

Abstract:

Pseudo-first-order rate constants (k_{obs}) for the reactions between pyrrolidine and *N*-(2-methoxyphenyl)phthalimide (**2**) as well as *N*-(4-nitrophenyl)phthalimide (**3**) in the absence and presence of DABCO in CH_3CN and THF, showed upward curvature with the increase in $[pyrrolidine]_T$. These observations indicate that pyrrolidine is acting as a nucleophile as well as a general base catalyst in the cleavage of these imides. The k_{obs} values for the pyrrolidinolysis of **2**, in the presence of CH_3CN , are larger than that in THF under comparable reaction conditions. Similar observations were obtained for **3** with pyrrolidine. The values of k_{obs} decreased slightly with the addition of DABCO into the reaction mixture for both **2** and **3** in CH_3CN . Spectrophotometric product characterization coupled with HPLC studies showed the formation of *N,N*-disubstituted diamide as the final product from the pyrrolidinolysis of imides.

Objectives:

- ✓ Develop the analytical method(s) for the determination of rate law for amine-catalyzed reactions with imides in non-aqueous solvents.
- ✓ Investigate the kinetics and mechanism of amine-catalyzed reactions with imides in non-aqueous solvents.
- ✓ Determine the types of molecular interactions and possible catalysis occurring in the aminolysis of imides in non-aqueous solvents.

Results:

Pseudo-first-order rate constants, k_{obs} , obtained within a range of $[Am]_T$ for **2** and **3** were fitted into Eqns (3) and (4), where $[Am]_T$ represents total pyrrolidine concentration, k_n and k_b represent respective second-order rate constant and third-order rate constant for amine assisted cleavage of imide.

$$k_{obs} = k_n [Am]_T + k_b [Am]_T^2 \quad (3)$$

$$k_{obs} / [Am]_T = k_n + k_b [Am]_T \quad (4)$$

Table 1. Values of Rate Constants, k_n and k_b , Calculated from Equation 3 for the Cleavage of *N*-Substituted Phthalimides in Non-Aqueous Solvents.^a

Substrate	[Pyrro] _T range M	[DABCO] M	10 ⁴ k _n M ⁻¹ s ⁻¹	10 ⁴ k _b M ⁻² s ⁻¹	Non-Aqueous Solvent
2 ^b	0.20 - 1.00	-	4.30 ± 0.82 ^c	3.74 ± 1.03 ^c	CH ₃ CN
	0.10 - 1.00	0.10	4.97 ± 0.44	1.54 ± 0.55	CH ₃ CN
	0.20 - 1.00	-	4.46 ± 0.41	1.43 ± 0.51	THF
3 ^d	0.05 - 0.75	-	59.3 ± 17.0	517 ± 27	CH ₃ CN
		^e 90.4 ± 10.3	^e 463 ± 22		
	0.20 - 1.00	0.10	30.0 ± 18.3	578 ± 22	CH ₃ CN
		^e 17.7 ± 11.7	^e 562 ± 18		
			^f 0	^f 526 ± 32	
0.05 - 0.70	-	152 ± 7	106 ± 13	THF	
		^e 170 ± 7	^e 70.0 ± 17.3		

^a T = 35°C. ^b $[2]_T = 1.0 \times 10^{-4}$ M and $\lambda = 290$ nm. ^c Error limits are standard deviations.

^d $[3]_T = 2.5 \times 10^{-5}$ M and $\lambda = 320$ nm. ^e Values of k_n and k_b are obtained from Eq. (4). ^f Calculated value of k_b from Eq. (4) when $k_n = 0$.

Discussion:

2 + pyrrolidine	3 + Pyrrolidine
% k_n contribution at $[Am]_T$ 0.50M: CH ₃ CN = 70% CH ₃ CN + DABCO = 89% THF = 92%	% k_n contribution at $[Am]_T$ 0.50M: CH ₃ CN = 19% CH ₃ CN + DABCO = 0% THF = 75%
<ul style="list-style-type: none"> • Pyrrolidine acts as mainly a nucleophile in the reaction → shown in > 70% k_n term in reaction rates. • Methoxy group creates steric hindrance to the reactive site of 2. • Electron-donating property of 2-OCH₃ by resonance → destabilizes the partial negative charges developed in the TS 	<ul style="list-style-type: none"> • Pyrrolidine acts as a nucleophile to carbonyl carbon of 3 as well as a general base catalyzing the reaction. • Electron-withdrawing property of 4-NO₂ by inductive and resonance effects destabilized the TS, helped to facilitate the proton transfer at TS to form product. → Increasing the k_n to > 13 - fold as compared to 2 • Another pyrrolidine acts as general base catalyst, encourage charge transfer to occur as shown in TS1, hence weakening the C-N bond. → Increasing the k_b to > 130 - fold as compared to 2 in CH₃CN. → k_b term reached 100% in the presence of DABCO • pyrrolidine behaves as stronger base in THF compared to CH₃CN → slight increase in nucleophilicity of pyrrolidine nitrogen in THF: observed slight decrease of k_b in THF by nearly 4 - fold.
Inhibition shown by DABCO is only due to the steric hindrance created by DABCO at the reactive sites (C=O) of 2 and 3 .	

Reference: (1) Khan, M. N. Micellar Catalysis. In *Surfactant Science Series*; CRC Press, Taylor & Francis Group: Boca Raton, FL, USA, 2006; vol. 133, Chapter 3 and references cited therein.

Acknowledgement : University of Malaya Research Grant UMRG (Grant No. RG-091/10AFR)

Kinetic Measurements:

The reaction rates were studied spectrophotometrically by monitoring the appearance of cleavage product of **2** at 290nm and the disappearance of **3** at 320nm as a function of time (t). Kinetic parameters, k_{obs} , δ_{app} , A_0 or A_∞ were calculated from Eqns (1) and (2), for appearance of product of **2** and disappearance of **3**, respectively.^[1] In Eqns (1) and (2), A_{obs} = observed absorbance of the reaction mixture at any reaction t, δ_{app} = apparent molar extinction coefficient of the reaction mixture, $[R_0]$ = initial concentration of **2** or **3**, A_0 = A_{obs} at t = 0 and A_∞ = A_{obs} at t = ∞ . The reactions were generally carried out for reaction period of > 7 halfives.

$$A_{obs} = \delta_{app} [R_0] [1 - \exp(-k_{obs} t)] + A_0 \quad (1)$$

$$A_{obs} = \delta_{app} [R_0] \exp(-k_{obs} t) + A_\infty \quad (2)$$

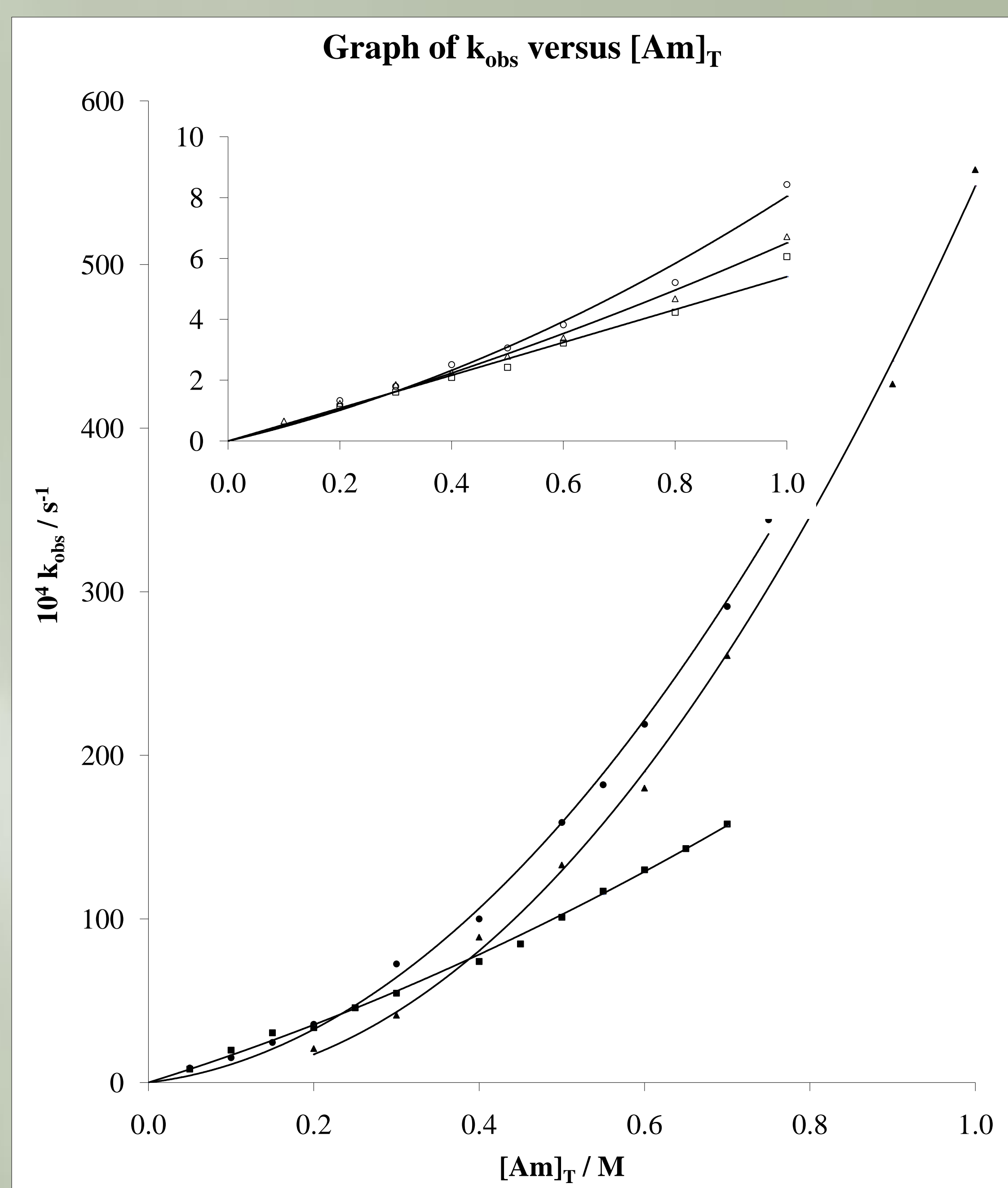
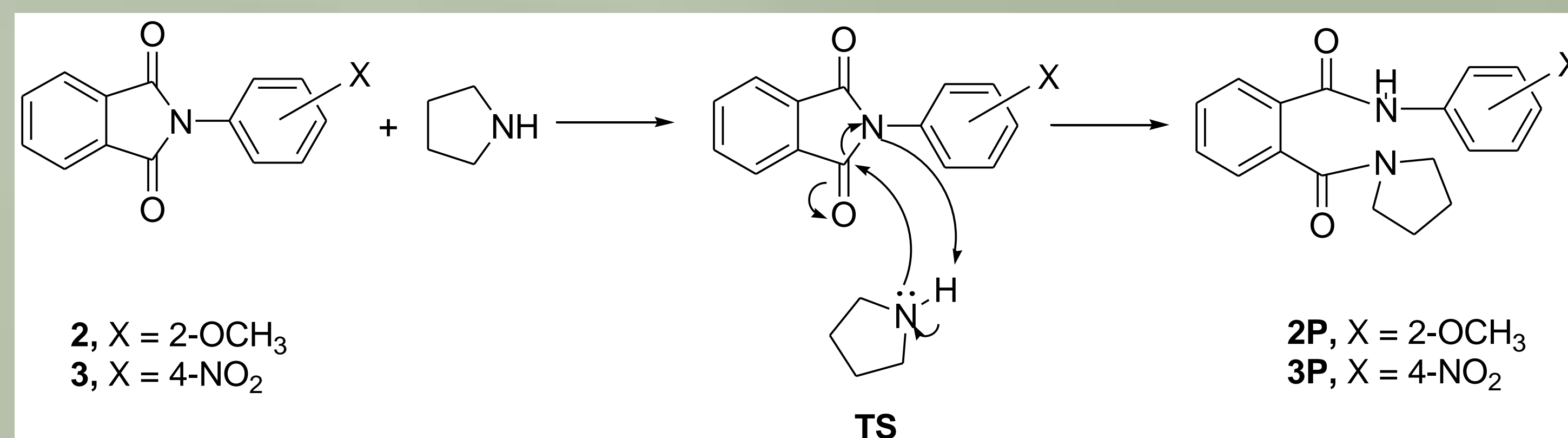


Figure 1. The plots showing the dependence of k_{obs} versus $[Am]_T$ for the cleavage of **2** and **3** where Am represents pyrrolidine, in the presence of MeCN (○), THF (□) and DABCO in MeCN (Δ) for **2** as well as MeCN (●), THF (■) and DABCO in MeCN (▲) for **3**, respectively. The solid lines are drawn through the calculated data points using Eq (3) as described in the text.

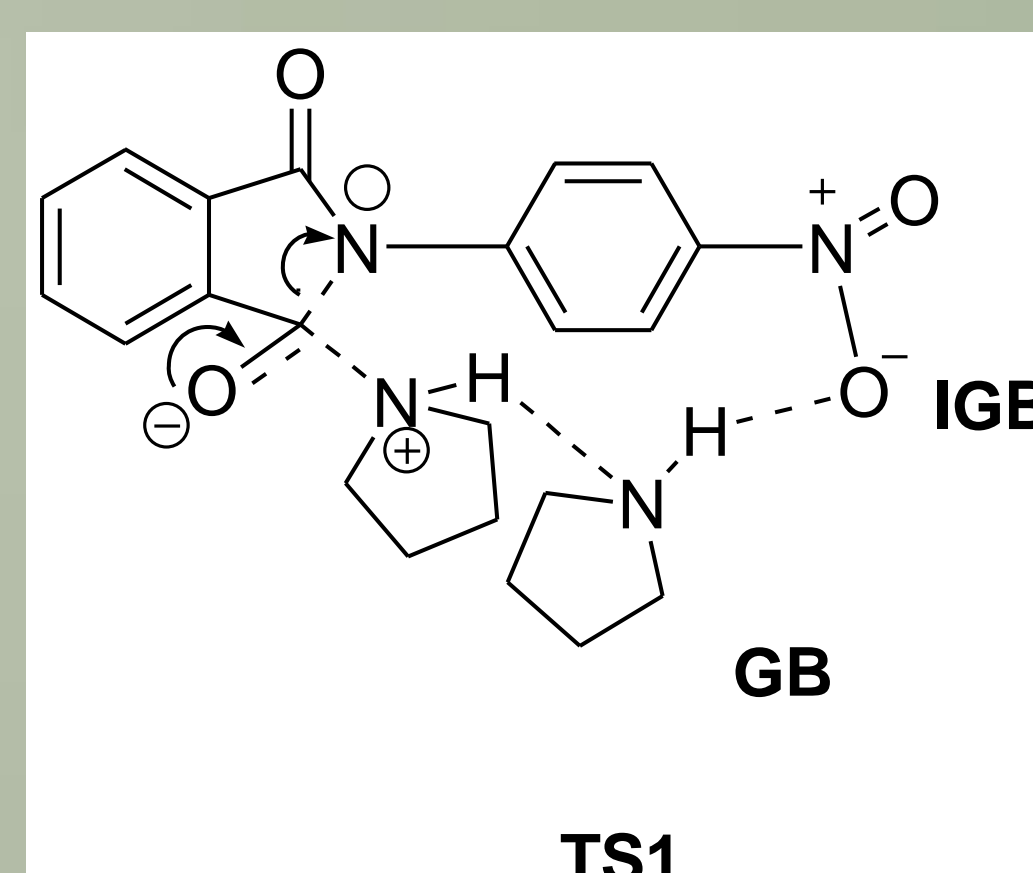


Scheme 1

Concerted mechanism: pyrrolidine acts as a nucleophile attacking the carbonyl carbon of **2** and **3** forming a stable product, *N,N*-disubstituted phthalamide.

❖ facilitated by electron-withdrawing group

❖ a partial negative charge developed at the reaction site in the TS → TS is more polar than reactant state



Conclusion:

- Remarkable 13 - and 130 - fold larger k_n and k_b increasing for pyrrolidinolysis of **3** compared to that of **2**
→ significant polar effect exhibited by 4-NO₂ as well as active participation of 4-NO₂ substituent in the TS in **3**
- 4-NO₂ of **3** is acting as intramolecular general base catalyst and a second pyrrolidine acting as intermolecular general base catalyst in the pyrrolidinolysis of **3**