

# A DFT study of the ring opening mechanism of tetraethyl-2-aryl-1,2-epoxygembisphosphonate

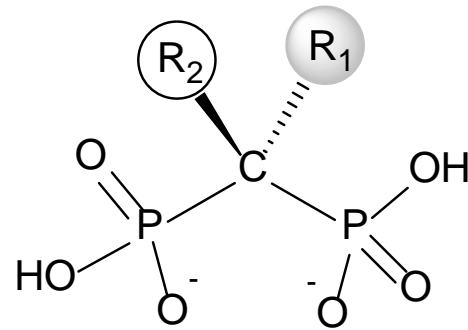
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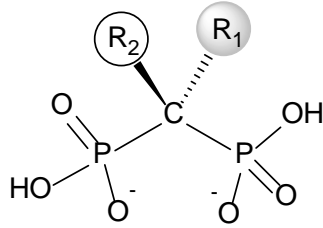
# Introduction

- History of diphosphonates dates as far back to the mid-1800s.
- Today they are commonly referred to as bisphosphonates.



- In the medical field bisphosphonates: class of drugs that are used for:
  - the prevention and treatment of rheumatoid arthritis, osteoporosis and Paget's disease,
  - also used to reduce pain in breast and lung cancer patients.

# Introduction



Bisphosphonate	R <sub>1</sub>	R <sub>2</sub>	
Non-nitrogen containing	Etidronic acid	-OH	
	Clodronic acid	-Cl	
	Tiludronic acid	-H	
Nitrogen containing	Pamidronic acid	-OH	
	Risedronic acid	-OH	
	Zoledronic acid	-OH	

- Classified as either nitrogen containing or non-nitrogen containing bisphosphonates.
- Nitrogen containing bisphosphonates are known to exhibit high potency when compared to non-nitrogen containing bisphosphonates.

Figure 1. Examples of non-nitrogen containing and nitrogen containing bisphosphonates the pharmaceutical industry.

# Introduction

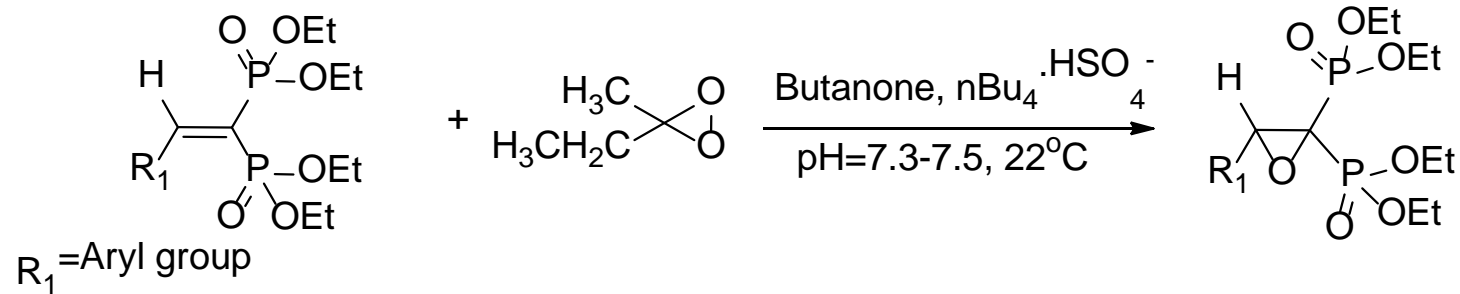
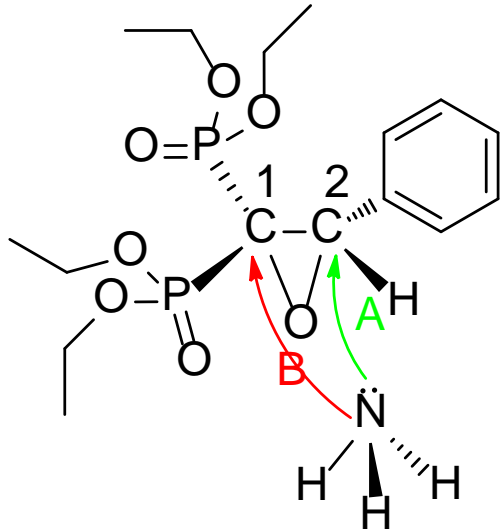


Figure 2. Synthesis of 2-aryl 1,2-epoxyethyl gembisphosphonates.

- Mbianda and co-workers (UJ) reported the synthesis of 2-aryl 1,2-epoxyethyl gembisphosphonates via dioxirane oxidation of vinylgembisphosphonates (Figure 2)
- First report of the epoxidation of substituted vinylgembisphosphonates featuring this class of epoxides.
- Reported new structures are of significant biological interest, since they may serve as important precursors for the synthesis of biologically active amino bisphosphonic acids.

# Introduction

- Theoretically examine the opening of the oxirane ring of tetraethyl-2-aryl-1,2-epoxygembisphosphonate using ammonia as the simplest nucleophile.



Reactant 1 + NH<sub>3</sub>

- Epoxide ring opening is usually associated with regioselectivity making both the  $\alpha$ - and  $\beta$ -carbon vulnerable to attack depending:
  - on the reaction conditions,
  - and the substituent on the oxirane ring.
- Thus the two mechanisms proposed (Figure 3) is based on nucleophilic attack at either C2 or C1.
- This study included the effect of varying the substituent on C2 as well as the effect of various solvents.

# Introduction

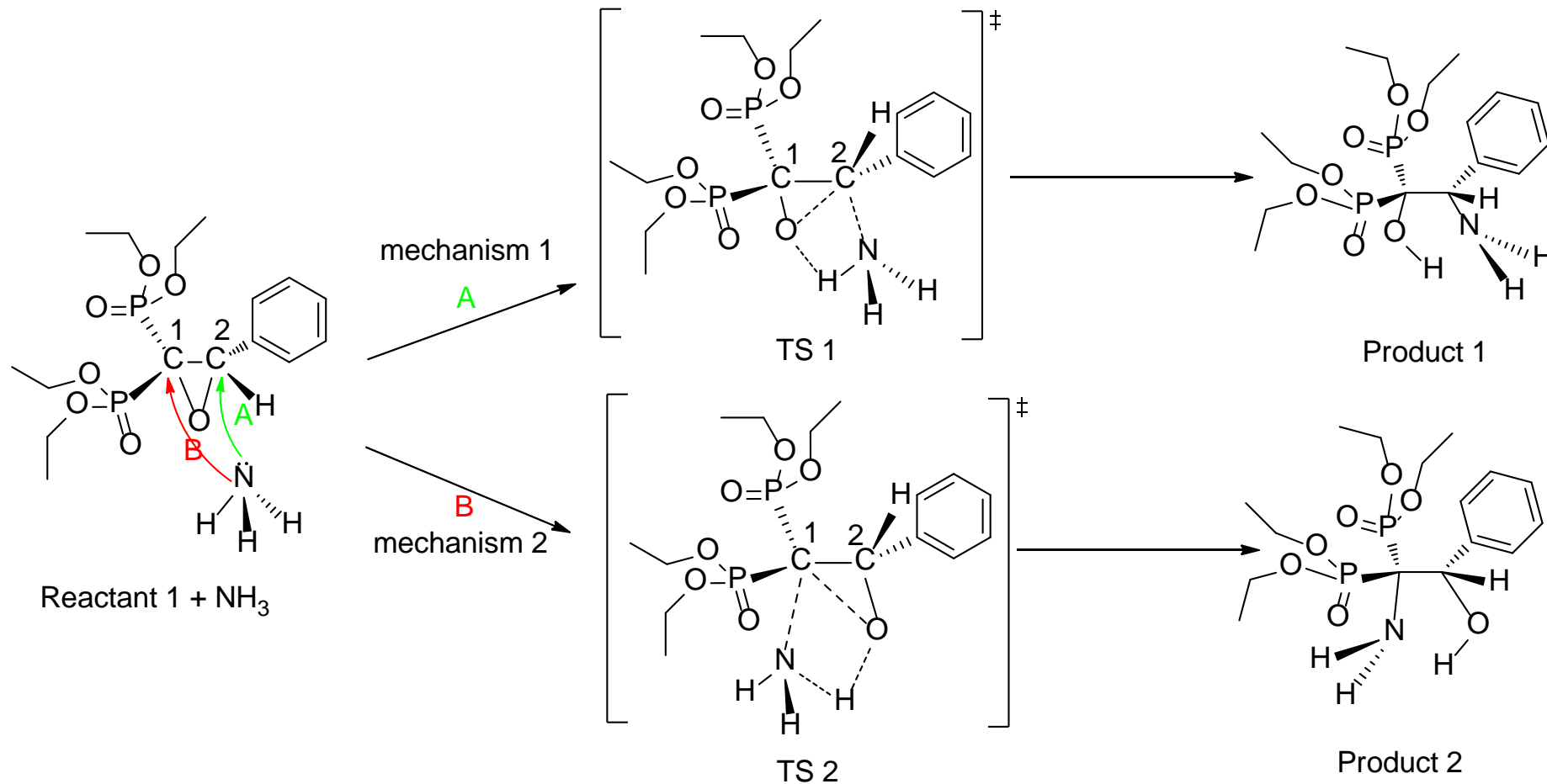
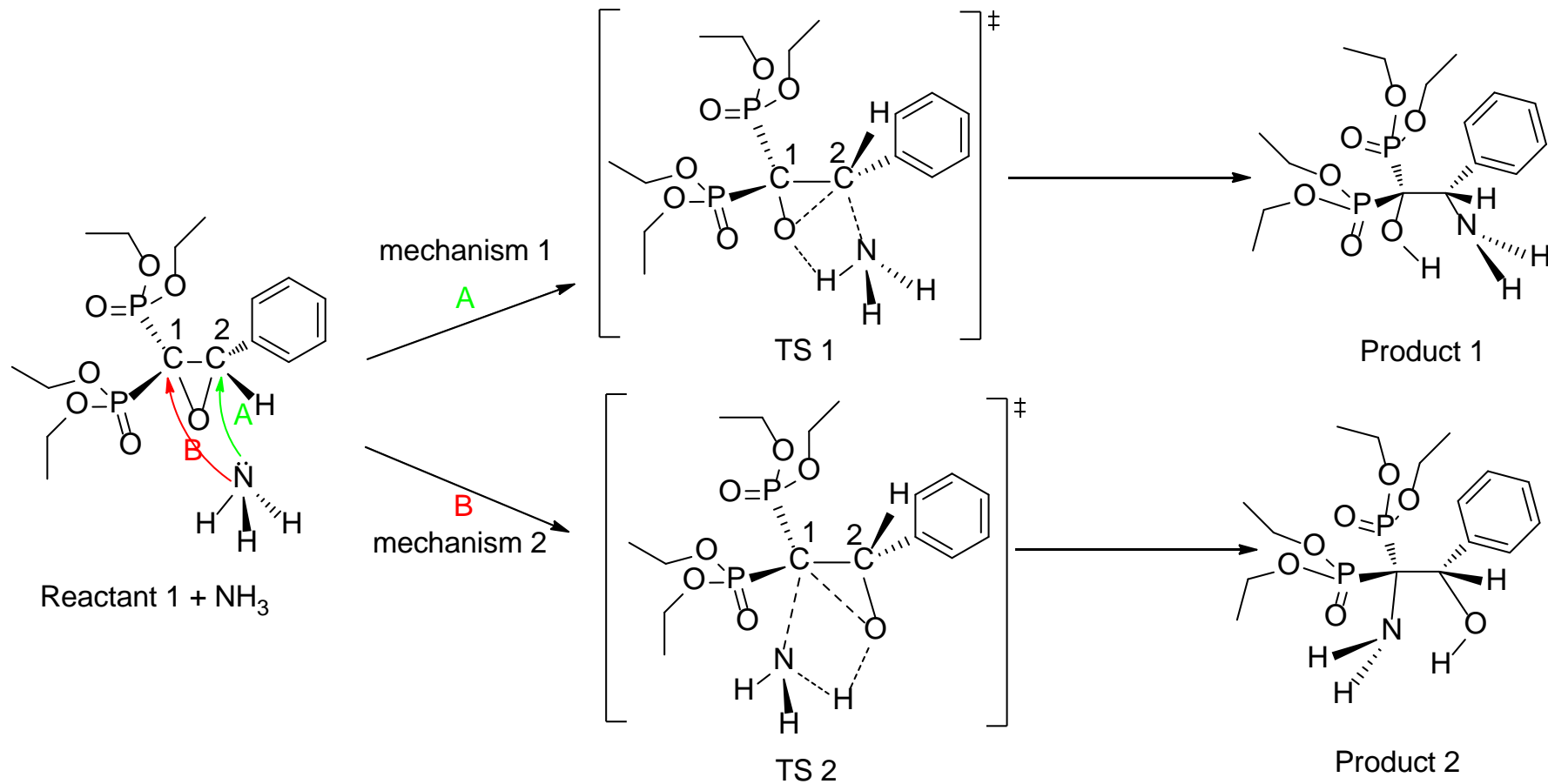


Figure 3. A: Proposed mechanism 1: ring opening at C2; B: Proposed mechanism 2: ring opening at C1.

# Computational Details

- BP86 functional, basis set combination: aug-cc-pVTZ for phosphorus and 6-311+G (d,p) for C, H, N, O
- Frequency calculations: to identify the stationary point as a minimum (zero imaginary frequency) and transition state (one imaginary frequency) and to provide all the thermochemical data
- Intrinsic reaction coordinate (IRC) calculations: to confirm that the TS connects the correct reactant and product on the PES.
- Effects of solvation: four polar solvents: H<sub>2</sub>O, MeOH, THF and toluene (TOL); and two dipolar solvents: dimethyl sulfoxide (DMSO) and dichloromethane (DCM).
- All the calculations were carried out with Gaussian 09 version D01.

# Results and Discussion



- Ammonia attaching at either C2 or C1 resulted in a 4-membered cyclic transition state and then proceeded to the product.



# Results and Discussion

- Frequency calculation: single negative value of  $-272.75 \text{ cm}^{-1}$ , showed
  - the breaking of the C2-O51 epoxide bond which has lengthened to 2.20 Å;
  - atom N53, from ammonia, moving towards C2 and,
  - proton H52, from ammonia, attaching to O3 forming Product 1

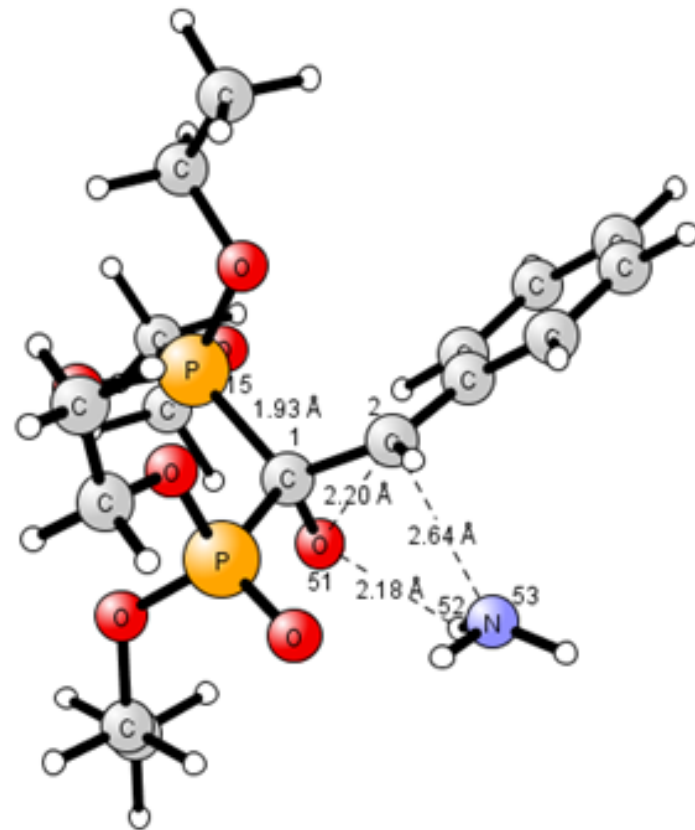


Figure 4. 4-membered TS 1 for mechanism 1

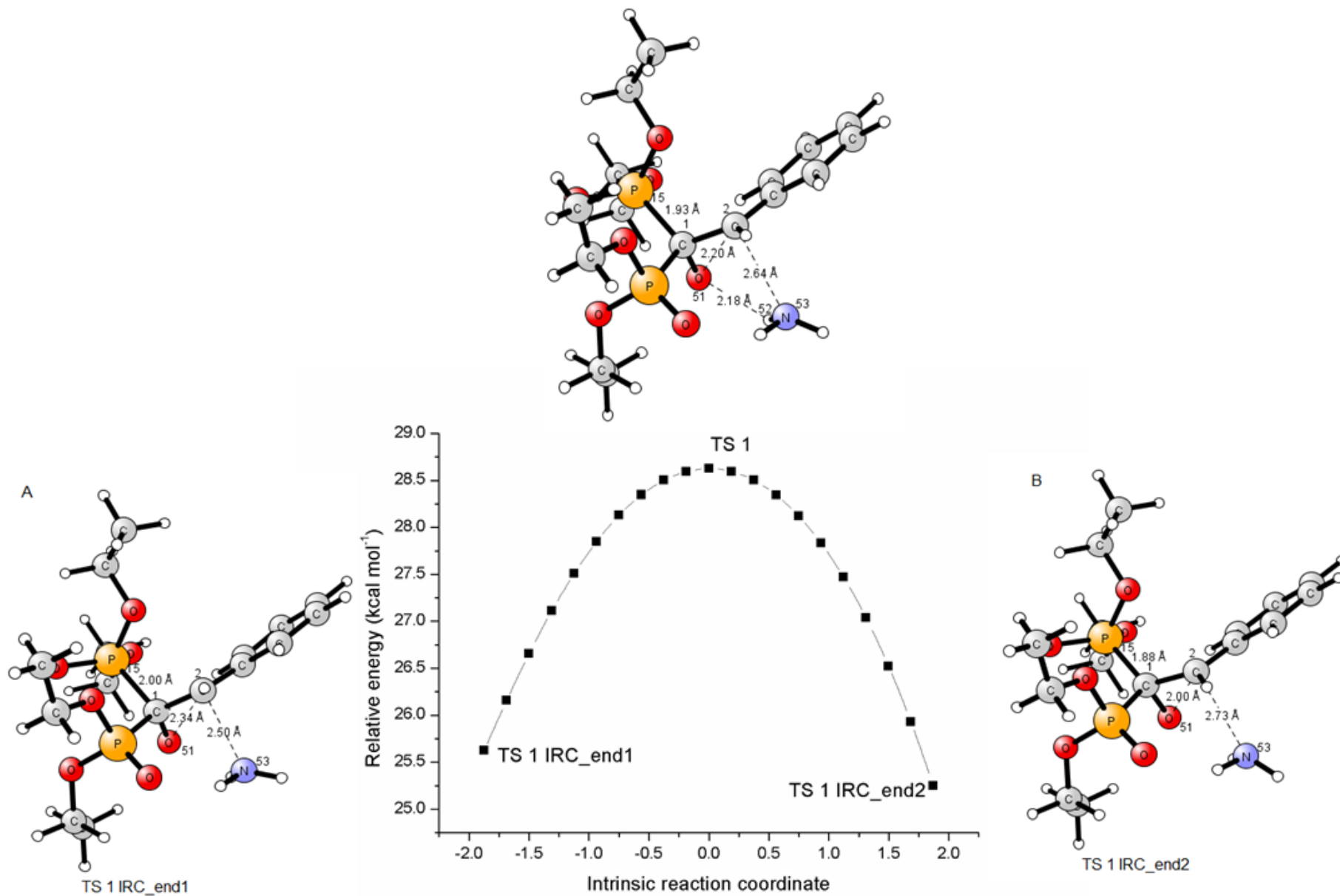


Figure 5: IRC for TS 1

# Results and Discussion

Table 1: Summary of the relative<sup>a</sup> thermochemical data for mechanism 1 and 2 in the gas phase

	$\Delta E$ (kcal mol <sup>-1</sup> )	$\Delta H$ (kcal mol <sup>-1</sup> )	$\Delta G$ (kcal mol <sup>-1</sup> )	$\Delta S$ (cal K mol <sup>-1</sup> )	$E_a$ (kcal mol <sup>-1</sup> )	ln A
Reactant 1+NH <sub>3</sub>	0.00	0.00	0.00	0.00	0.00	0.00
TS 1	27.79	27.40	39.29	-39.86	27.99	9.38
TS 2	38.60	38.37	50.89	-42.00	38.96	8.31
Product 1	-21.79	-19.31	-5.88	-45.04	-18.72	6.78
Product 2	-18.69	-78.32	-2.45	-46.08	-77.73	6.25

<sup>a</sup> Energies are relative to Reactant 1 + NH<sub>3</sub> (the energy of the starting materials).

Table 2: Summary of the relative energies<sup>a</sup> ( $\Delta E$ /kcal mol<sup>-1</sup>) for mechanism 1 and 2 in various solvents

	H <sub>2</sub> O	MeOH	THF	DMSO	TOL	DCM
Reactant 1+NH <sub>3</sub>	0.00	0.00	0.00	0.00	0.00	0.00
TS 1	28.04	28.16	28.58	27.37	29.47	28.49
TS 2	41.42	41.38	41.13	41.40	40.33	41.18
Product 1	-18.60	-18.68	-18.51	-18.63	-19.64	-15.95
Product 2	-15.50	-15.57	-16.05	-15.54	-17.20	2.02

<sup>a</sup> Energies are relative to Reactant 1 + NH<sub>3</sub> (the energy of the starting materials).

At room temperature all molecules have an average thermal energy of 0.6 kcal.mol<sup>-1</sup>. So if the energy barrier, that the starting materials need to overcome before they can react to form the product, is as high as 25 kcal.mol<sup>-1</sup>, then heat must be added to the reaction.

# Results and Discussion

- Change the substituent on C2 to lower the energy

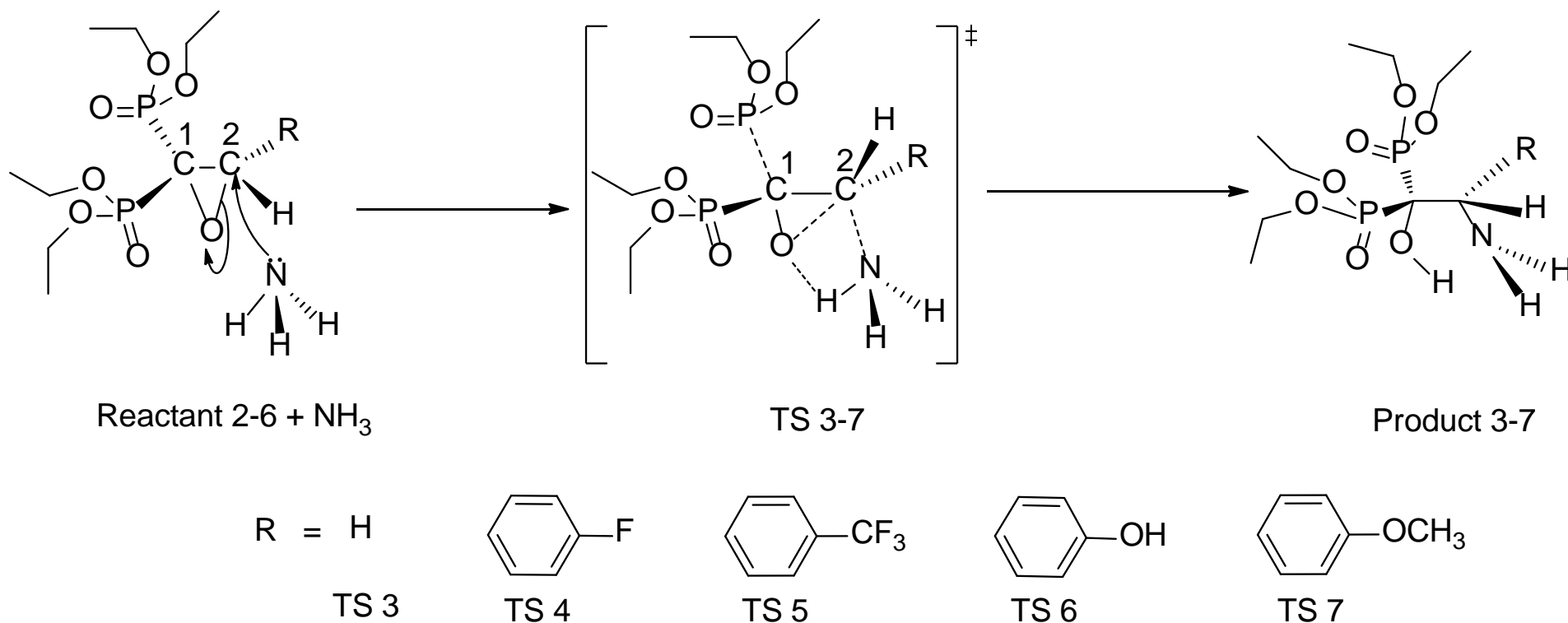
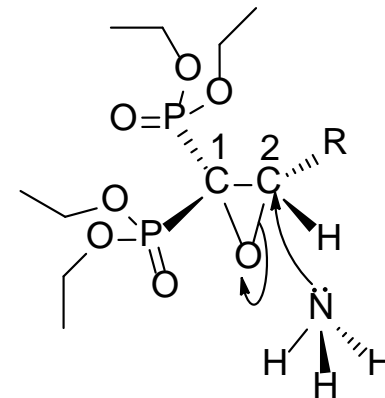
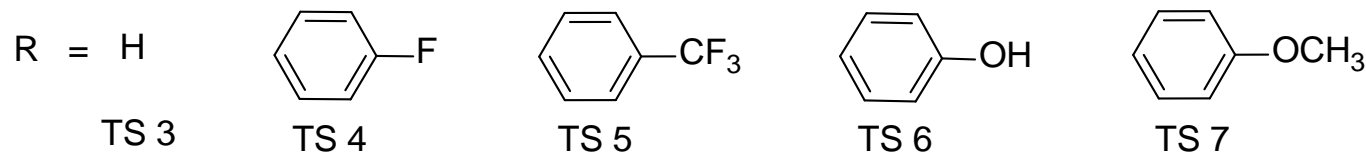


Figure 6. Electron-withdrawing and -donating substituents

# Results and Discussion



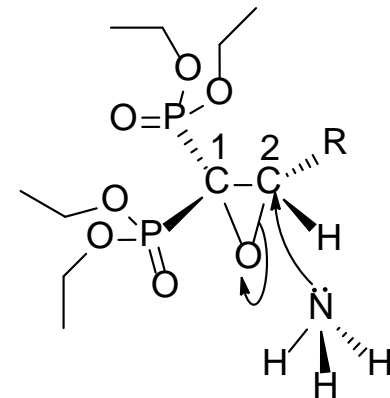
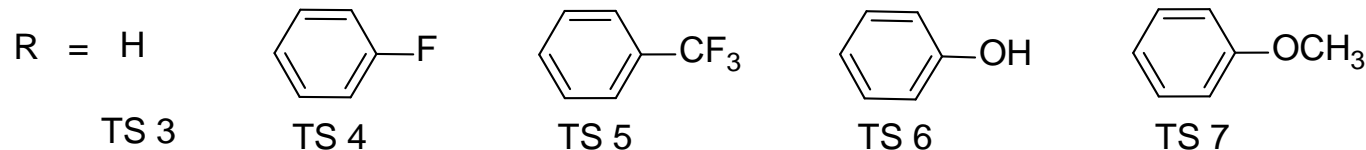
Reactant 2-6 + NH<sub>3</sub>

Table 3: Summary of the relative<sup>a</sup> thermochemical data for electron-withdrawing and -donating groups in the gas phase

	$\Delta E(\text{kcal mol}^{-1})$	$\Delta H(\text{kcal mol}^{-1})$	$\Delta G(\text{kcal mol}^{-1})$	$\Delta S(\text{cal K mol}^{-1})$	$E_a(\text{kcal mol}^{-1})$	$\ln A$
Reactant 2-6+NH <sub>3</sub>	0.00	0.00	0.00	0.00	0.00	0.00
TS 3	34.18	33.91	45.51	-38.90	34.50	9.87
TS 4	27.03	26.63	38.48	-39.73	27.23	9.45
TS 5	29.28	28.93	40.45	-38.66	29.52	9.99
TS 6	24.68	24.30	36.22	-39.98	24.89	9.33
TS 7	24.23	23.85	35.08	-37.67	24.44	10.49
Product 3	-26.87	-24.32	-11.50	-43.02	-23.73	7.80
Product 4	-21.88	-19.49	-6.21	-44.54	-18.90	7.03
Product 5	-21.80	-19.50	-7.51	-40.23	-18.91	9.20
Product 6	-21.87	-19.41	-5.84	-45.51	-18.82	6.54
Product 7	-21.78	-19.41	-6.70	-42.63	-18.21	7.99

<sup>a</sup> Energies are relative to Reactant 2-6 + NH<sub>3</sub> (the energy of the starting materials).

# Results and Discussion



Reactant 2-6 + NH<sub>3</sub>

Table 4: Summary of the relative energies<sup>a</sup> ( $\Delta E/\text{kcal mol}^{-1}$ ) for electron-withdrawing and -donating groups in various solvents

	H <sub>2</sub> O	MeOH	THF	DMSO	TOL	DCM
Reactant 2-6+NH <sub>3</sub>	0.00	0.00	0.00	0.00	0.00	0.00
TS 3	35.96	36.02	36.31	35.98	35.67	35.90
TS 4	27.17	27.24	27.67	27.20	28.70	27.59
TS 5	32.55	32.50	32.18	32.53	31.24	32.25
TS 6	21.80	21.93	22.71	21.87	24.31	22.56
TS 7	20.86	21.03	18.90	20.95	23.48	21.64
Product 3	-24.37	-24.40	-24.70	-24.39	-25.05	-24.64
Product 4	-18.26	-18.32	-18.71	-18.29	-19.79	-18.62
Product 5	-18.25	-18.31	-18.70	-18.28	-19.73	-18.62
Product 6	-18.60	-18.67	-18.52	-18.64	-19.68	-18.42
Product 7	-17.99	-18.06	-18.48	-18.03	-19.61	-18.39

<sup>a</sup> Energies are relative to Reactant 2-6 + NH<sub>3</sub> (the energy of the starting materials).

# Conclusion

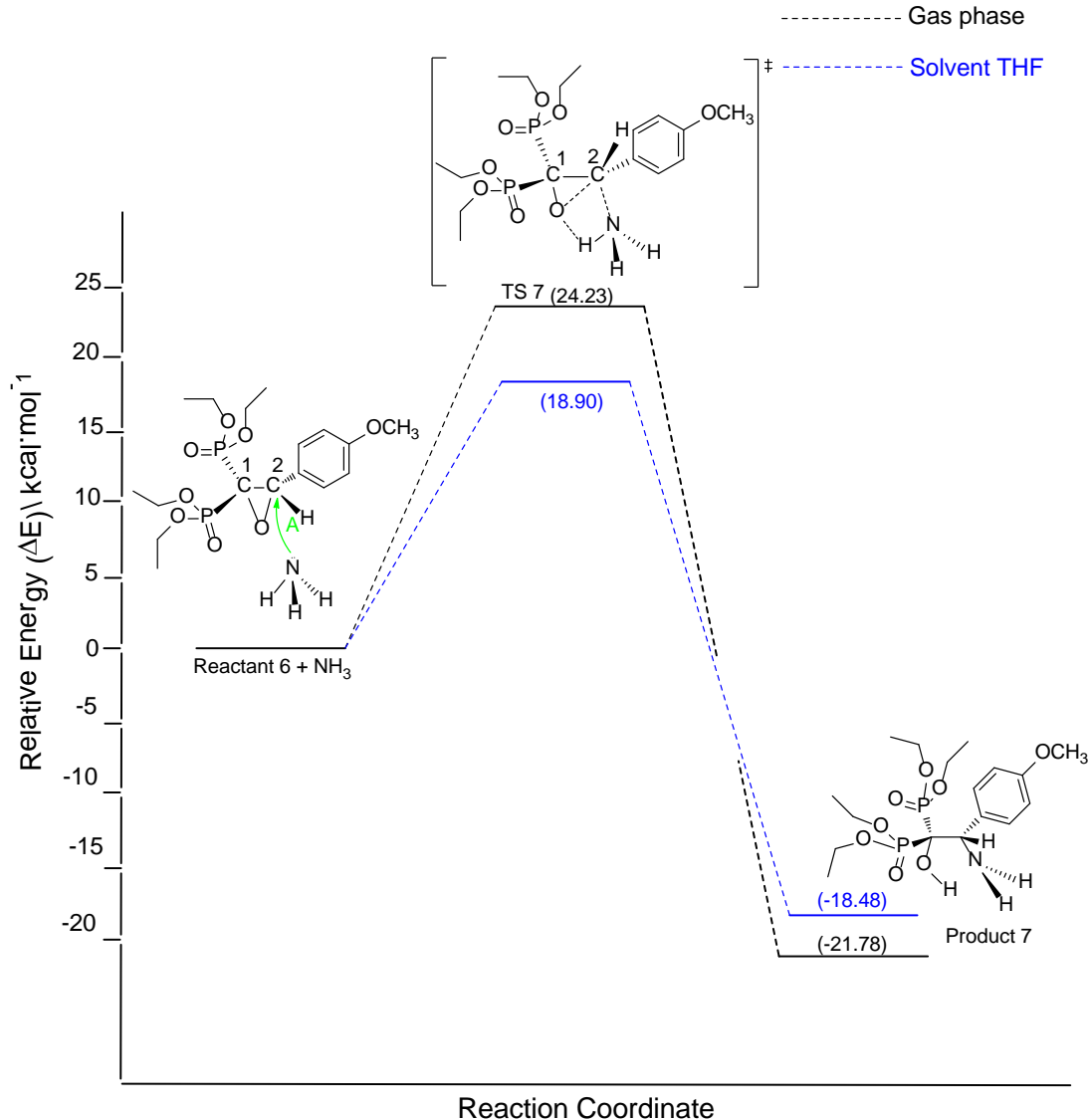


Figure 7. Relative energy reaction profile for TS 7 in gas and solvent

- Ring opening is favoured at the less hindered C2 of the oxirane ring.
- Variation of the substituent on C2 revealed electron-donating methoxybenzene to be the best substituent in this study.
- Further work:
  - attempt using methanol as the nucleophile and,
  - Vary the substituent on C2 using different electron-donating groups.

# Acknowledgments



Ephraim F. Marondedze

