0.120 and 0.116 using M06/6-31G+(d,p) and M06-2X/6-31G(d,p) levels of theory, respectively. The product formed is methyl 1-benzyl-1H-1,2,3-triazole-4-carboxylate. Trends of calculated values of $\Delta E_{A(desolv)}$, $\Delta E_{B(desolv)}$, $\Delta E_{AB(desolv)}$, ΔE_{desolv}^{net} , and $\Delta E_{SE(AB)}^{solvent}$ with variation of solvent polarity are observed to be similar to those obtained in MTO-pyridine adduct formation process [sub-section 3.4(a)]. So, again in both the methods, the stabilization energy is found to be maximum (i.e., the most negative) in gas phase and minimum in the solvent of highest polarity (i.e., dimethylsulfoxide, among the chosen ones).

Table 3.5. The $\Delta E_{A(desolv)}$, $\Delta E_{B(desolv)}$, $\Delta E_{AB(desolv)}$, ΔE_{desolv}^{net} , and $\Delta E_{SE(AB)}^{solvent}$ values (in kcal mol⁻¹) in the formation of methyl 1-benzyl-1H-1,2,3-triazole-4-carboxylate. In this case donor (B) is (azidomethyl)benzene and acceptor(A) is methylpropiolate. All the calculations are carried out at M06/6-31G+(d,p) level of theory. The solvation model used here is IEF-PCM.

Entry	Medium	Dielectric constant (ϵ)	$\Delta E_{B(desolv)}$	$\Delta E_{A(desolv)}$	$\Delta E_{AB(desolv)}$	ΔE_{desolv}^{net}	$\Delta E_{SE(AB)}^{solvent}$
1	gas	1.00	0.00	0.00	0.00	0.00	-3.49
2	toluene	2.37	1.60	3.21	3.17	1.64	-1.85
3	tetrahydrofuran	7.42	2.92	5.66	5.78	2.80	-0.69
4	dichloromethane	8.93	3.04	5.9	6.08	2.86	-0.63
5	acetone	20.49	3.44	6.58	6.89	3.13	-0.36
6	acetonitrile	35.69	3.56	6.83	7.18	3.21	-0.28
7	dimethylformamide	37.22	3.59	6.84	7.20	3.23	-0.26
8	dimethylsulfoxide	46.82	3.72	7.01	7.39	3.34	-0.15

Table 3.6. The $\Delta E_{A(desolv)}$, $\Delta E_{B(desolv)}$, $\Delta E_{AB(desolv)}$, ΔE_{desolv}^{net} , and $\Delta E_{SE(AB)}^{solvent}$ values (in kcal mol⁻¹) in the formation of methyl 1-benzyl-1H-1,2,3-triazole-4-carboxylate. In this case donor (B) is (azidomethyl)benzene and acceptor(A) is methylpropiolate. All the calculations are carried out at M06-2X/6-31G(d,p) level of theory. The solvation model used here is IEF-PCM.

Entry	Medium	Dielectric constant (ϵ)	$\Delta E_{B(desolv)}$	$\Delta E_{A(desolv)}$	$\Delta E_{AB(desolv)}$	ΔE_{desolv}^{net}	$\Delta E_{SE(AB)}^{solvent}$
1	gas	1.00	0.00	0.00	0.00	0.00	-1.8
2	toluene	2.37	1.51	2.05	3.05	0.51	-1.29
3	tetrahydrofuran	7.42	2.77	3.56	5.55	0.78	-1.02
4	dichloromethane	8.93	2.89	3.70	5.81	0.78	-1.02
5	acetone	20.49	3.27	4.11	6.56	0.82	-0.98
6	acetonitrile	35.69	3.40	4.25	6.83	0.82	-0.98
7	dimethylformamide	37.22	3.41	4.26	6.84	0.83	-0.97
8	dimethylsulfoxide	46.82	3.44	4.30	6.91	0.83	-0.97

As no experimental value of formation constant (K_f) is available for the adduct formation process between (azidomethyl)benzene and methyl propiolate we can get some idea about the trend of stabilization energy in different solvents from the corresponding chemical hardness (η) values. The η - values computed through Δ SCF method in different solvents are shown in Table 3.7 (a) [the corresponding values calculated through Koopmans' approximation are given in Table 3.7 (b)]. It is clear from the generated values of η that as the solvent polarity increases the stability of the adduct (and hence the stabilization energy, $\Delta E_{SE(AB)}^{solvent}$ of the adduct formation process) decreases.

Table 3.7 (a). Hardness (η) values (in kcal mol⁻¹) of methyl 1-benzyl-1H-1,2,3-triazole-4-carboxylate in different solvents through Δ SCF method. The solvation model used here is IEF-PCM.

Entry	Medium	Hardness (η)	
		M06/631G+(d,p)	M06-2X/6-31G(d,p)
1	gas	103.71	112.95
2	toluene	80.42	87.49
3	tetrahydrofuran	68.02	73.65

4	dichloromethane	66.99	72.51
5	acetone	64.93	69.26
6	acetonitrile	64.28	67.29
7	dimethylformamide	62.81	66.30
8	dimethylsulfoxide	62.21	65.83

Table 3.7 (b). Hardness (η) values (in kcal mol⁻¹) of methyl 1-benzyl-1H-1,2,3-triazole-4-carboxylate in different solvents through Koopmans' approximation. The solvation model used here is IEF-PCM.

Entry	Medium	Hardness (η)	
		M06/6-31G+(d,p)	M06-2X/6-31G(d,p)
1	gas	69.28	91.06
2	toluene	69.20	90.97
3	tetrahydrofuran	68.72	90.87
4	dichloromethane	68.65	90.86
5	acetone	68.62	90.82
6	acetonitrile	68.51	90.82
7	dimethylformamide	68.50	90.80
8	dimethylsulfoxide	68.23	90.80

When $\Delta E_{SE(AB)}^{solvent}$ (Tables 3.1, 3.2, 3.5, 3.6) are plotted against the Onsager function, $(\epsilon - 1)/(2\epsilon + 1)$,^{38,39} reasonably reliable linear fitting is obtained (as evidenced from high adjusted R² values, Figures 3.3 - 3.6). In all these plots $\Delta E_{SE(AB)}^{solvent}$ values becoming numerically less negative with the increase in the value of $(\epsilon - 1)/(2\epsilon + 1)$.

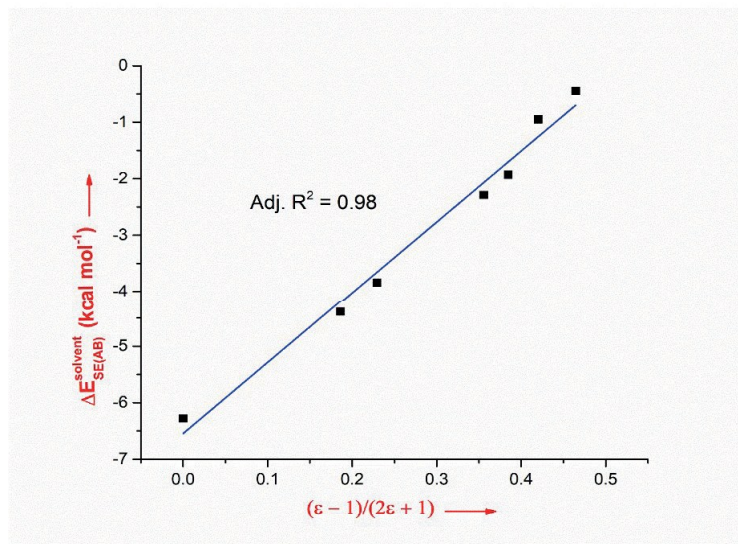


Figure 3.3. Plot representing variation of stabilization energy, $\Delta E_{SE(AB)}^{solvent}$, in the process of MTO-pyridine adduct formation versus Onsager function, $(\epsilon - 1)/(2\epsilon + 1)$. All the calculations are carried out at M06-2X/Def2SVP level of theory using IEF-PCM solvation model.

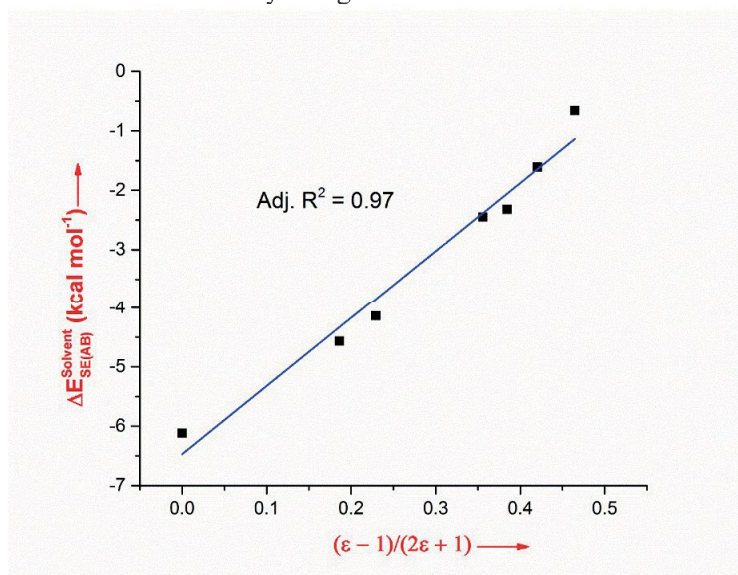


Figure 3.4. Plot representing variation of stabilization energy, $\Delta E_{SE(AB)}^{solvent}$, in the process of MTO-pyridine adduct formation versus Onsager function, $(\epsilon - 1)/(2\epsilon + 1)$. All the calculations are carried out at M06/6-31G(d,p), LANL2DZ (for Re) level of theory using IEF-PCM solvation model.

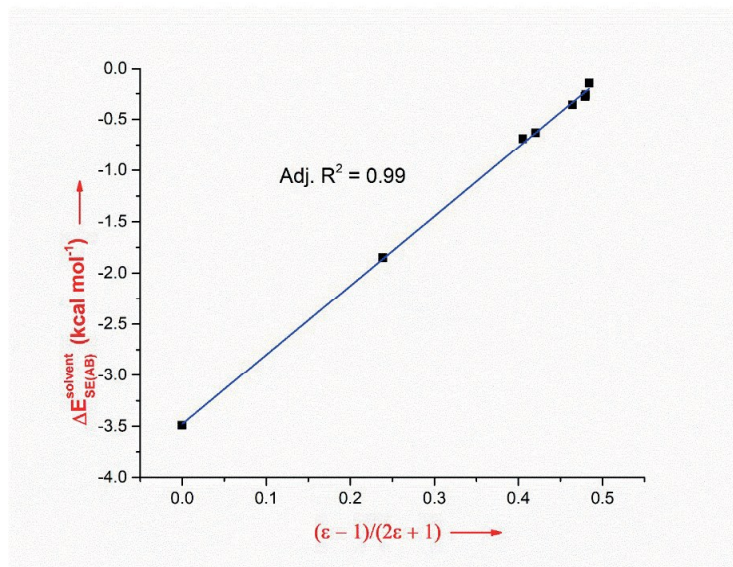


Figure 3.5. Plot representing variation of stabilization energy, $\Delta E_{SE(AB)}^{solvent}$, in the process of methyl 1-benzyl-1H-1,2,3-triazole-4-carboxylate formation versus Onsager function, $(\epsilon - 1)/(2\epsilon + 1)$. All the calculations are carried out at M06/6-31G+(d,p) level of theory using IEF-PCM solvation model.

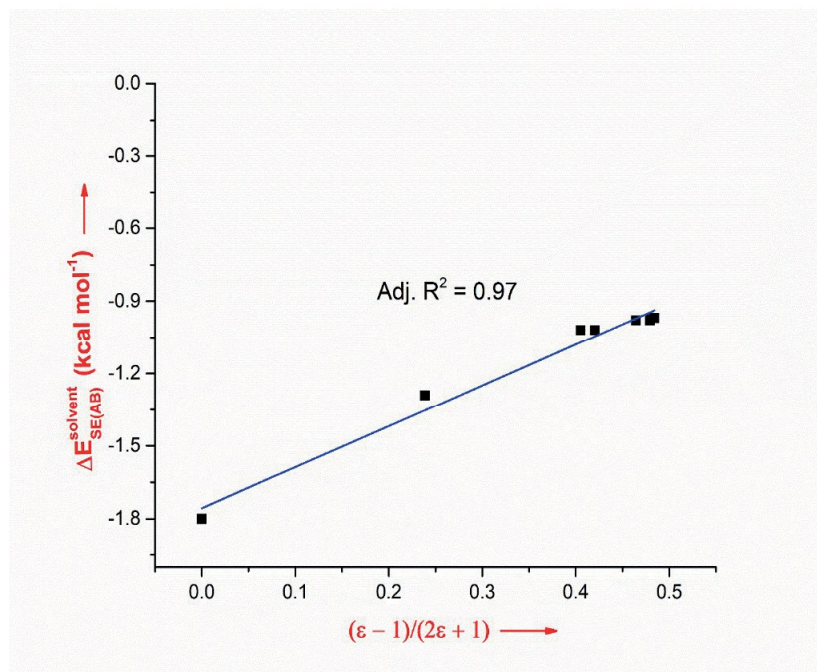


Figure 3.6. Plot representing variation of stabilization energy, $\Delta E_{SE(AB)}^{solvent}$, in the process of methyl 1-benzyl-1H-1,2,3-triazole-4-carboxylate formation versus Onsager function, $(\epsilon - 1)/(2\epsilon + 1)$. All the calculations are carried out at M06-2X/6-31G(d,p) level of theory using IEF-PCM solvation model.

The values of $\Delta E_{A(desolv)}$, $\Delta E_{B(desolv)}$, $\Delta E_{AB(desolv)}$ and ΔE_{desolv}^{net} , (and hence $\Delta E_{SE(AB)}^{solvent}$), calculated so far (Tables 3.1, 3.2, 3.5 and 3.6) are based on IEF-PCM solvation model. However, IEF-PCM solvation model is sometimes criticized for not taking care of the non-covalent interactions properly. To verify the trend of $\Delta E_{SE(AB)}^{solvent}$ with solvent polarity the values are generated in SMD solvation model also and are shown in Tables 3.8 - 3.11.

Table 3.8. The $\Delta E_{A(desolv)}$, $\Delta E_{B(desolv)}$, $\Delta E_{AB(desolv)}$, ΔE_{desolv}^{net} and $\Delta E_{SE(AB)}^{solvent}$ values (in kcal mol⁻¹) in MTO-pyridine adduct formation process. In this case the donor (B) is pyridine and the acceptor (A) is methyltrioxorhenium (MTO). All the calculations are carried out at M06-2X/Def2SVP level of theory. The solvation model used here is SMD.

Entry	Medium	Dielectric constant (ϵ)	$\Delta E_{A(desolv)}$	$\Delta E_{B(desolv)}$	$\Delta E_{AB(desolv)}$	ΔE_{desolv}^{net}	$\Delta E_{SE(AB)}^{solvent}$
1	gas	1.00	0.00	0.00	0.00	0.00	-6.28
2	n-hexane	1.89	3.69	4.35	7.25	0.79	-5.49
3	benzene	2.27	4.98	4.08	8.49	0.57	-5.71
4	chloroform	4.70	6.72	5.90	9.11	3.51	-2.77
5	ethylacetate	6.00	7.87	5.33	10.52	2.68	-3.6
6	dichloromethane	8.90	7.45	6.53	10.36	3.62	-2.66
7	acetone	20.70	9.34	6.07	11.55	3.86	-2.42

Table 3.9. The $\Delta E_{A(desolv)}$, $\Delta E_{B(desolv)}$, $\Delta E_{AB(desolv)}$, ΔE_{desolv}^{net} , and $\Delta E_{SE(AB)}^{solvent}$ values (in kcal mol⁻¹) in MTO-pyridine adduct formation process. In this case the donor is pyridine and the acceptor is methyltrioxorhenium (MTO). All the calculations are carried out at M06/6-31G(d,p), LANL2DZ (for Re) level of theory. The solvation model used here is SMD.

Entry	Medium	Dielectric constant (ϵ)	$\Delta E_{A(desolv)}$	$\Delta E_{B(desolv)}$	$\Delta E_{AB(desolv)}$	ΔE_{desolv}^{net}	$\Delta E_{SE(AB)}^{solvent}$
1	gas	1.00	0.00	0.00	0.00	0.00	-6.12
2	n-hexane	1.89	3.56	4.27	7.18	0.65	-5.47
3	benzene	2.27	4.68	4.67	8.33	1.02	-5.10
4	chloroform	4.70	5.89	5.80	8.69	3.00	-3.12
5	ethylacetate	6.00	7.41	5.21	10.34	2.28	-3.84

6	dichloromethane	8.90	6.61	6.42	9.93	3.10	-3.02
7	acetone	20.70	8.70	5.95	11.27	3.38	-2.47

Table 3.10. The $\Delta E_{A(desolv)}$, $\Delta E_{B(desolv)}$, $\Delta E_{AB(desolv)}$, ΔE_{desolv}^{net} , and $\Delta E_{SE(AB)}^{solvent}$ values (in kcal mol⁻¹) in the formation of methyl 1-benzyl-1H-1,2,3-triazole-4-carboxylate. In this case donor (B) is (azidomethyl)benzene and acceptor(A) is methylpropiolate. All the calculations are carried out at M06/6-31G+(d,p) level of theory. The solvation model used here is SMD.

Entry	Medium	Dielectric constant (ϵ)	$\Delta E_{A(desolv)}$	$\Delta E_{B(desolv)}$	$\Delta E_{AB(desolv)}$	ΔE_{desolv}^{net}	$\Delta E_{SE(AB)}^{solvent}$
1	gas	1.00	0.00	0.00	0.00	0.00	-3.49
2	toluene	2.37	3.36	3.38	7.80	-1.06	-4.55
3	tetrahydrofuran	7.42	4.78	4.32	10.09	-0.99	-4.48
4	dichloromethane	8.93	4.92	5.92	11.87	-1.03	-4.52
5	acetone	20.49	5.50	5.52	11.86	-0.84	-4.33
6	acetonitrile	35.67	5.18	5.49	11.85	-1.18	-4.67
7	dimethylformamide	37.22	5.18	4.36	10.90	-1.36	-4.58
8	dimethylsulfoxide	46.82	4.54	3.26	9.42	-1.62	-5.11

Table 3.11. The $\Delta E_{A(desolv)}$, $\Delta E_{B(desolv)}$, $\Delta E_{AB(desolv)}$, ΔE_{desolv}^{net} , and $\Delta E_{SE(AB)}^{solvent}$ values (in kcal mol⁻¹) in the formation of methyl 1-benzyl-1H-1,2,3-triazole-4-carboxylate. In this case donor (B) is (azidomethyl)benzene and acceptor(A) is methylpropiolate. All the calculations are carried out at M06-2X/6-31G(d,p) level of theory. The solvation model used here is SMD.

Entry	Medium	Dielectric constant (ϵ)	$\Delta E_{A(desolv)}$	$\Delta E_{B(desolv)}$	$\Delta E_{AB(desolv)}$	ΔE_{desolv}^{net}	$\Delta E_{SE(AB)}^{solvent}$
1	gas	1.00	0.00	0.00	0.00	0.00	-1.80
2	toluene	2.37	3.62	3.50	7.43	-0.31	-2.11
3	tetrahydrofuran	7.42	5.21	4.51	9.80	-0.08	-1.88
4	dichloromethane	8.93	5.46	6.12	11.31	-0.27	-1.53
5	acetone	20.49	6.04	5.72	12.03	-0.27	-2.07
6	acetonitrile	35.67	5.77	5.71	11.79	-0.31	-2.11
7	dimethylformamide	37.22	5.70	4.58	10.43	-0.15	-1.95

8	dimethylsulfoxide	46.82	5.06	3.48	9.40	-0.86	-2.66
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The corresponding global hardness (η) values generated by Δ SCF method are shown in Tables 3.12 and 3.13.

Table 3.12. Hardness (η) values (in kcal mol⁻¹) of Methyltrioxorhenium(MTO)-pyridine adduct in different solvents using Δ SCF method. The solvation model used here is SMD.

Entry	Medium	Hardness (η)	
		M06-2X/Def2SVP	M06/6-31G(d,p), LANL2DZ (For Re)
1	gas	111.99	109.01
2	n-hexane	86.78	84.90
3	benzene	81.63	80.04
4	chloroform	66.70	67.26
5	ethylacetate	65.72	65.76
6	dichloromethane	61.12	60.86
7	acetone	58.00	57.73

Table 3.13. Hardness (η) values (in kcal mol⁻¹) of 1-benzyl-1H-1,2,3-triazole-4-carboxylate in different solvents through Δ SCF method. The solvation model used here is SMD.

Entry	Medium	Hardness (η)	
		M06/631G+(d,p)	M06-2X/6-31G(d,p)
1	gas	103.71	112.95
2	toluene	86.40	76.28
3	tetrahydrofuran	72.61	59.93
4	dichloromethane	69.83	58.65
5	acetone	66.71	58.08
6	acetonitrile	65.91	57.37
7	dimethylformamide	65.90	51.12
8	dimethylsulfoxide	62.21	50.81

Unfortunately the generated trends of $\Delta E_{SE(AB)}^{solvent}$ are irregular and not as expected from experimentally observed K_f values or theoretically generated (and well trusted) η values.

Moreover, the generated ΔE_{desolv}^{net} values for the adduct formation process between (azidomethyl)benzene and methylpropiolate at M06-2X/6-31G(d,p) level of theory are coming to be negative, apparently giving an impression that the adduct formation is a thermodynamically unfavourable process (which, in reality, is not true).

Miguel *et al.*⁴⁰ have shown that SMD solvation model performs poorly in predicting free energy barriers (i.e., difference in solvation free energy of transition states and the reactants) for nucleophilic substitution reactions in dipolar aprotic solvents. The cause of this poor performance was attributed to the inability of the SMD model to introduce fully variable solute cavity in different solvents. As in the present study the $\Delta E_{SE(AB)}^{solvent}$ is also calculated from ΔE_{desolv}^{net} , which is the difference of the desolvation energies of the reactants (A and B) and the product (AB), the above argument may apply here also. Additionally, the solvents used in both the chosen set of reactions in the present study are also aprotic.

Again, to take care of the explicit solvent effect on the stabilization energy, the net complexation energy ($\Delta E_{complexation}^{net}$) (between the adduct methyl 1-benzyl-1H-1,2,3-triazolecarboxylate and one molecule of solvent) values are computed at M06-2X/6-31G(d,p) level of theory. The corresponding values of ΔE_{desolv}^{net} and the relevant equations are given in Table 3.14.

Table 3.14. ΔE_{desolv}^{net} values (in kcal mol⁻¹) in the formation of methyl 1-benzyl-1H-1,2,3-triazole-4-carboxylate in three solvents (viz., acetone, acetonitrile and dimethylsulfoxide) using explicit solvent model (one solvent molecule). All the calculations are carried at M06-2X/6-31G(d,p) level of theory. Basis set superposition error is taken care by counterpoise correction.

Entry	Solvent	$\Delta E_{complexation}^{A-solvent}$	$\Delta E_{complexation}^{B-solvent}$	$\Delta E_{complexation}^{AB-solvent}$	ΔE_{desolv}^{net}
1	acetone	-4.25	-7.63	-3.89	7.99
2	acetonitrile	-3.94	-7.52	-5.45	6.01
3	dimethylsulfoxide	-7.00	-9.12	-0.59	15.53

where,

$$\Delta E_{desolv}^{net} = -[(\Delta E_{complexation}^{A-solvent} + (\Delta E_{complexation}^{B-solvent}))] - \Delta E_{complexation}^{AB-solvent} = -\Delta E_{complexation}^{net}$$

$\Delta E_{complexation}^{A-solvent}$ = Complexation energy (in kcal mol⁻¹) of acceptor (A) methylpropiolate with solvent,

$\Delta E_{complexation}^{B-solvent}$ = Complexation energy (in kcal mol⁻¹) of donor (B) (azidomethyl)benzene with solvent,

$\Delta E_{complexation}^{AB-solvent}$ = Complexation energy (in kcal mol⁻¹) of adduct (AB) methyl 1-benzyl-1H-1,2,3-triazole-4-carboxylate with solvent.

It is obvious that the generated trend of ΔE_{desolv}^{net} is not as per expectation from the η values. One of the probable reasons of unexpected trend of ΔE_{desolv}^{net} values is limited understanding about the number of solvent molecules to be considered in the explicit model, which again may vary from solvent to solvent.

3.5. Conclusions:

The study reported in the present chapter provides some insight into the effect of solvent polarity on the stabilization energy [$\Delta E_{SE(AB)}^{solvent}$] in the adduct (or product) formation process. The representative examples chosen here are adduct (or product) formation between (i) methyltrioxorhenium (MTO) with pyridine and (ii) (azidomethyl)benzene with methylpropiolate. MTO-pyridine complex formed as a result of interaction between MTO and pyridine is an adduct in which the nitrogen atom of pyridine is bonded to rhenium (Re) atom of MTO by a coordinate covalent bond (in conventional nomenclature). On the other hand methyl 1-benzyl-1H-1,2,3-triazole-4-carboxylate is a stable [3+2] cycloaddition product formed by the reaction between (azidomethyl)benzene and methylpropiolate. For both these pairs, it is observed that the stabilization energy is highest (i.e., the most negative) in the gas phase for adduct (or product) formation process and decreases (i.e., becomes less negative) as the solvent polarity increases. To take care of the effect of solvent polarity on stabilization energy a very simple (from conceptual and analytical point of view) and easy to compute definition of ‘net desolvation energy’ is proposed keeping in mind the thermodynamic cycle involved in the process of adduct formation. The ‘net desolvation energy’, as defined in the present study, is identified to be equivalent to the ‘binding free energy’ as well as to the negative of ‘net free energy of solvation’. When the values of this ‘net desolvation energy’ is added to the gas phase stabilization energy (generated by DFRT based method) the expected trend of stabilization energy values in different solvents is obtained. This is further supported by global hardness (η) parameter of the adduct (or product), the value of which decreases as the solvent polarity increases. The argument laid down here is that less the stabilization energy (i.e., less negative values) more unstable the adduct formed decreasing its global hardness (η). In case of MTO-pyridine adduct formation process when the experimentally

generated formation constant (K_f) values in different solvents are compared with the stabilization energy values the trends are observed to be in perfect match. This shows decreasing stability of the product as the solvent polarity increases. The computed stabilization energy values in different solvents also claim the same which is verified by plotting $\Delta E_{SE(AB)}^{solvent}$ vs. $(\epsilon-1)/(2\epsilon+1)$ (i.e., Onsager function). The plots show clearly that as solvent dielectric constant (ϵ) increases [hence $(\epsilon-1)/(2\epsilon+1)$ increases] the value of $\Delta E_{SE(AB)}^{solvent}$ becomes less negative. Similar is the observation for the adduct formation process between (azidomethyl)benzene and methylpropiolate. In this case also as solvent polarity increases [i.e., $(\epsilon-1)/(2\epsilon+1)$ increases] $\Delta E_{SE(AB)}^{solvent}$ becomes less negative and global hardness (η) also decreases.

It is worth mentioning here that the SMD solvation model is known to be superior to IEF-PCM model (the way these two solvation models are implemented in Gaussian 09²⁶) because the former takes care of electrostatic and other non-covalent interactions while the later takes care of only the electrostatic interactions. However, in the present study it is observed that the $\Delta E_{SE(AB)}^{solvent}$ are more reliable when computed through IEF-PCM model as trend of these values match with experimentally generated formation constant (K_f) and theoretically computed global hardness (η) values. The values of $\Delta E_{SE(AB)}^{solvent}$ generated by SMD model shows irregular trends. It is interesting to note that the values of η generated by SMD model are as per expectation. This is because of the fact when using the Δ SCF method, non-electrostatic interactions cancel each other, and do not influence the hardness parameter. As IEF-PCM model considers only electrostatic interactions a good correlation occurs between Onsager function and $\Delta E_{SE(AB)}^{solvent}$. On the other hand SMD model considers both electrostatic and non-electrostatic interactions (cavitation and dispersion-repulsion interactions) which are independent on polarity of the system. So, the trend of stabilization energy is not as expected in case of SMD model.

To take care of solvent effect on stabilization energy explicitly, the complexation energy values in three different solvents are computed using explicit solvation model (using one solvent molecule). The 'net desolvation energy' (ΔE_{desolv}^{net}) values calculated from the complexation energy values of the donor (B), the acceptor (A) and the adduct (AB) in case of adduct formation between (azidomethyl)benzene and methyl propiolate are shown in Table 3.14. Again, the trend is not as per expectation. The probable cause of this irregular trend is assigned to the lack of

knowledge regarding the number of solvent molecules to be considered in the explicit model and again this number may vary when one moves from one solvent to another one.

Finally, the present chapter reports an investigation on the solvent effect in the stabilization of the adduct (or product) formation process. To execute this, an interpretation on the basis of the extended expression of stabilization energy [which takes care of external potential perturbation of the interacting atoms, equation (2.19)], is used. However, it remains to be investigated whether the same equation (2.19), can be exploited (in the spirit of CDASE scheme⁴) to explain the solvent effect on the kinetics (i.e., rate) of adduct (or product) formation process.

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