Michael–type reactions of β-nitrostyrenes with piperidine:

Effect of solvents on reactivity and reaction mechanism.

A Dissertation
Submitted for the partial fulfilment

FOR THE DEGREE OF
MASTER OF SCIENCE IN CHEMISTRY

Under Academic Autonomy
NATIONAL INSTITUTE OF TECHNOLOGY, ROURKELA

By

Tushar Kanta Sahu and Sameer Kumar Meher

Under the Guidance Of

Dr. Sabita Patel
Department Of Chemistry
NATIONAL INSTITUTE OF TECHNOLOGY
ROURKELA – 769008, ODISHA

Dr. Sabita Patel
Assistant Professor
Department of Chemistry
National Institute of Technology
Rourkela-769008, India

CERTIFICATE

This is to certify that the dissertation entitled "**Michael–type reactions of β-nitrostyrenes with piperidine: Effect of solvents on reactivity and reaction mechanism**" being submitted by Mr. Tushar Kanta Sahu and Mr. Sameer Kumar Meher to the Department Of Chemistry, National Institute Of Technology, Rourkela-769008, for the award of the degree of Master Of Science in Chemistry, is a record of bonafide research carried out by them under my supervision and guidance. The dissertation report has reached the standard fulfilling the requirements of the regulations relating to the nature of the degree.

I further certify that to the best of my knowledge Mr. Tushar Kanta Sahu and Mr. Sameer Kumar Meher bear good moral character.

NIT-Rourkela   (**Sabita Patel**)

Date:

ACKNOWLEDGEMENT

We owe cordial gratitude to our respected teacher and supervisor Dr. Sabita Patel, Assistant Professor, Department of Chemistry, National Institute of Technology, Rourkela, whose splendid guidance, authentic supervision, assiduous cooperation, moral support and constant encouragement enabled us to make our research work in the present form.

It is our great pleasure to acknowledge to Prof. N. Panda, Head of the Chemistry Department, National Institute of Technology, Rourkela for providing us the necessary facilities for making this research work a success.

We are highly indebted to all the teachers of this department for their kind help and expert suggestions.

We express our profound gratitude to Ms. Sarita Garnayak & Mr. Prakash Kumar Malik for their ceaseless encouragement, immense help and hearty encouragement during our project work.

We wish to thank all our friends for making our stay in this institute a memorable experience.

Finally, we must record our special attention to our Parents and GOD who have always been a source of our strength, inspiration and achievements.

Tushar Kanta Sahu   **Sameer Kumar Meher**

CONTENTS

1. Introduction

The Michael addition involves the addition of a nucleophile, called a 'Michael donor,' to an activated electrophilic olefin, the 'Michael acceptor', resulting in a 'Michael adduct'(Scheme 1).[1-3]Although, the Michael addition is generally considered the addition of enolate nucleophiles to activated olefins, a wide range of functional groups possess sufficient nucleophilicity to perform as Michael donors. Reactions involving non-enolate nucleophiles such as amines, thiols, and phosphines are typically referred to as 'Michael-type additions'.[1-3] The Michael acceptor possesses an electron withdrawing and resonance stabilizing activating group, which stabilizes the anionic intermediate. Michael addition acceptors are far more numerous and varied than donors, due to variety of electron withdrawing activating groups that enable the Michael addition to olefins and alkynes. Acrylate esters, acrylonitrile, acrylamides, maleimides, alkyl methacrylates, cyanoacrylates and vinyl sulfones serve as Michael acceptors and are commercially available. Less common, but equally important, vinyl ketones, nitro ethylenes, α,β-unsaturated aldehydes, vinyl phosphonates, acrylonitrile, vinyl pyridines, azo compounds and even β-keto acetylenes and acetylene esters also serve as Michael acceptors. Over the years, the scope of this reaction has increased dramatically to include a broad range of acceptors and the Michael-type additions of non-carbon donors.
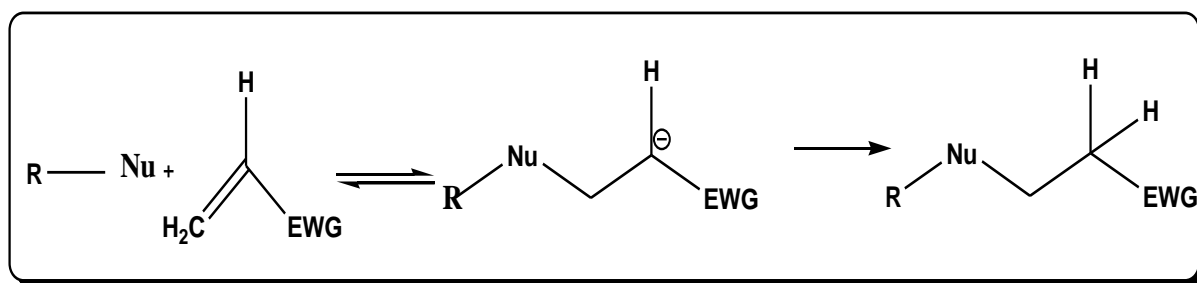
Scheme1

The mechanism of Michael type addition of activated olefins with various anionic and neutral nucleophiles is not well understood but remains controversial. The mechanism differs with change in the nature of nucleophile as well as with change in the solvent from acetonitrile to water.[1-34] Further there are few reports on the effects of solvent on the mechanism of Michael type addition and the reports are also limited to acetonitrile, DMSO and water. Thus to have more insight to the reaction mechanism and the effect of solvent on reaction mechanism, herein we have concentrated our research on the effect of different types of solvents on the reactivity and mechanism of the reaction of β-nitrostyrene with piperidine.

2. Experimental

Materials: All the solvents were purchased from Merck India and purified using standard procedure.[35] Acetonitrile was purified by distilling with calcium chloride.

Synthesis of β-nitrostyrene: β-nitrostyrene was synthesised by following the standard procedure.[36] 10.2 g (8.94ml) of Nitromethane, 17.6 g (16.92ml) of Benzaldehyde and 33.32 ml of Methanol were placed in a three naked flask with a thermometer and cooled at about -10ºC. 7gm of NaOH was diluted to 15 ml with ice and water and was added with a vigorous stirring, to the mixture at such a rate that the temperature was held at 15ºC. The temperature was maintained by addition of crushed ice. A bulky white precipitate formed, to which about 4ml of methanol was added. 116 ml of ice water was added to it. The resulting solution was run immediately with stirring into a flask contain 33.2 ml HCl. A pale yellow crystalline precipitate separated almost as soon as the alkaline medium solution mixed with the acid. The solid settled into the bottom of the flask when the stirrer was stopped. The residue was filtered by suction and washed with water until free from chlorides. The solid was transferred into a beaker immersed in hot water, two layers formed & on cooling again, the lower layer of nitrostyrene solidified, the upper water layer was poured off. The crude nitrostyrene was recrystallised in ethanol. Yield = 95%, M. P. = 57^0.

Kinetic Measurements: The kinetics of Michael-type reaction of β-nitrostyrene with piperidine in different solvents was carried out using UV−VIS spectrophotometer. The temperature in the reaction cell was controlled by circulating water by using Lauda thermostat within a temperature fluctuation of 0.05ºC. The reactions were followed by monitoring the disappearance of the substrate at 309 nm from which the first-order rate constant, k_{obs}, was obtained from the linear plot of log A_t versus t for up to 80% completion of the reaction. All reactions were carried out under pseudo-first-order conditions in which the amine concentrations were at least 20 times greater than the substrate concentration.

3. Results and Discussions

In order to study the effect of solvents on reactivity and reaction mechanism, kinetic study was undertaken spectrophotometrically in a range of solvents by monitoring the decrease in the concentration of β-Nitrostyrene (BNS) at the analytical wavelength of 309 nm with a time interval of 30 sec. Pseudo-first-order conditions were maintained by taking excess concentration of amines as compared to the concentration of BNS. First-order kinetics was obeyed by all the reactions and their observed rate constants (k_{obs}) were calculated using equation (1).

$$\ln A_t = -k_{obs} t + C \qquad (1)$$

Where A_t represents the absorbance at time t. The plots of $\ln A_t$ versus t were almost linear with correlation coefficient (R^2) around 0.99. The reaction was found to be 1st order with respect to BNS. With increase in the concentration of piperidine (PIP), there is a slow increase in the observed rate constant at lower [PIP] while sharp increase was observed at higher concentration in all the solvents. These kinds of upward curvature in the plots of kobs

vs. [PIP] are typical general acid/base catalysed reactions where a second molecule of the reactant behaves as a catalyst. Um et al. suggested both catalysed and un-catalysed route for the reaction of BNS with PIP in acetonitrile following a stepwise mechanism (Scheme 2).[37] On the basis of the proposed mechanism, they dissected the k_{obs} into Kk_2 and Kk_3. Accordingly the rate expression can be derived as follows.

$$\text{BNS} + \text{PIP} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \text{I}$$

$$\text{I} \xrightarrow{k_2} \text{P}$$

$$\text{I} + \text{PIP} \xrightarrow{k_3} \text{P} + \text{PIP}$$
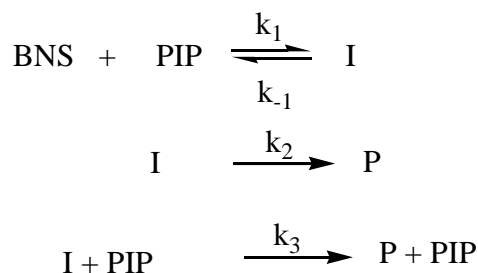
(Scheme 2)

$$k_{obs} = \frac{k_1 k_2 [\text{PIP}] + k_1 k_3 [\text{PIP}]^2}{k_{-1} + k_2 + k_3 [\text{PIP}]^2}$$

Under the assumption $k_{-1} \gg k_2 + k_3 [\text{NH}]$

$$k_{obs} = Kk_2 [\text{PIP}] + Kk_3 [\text{PIP}]^2 \text{, where } K = k_1/k_{-1}$$

$$\frac{k_{obs}}{[\text{PIP}]} = Kk_2 + Kk_3 [\text{PIP}]$$

To shed light on the effect of solvents on reactivity and mechanism of Michael type addition of amine nucleophiles with β-nitrostyrene we have taken the following solvents groups.

(i) Non-polar solvents (benzene, toluene and hexane)

(ii) Polar aprotic solvents (Acetonitrile, DMSO, DMF, Ethyl acetate)

(iii) Polar protic solvents (Methanol, Butanol, Hexanol, octanol)

(iv) Other solvent (Chloroform)

In the present study, the plots of k_{obs}/[PIP] versus [PIP] are also found to be linear in all the studied solvents except octanol (figure 1B-12-B). Thus, except octanol, the above mechanism and the assumptions are supposed to be valid in all the solvents taken. The linear plots of k_{obs}/[PIP] versus [PIP] gives the values of Kk_2 (rate constant for un catalysed route) and Kk_3 (rate constant for catalysed route) from the intercept and slope, respectively. The calculated values of Kk_2 and Kk_3 for different solvents are represented in Table 1.
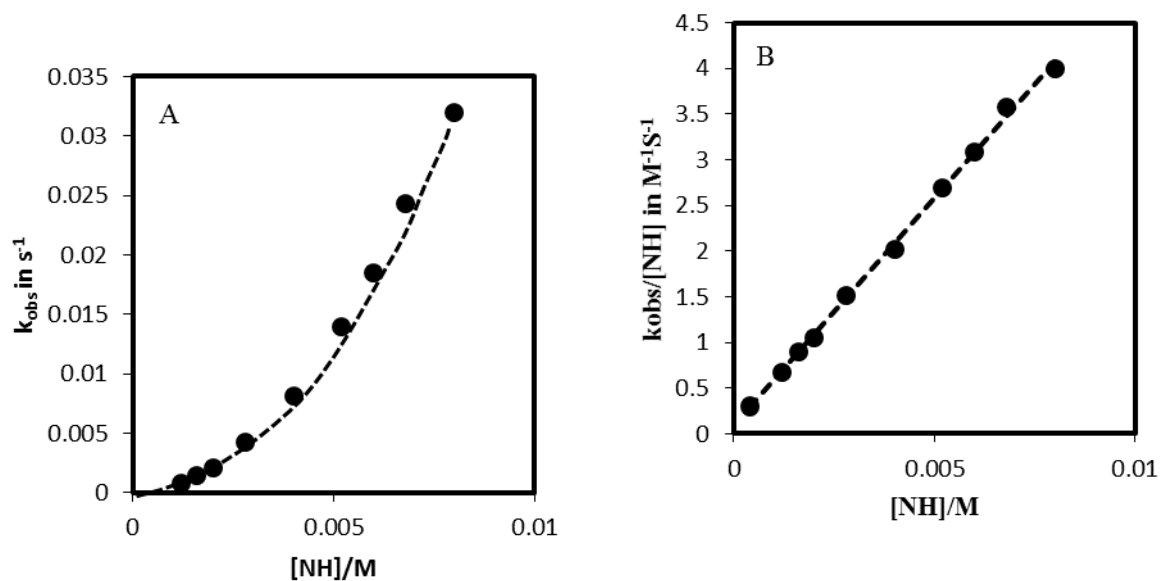
Figure 1. Plots of k_{obs} vs [NH] (A) and k_{obs}/[NH] vs [NH] (B) for the reaction of β-nitro styrene with pyridine in Acetonitrile at 25˚C.
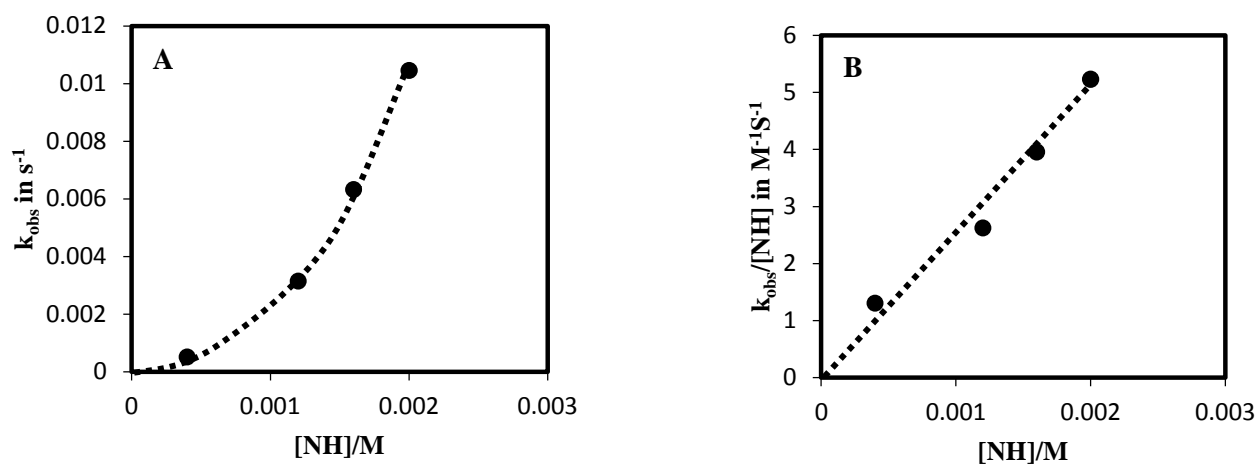
Figure 2. Plots of k_{obs} vs [NH] (A) and k_{obs}/[NH] vs [NH] (B) for the reaction of β-nitro styrene with pyridine in DMSO at 25˚C.
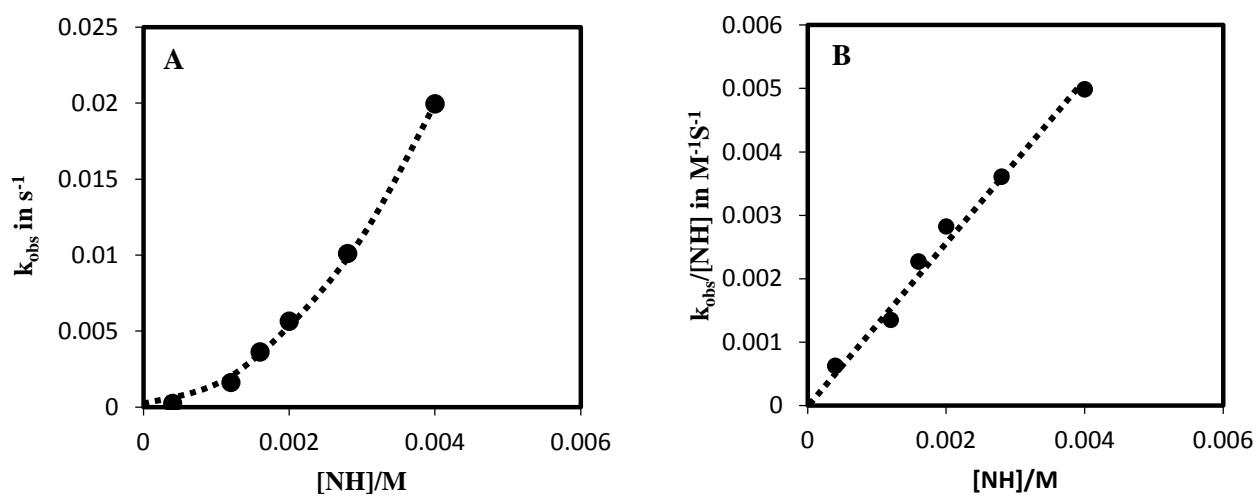

Figure 3. Plots of k_{obs} vs [NH] (A) and k_{obs}/[NH] vs [NH] (B) for the reaction of β-nitro styrene with pyridine in DMF at 25˚C.
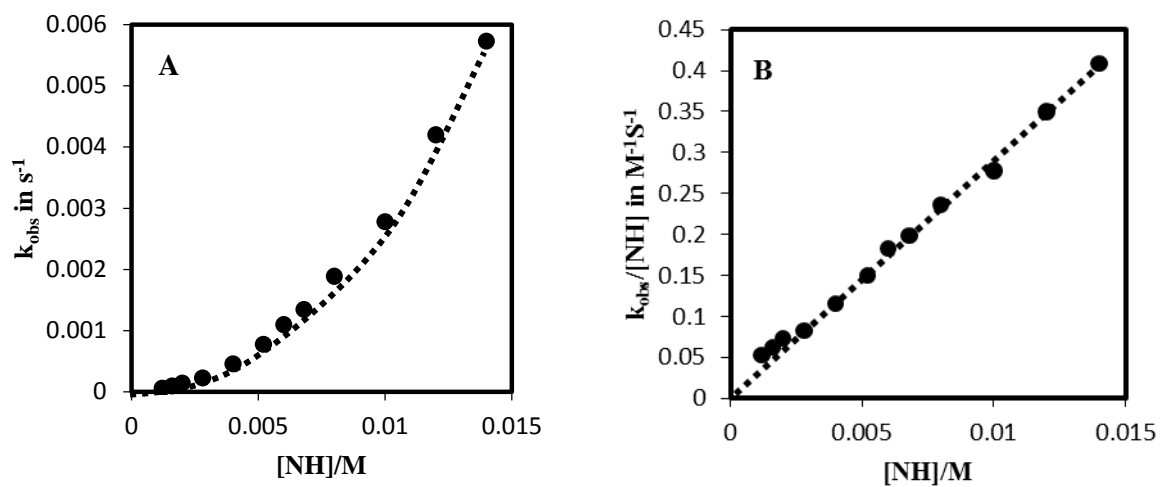
Figure 4. Plots of k_{obs} vs [NH] (A) and k_{obs}/[NH] vs [NH] (B) for the reaction of β-nitro styrene with pyridine in ethyl acetate at 25˚C.
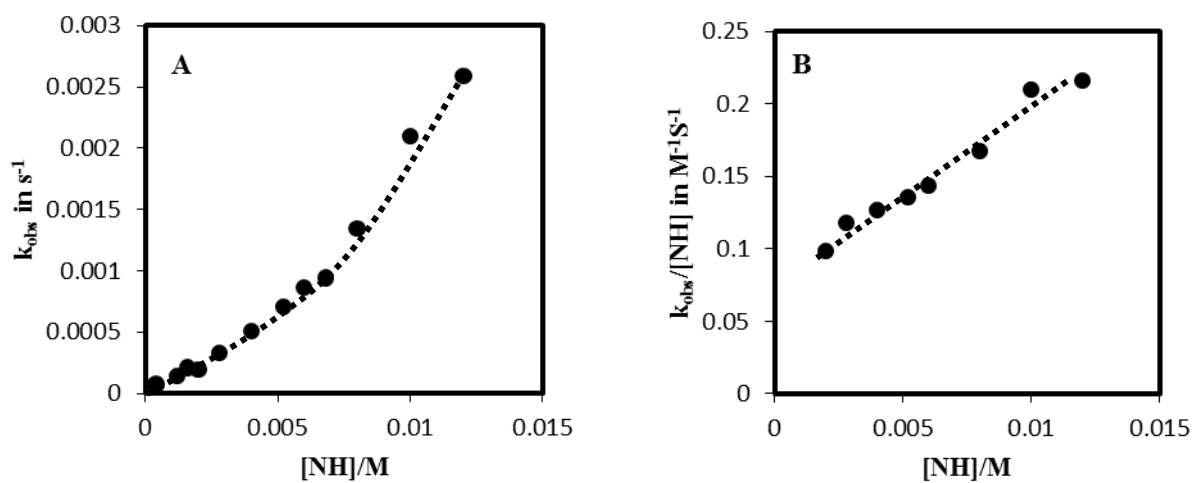

Figure 5. Plots of k_{obs} vs [NH] (A) and k_{obs}/[NH] vs [NH] (B) for the reaction of β-nitro styrene with pyridine in Methanol at 25˚C.
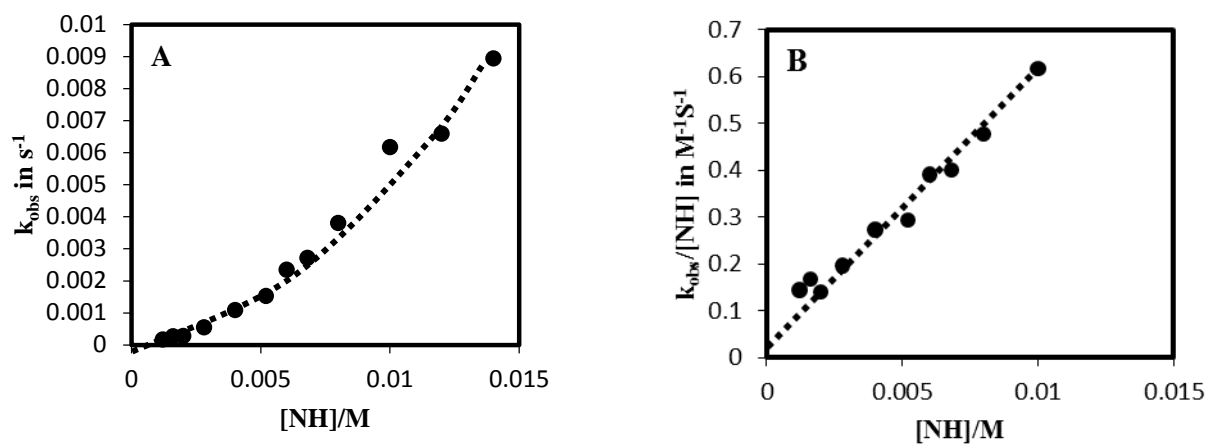
Figure 6. Plots of k_{obs} vs [NH] (A) and k_{obs}/[NH] vs [NH] (B) for the reaction of β-nitro styrene with pyridine in Butanol at 25˚C.

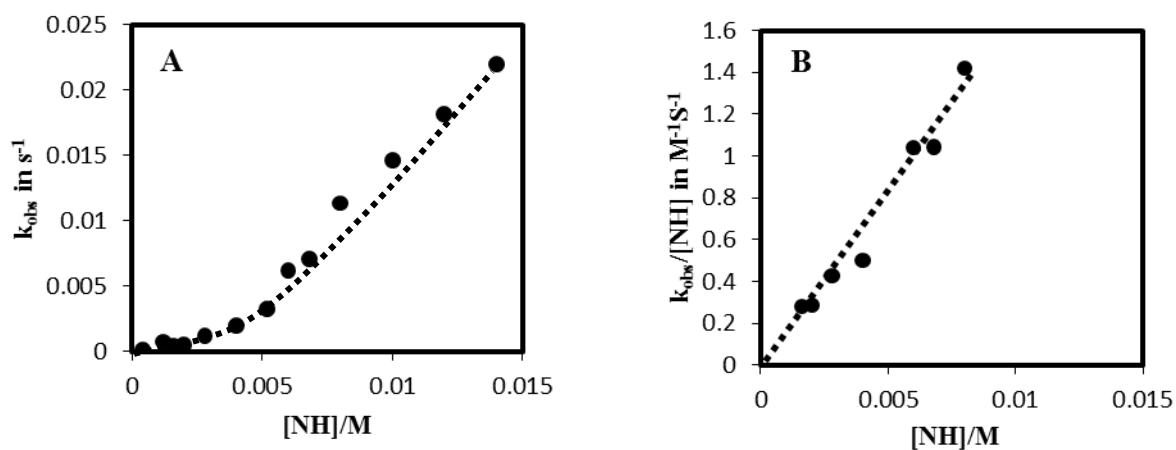**Figure 7**. Plots of k_{obs} vs [NH] (A) and k_{obs}/[NH] vs [NH] (B) for the reaction of β-nitro styrene with pyridine in Hexanol at 25˚C.

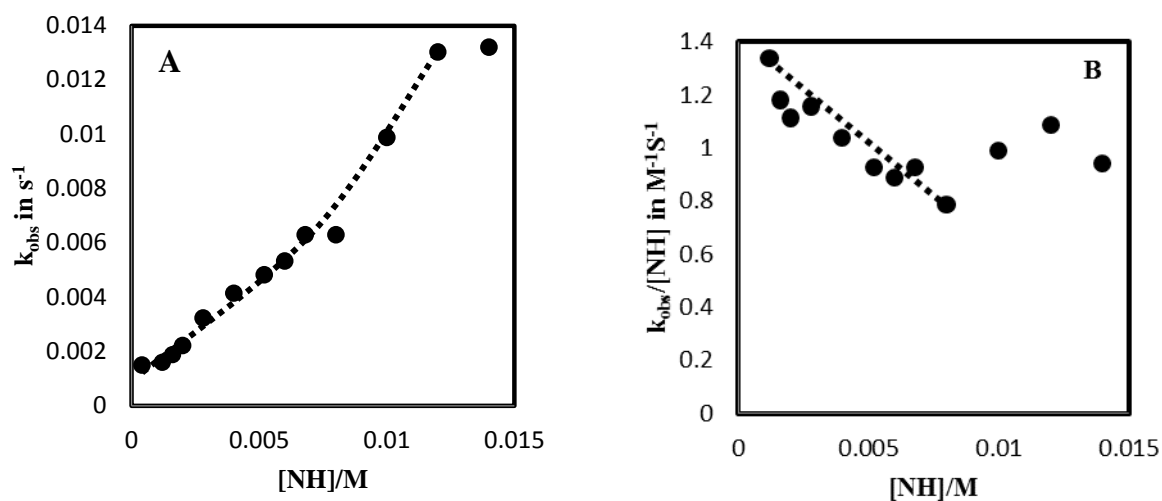**Figure 8.** Plots of k_{obs} vs [NH] (A) and k_{obs}/[NH] vs [NH] (B) for the reaction of β-nitro styrene with pyridine in Octanol at 25˚C.
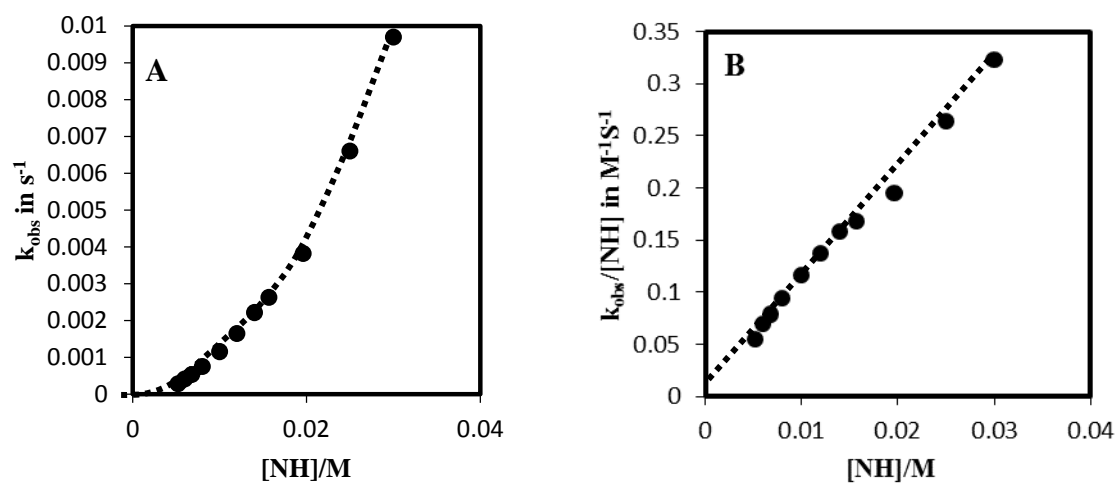
Figure 9. Plots of k_{obs} vs [NH] (A) and k_{obs}/[NH] vs [NH] (B) for the reaction of β-nitro-styrene with pyridine in Chloroform at 25˚C.

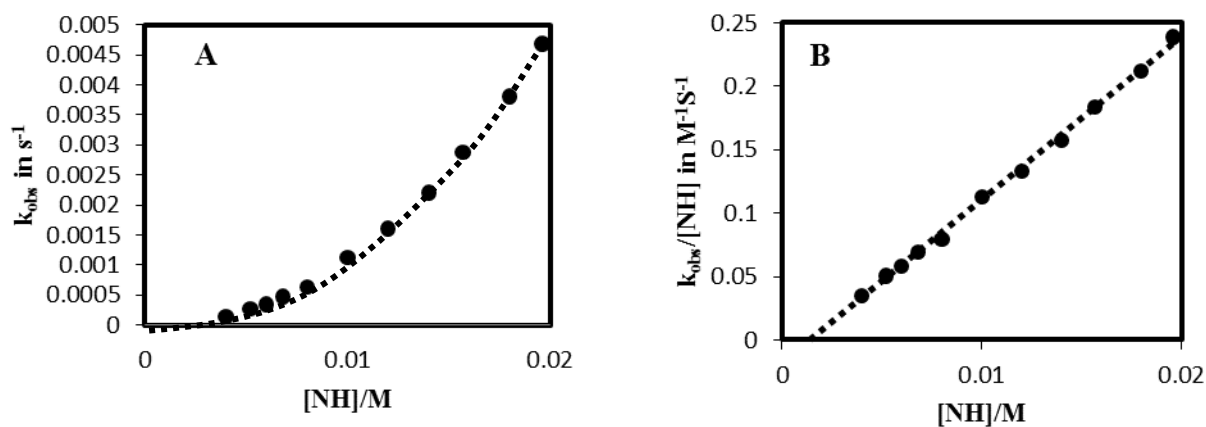**Figure 10**. Plots of k_{obs} vs [NH] (A) and k_{obs}/[NH] vs [NH] (B) for the reaction of β-nitrostyrene with pyridine in Toluene at 25˚C.

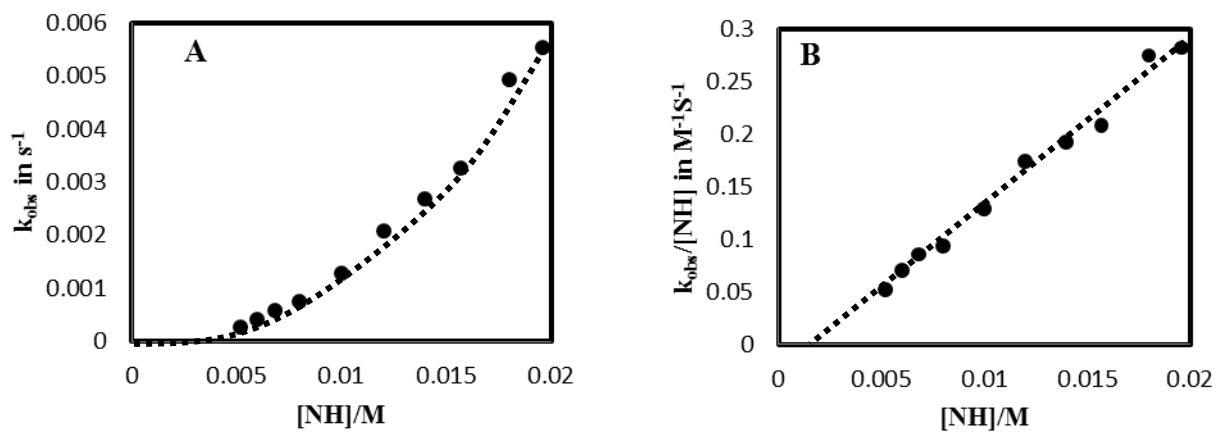**Figure 11**. Plots of k_{obs} vs [NH] (A) and k_{obs}/[NH] vs [NH] (B) for the reaction of β-nitrostyrene with pyridine in Benzene at 25˚C.
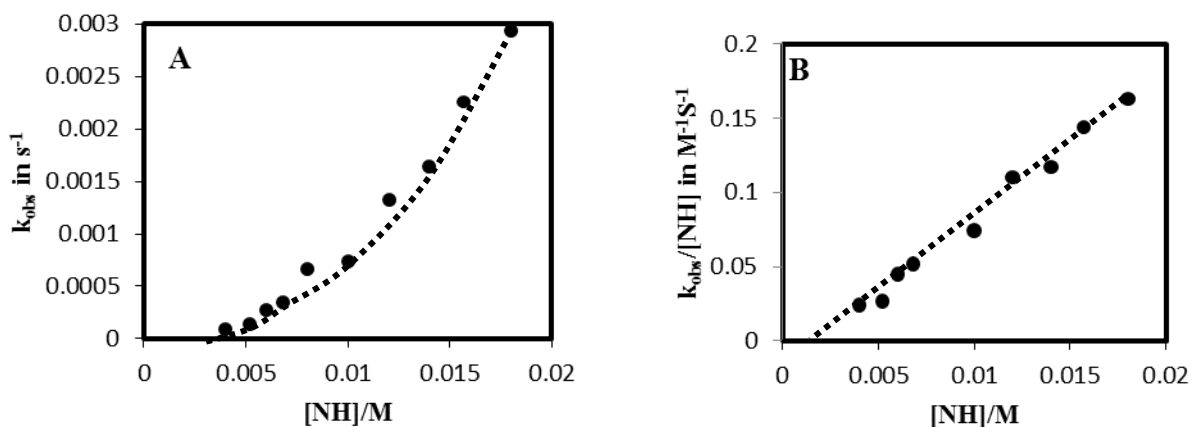
Figure 12. Plots of kobs vs [NH] (A) and kobs/[NH] vs [NH] (B) for the reaction of β-nitrostyrene with pyridine in Hexane at 25˚C.

Table 1. Summary of Kinetic Data for the Reaction of β-nitrostyrene with Piperidine in different Solvents at 25˚C.

Solvent Type	Solvent Name	$Kk_3/M^{-1}s^{-1}$	$Kk_2/M^{-1}s^{-1}$
Non-Polar	Hexane	10	-0.0098
	Toluene	12.89	-0.0189
	Benzene	16	-0.029
Polar Aprotic	DMSO	2434.7	0.1145
	DMF	1234	0.142
	Acetonitrile	498.38	0.0865
	Ethyl acetate	27.83	0.012
Polar protic	Methanol	11.16	0.08
	Butanol	53.3	0.056
	Hexanol	189.67	0.099
Other	Chloroform	10.29	0.0085

4. Conclusions

From all the above results and the values of Kk_2 and Kk_3 discussions the following conclusions can be drawn.

1. The curved plot of k_{obs} vs. [NH] in all the solvents suggests that a second molecule of piperidine acts as catalyst for the reaction.

2. The reactions proceed through both catalysed and unanalysed routes for polar aprotic and aprotic solvents whereas in nonpolar solvents only catalysed route is present.

3. The rate of reaction is higher in polar aprotic solvents as compared to polar protic solvents as compared to other solvents.

4. A stepwise mechanism is proposed for polar protic and aprotic solvents whereas in nonpolar solvents it proposed to proceed through concerted process.

5. The difference in mechanism and reactivity is based on the differential solvation of nucleophile and the zwitterionic intermediates due to difference in polarity, hydrophobicity, hydrogen bond donor and acceptor capabilities of the solvents.

5. References

1. Smith, M. B.; March, J. *March's Advanced Organic Chemistry, 5th ed.; Wiley-Interscience: New York,* **2001**; p 976.

2. Lowry, T. H.; Richardson, K. S. *Mechanism and Theory in Organic Chemistry, 3rd ed.; Harper Collins Publishers: New York*, **1987**; p 622.

3. Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry Part B: Reactions and Synthesis, 3rd ed.; Plenum Press: New York*, **1990**; pp 39−46.

4. Mortezaei, S.; Catarineu, N. R.; Canary, J. W. *J.Am.Chem.Soc.***2012**, *134*, 8054−8057.

5. Sharma, A. K.; Sunoj, R. B. *J. Org. Chem.***2012**, *77*, 10516−10524.

6. Liu, Y. Z.; Cheng, R. L.; Xu, P. F. *J. Org. Chem.* **2011**, *76*, 2884−2887.

7. Anderson, J. C.; Stepney, G. J.; Mills, M. R.; Horsfall, L. R.; Blake, A. J.; Lewis, W. *J. Org. Chem.***2011**, *76*, 1961−1971.

8. Trost, B. M.; Hirano, K. *Angew. Chem., Int. Ed.***2012**, *51*, 6480−6483.

9. Tuchman-Shukron, L.; Miller, S. J.; Portnoy, M. *Chem.Eur. J.***2012**, *18*, 2290−2296.

10. Nugent, T. C.; Bibi, A.; Sadiq, A.; Shoaib, M.; Umar, M. N.; Tehrani, F. N. *Org.Biomol. Chem.***2012**, *10*, 9287−9294.

11. Zhou, J.; Chang, Q.; Gan, L. H.; Peng, Y. G. *Org.Biomol.Chem.***2012**, *10*, 6732−6739.

12. Puglisi, A.; Benaglia, M.; Raimondi, L.; Lay, L.; Poletti, L. *Org. Biomol. Chem.***2011**, *9*,3295−3302.

13. Bernasconi, C. F. *Acc. Chem. Res.***2011**, *44*, 1253−1254.

14. Bernasconi, C. F. *Adv. Phys. Org. Chem*. **2010**, *44*, 223−324.

15. Bernasconi, C. F.; Rappoport, Z. *Acc. Chem. Res.***2009**, *42*, 993−1003.

16. Bernasconi, C. F. *Pure Appl. Chem.***2009**, *81*, 649−665.

17. Gu, K.; Yang, G.; Zhang, W.; Liu, X.; Yu, Z.; Han, X.; Bao, X. *J. Organ. Chem.*, **2006**, *691*, 1984-1992

18. Um, I. H.; Hwang, S. J. *Bull. Korean Chem. Soc.***2008**, *29*, 767-771.

19. Um, I. H.; Yuk, S.M; Yoon, S.I. *Bull. Korean Chem. Soc.***2000**, *21*, 553.

20. Wang, C.; Qi, C. *Tetrahedron,***2013**, *69*, 5348-5354

21. Gurjar, A.; Poonia, P.; Sinha, P.; Bansal, R.K. *Tetrahedron Letters.***2014**, *55*, 2504–2507.

22. Varghese, B.; Kothari, S.; Banerji, K. K. J. *Chem. Res., Synop.***1998**, 422−423.

23. Jalani, N.; Kothari, S.; Banerji, K. K. *Can. J. Chem.***1996**, *74*, 625−629.

24. Popov, A. F.; Perepichka, I. F.; Kostenko, L. I. *J. Chem. Soc., Perkin Trans. 2* **1989**, 395−400.

25. Oh, H. K.; Yang, J. H.; Sung, D. D.; Lee, I. *J. Chem. Soc., Perkin Trans. 2* **2000**, 101−105.

26. Oh, H. K.; Kim, I. K.; Lee, H. W.; Lee, I. *J. Org. Chem.***2004**, *69*, 3806−3810.

27. Oh, H. K.; Yang, J. H.; Lee, H. W.; Lee, I. *J. Org. Chem.***2000**, *65*, 5391−5395.

28. Oh, H. K.; Yang, J. H.; Lee, H. W.; Lee, I. *J. Org. Chem.***2000**, *65*, 2188−2191.

29. Kim, S. I.; Baek, H. W.; Um, I. H.*Bull. Korean Chem. Soc.***2009**, *30*, 2909.

30. Horvath, A. *Tetrahedron Letters.***1996**, *37*, 4423-4426.

31. Bernasconi, C. F.; Paschalis, P. *J. Am. Chem. Soc.***1989**, *111*, 5893−5902.

32. Bernasconi, C. F.; Renfrow, R. A.; Tia, P. R. *J. Am. Chem. Soc.***1986**, *108*, 4541−4549.

33. Bernasconi, C. F.; Schuck, D. F. *J. Org. Chem.***1992**, *57*, 2365−2373.

34. Bernasconi, C. F.; Zitomer, J. L.; Schuck, D. F. *J. Org. Chem.***1992**, *57*, 1132−1139.

35. Riddick, J. A.; Bunger, W. B. Organic SolVents; *Techniques of Chemistry, Vol. II, Wiley-Interscience: New York*, **1970**.

36. Worrall, D.E.*Org. Synth*. **1929**, 9, 66.

37. Um, I.H.; Kang, J.S.; Park, Y.M. *J.Org.Chem.***2013**, *78*, 5604-5610.