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DFT study on mechanism of α-amino acid N-carboxyanhydride (NCA) polymerization: Initiation route of N-TMS amine

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Introduction

Ring opening polymerization of α-amino acid N-carboxyanhydride is the most promising technique to obtain polypeptides and clarifying the mechanism is essential towards designing backbone and topological structures. Normal amine mechanism (NAM) is proposed for several years for non-ionic initiators and mechanism of primary and secondary amines through proton transfer route is demonstrated by our previous work. However, proton transfer is not the only possible route. According to our calculations, N-TMS amine route proceeds through TMS group transfer rather than proton, further shifts rate determining step to decarboxylation because of enlarged energy barrier between observed intermediate with carboxyl-TMS end group and next TS.

NAM-H VS NAM-TMS

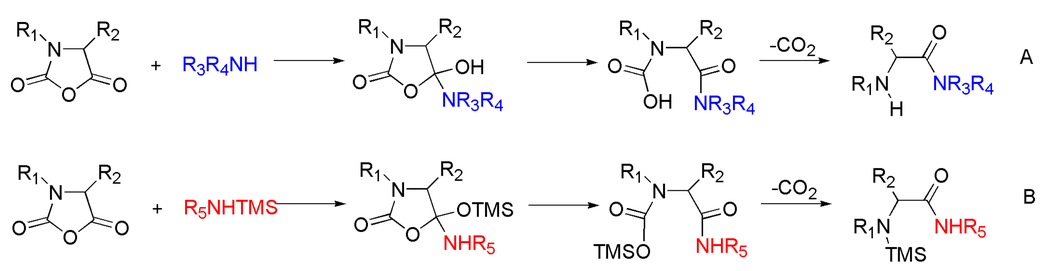


Fig. 1. Normal amine mechanism with transfers of proton atom (NAM-H) (A) and TMS group (NAM-TMS) (B) of ROPs of Ala-NCA (R_1=H, R_2=Me) or Sar-NCA (R_1=Me, R_2=H). Three major elemental steps consists of carbonyl addition, ring-opening, and decarboxylation.

Gibbs energy plots

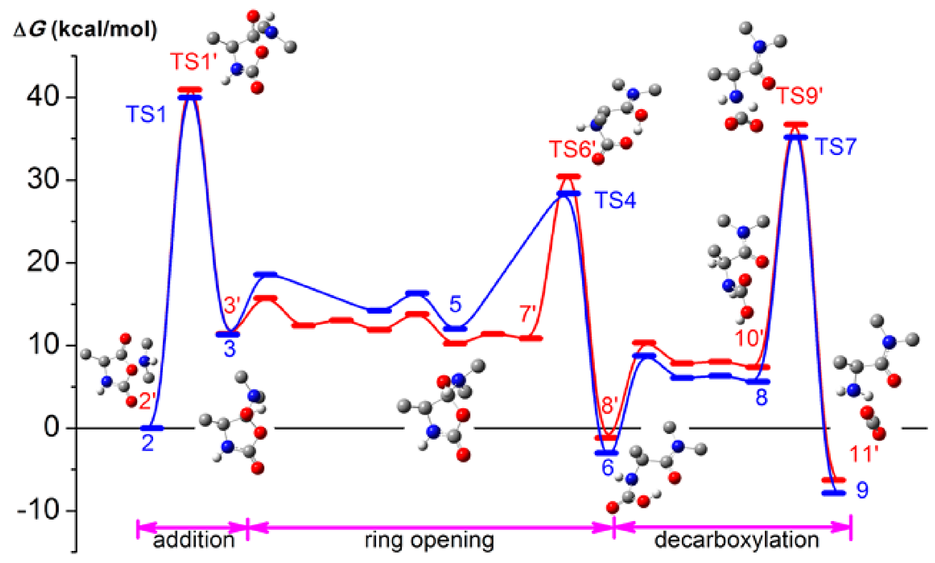


Fig. 2. Calculated Gibbs free energy profiles of the ring opening reaction of L-alanine-NCA initiated by Me_2NH (blue line) and $EtNH_2$ (red line). Some crucial intermediates and TSs of secondary amine pathway are illustrated by 3D models where some hydrogen atoms are neglected for clarity.

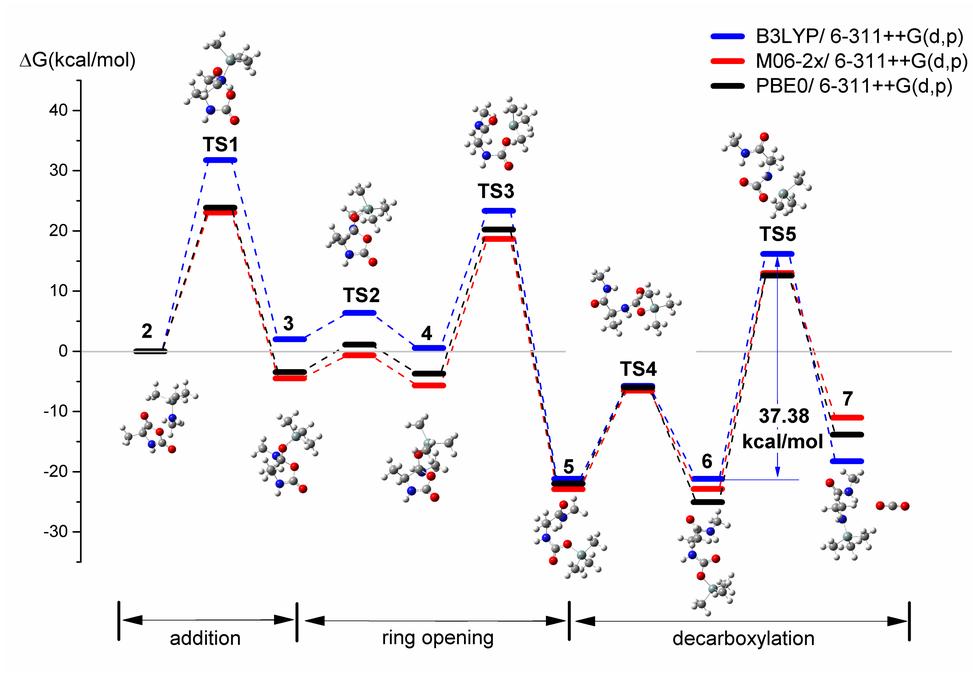
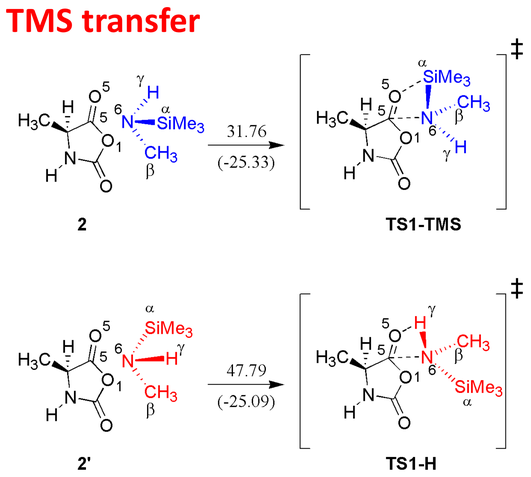


Fig. 3. Calculated Gibbs free energy profiles of ROP of Ala-NCA initiated by MeNHTMS using various methods of B3LYP (blue), M06-2x (red) and PBE0 (black) at the same basis of 6-311++G(d,p). All TSs and intermediates are illustrated in 3-D models.

Proton transfer VS TMS transfer



	C^5 charge	O^5 charge	N^6 charge	H^γ or Si^α charge	$D_{O\text{-}H}$ or $D_{O\text{-}Si}$ (Å)
TS1-TMS in NAM-TMS	0.751	-0.79	-0.777	1.776	2.271
TS1-H in NAM-H	0.769	-0.809	-0.928	0.288	1.317

Fig. 4. DFT calculated carbonyl addition step of L-Alanine-NCA initiated by MeNHTMS through TMS-transfer route (blue) and H-transfer route (red) with ΔG (kcal·mol^{-1}) and ΔS (cal·mol^{-1}·K^{-1}) in parentheses using b3lyp/6-311++G(d,p) method. Selected geometrical parameters and charges of TS1 are shown in the table.

Mechanism details of NAM-TMS

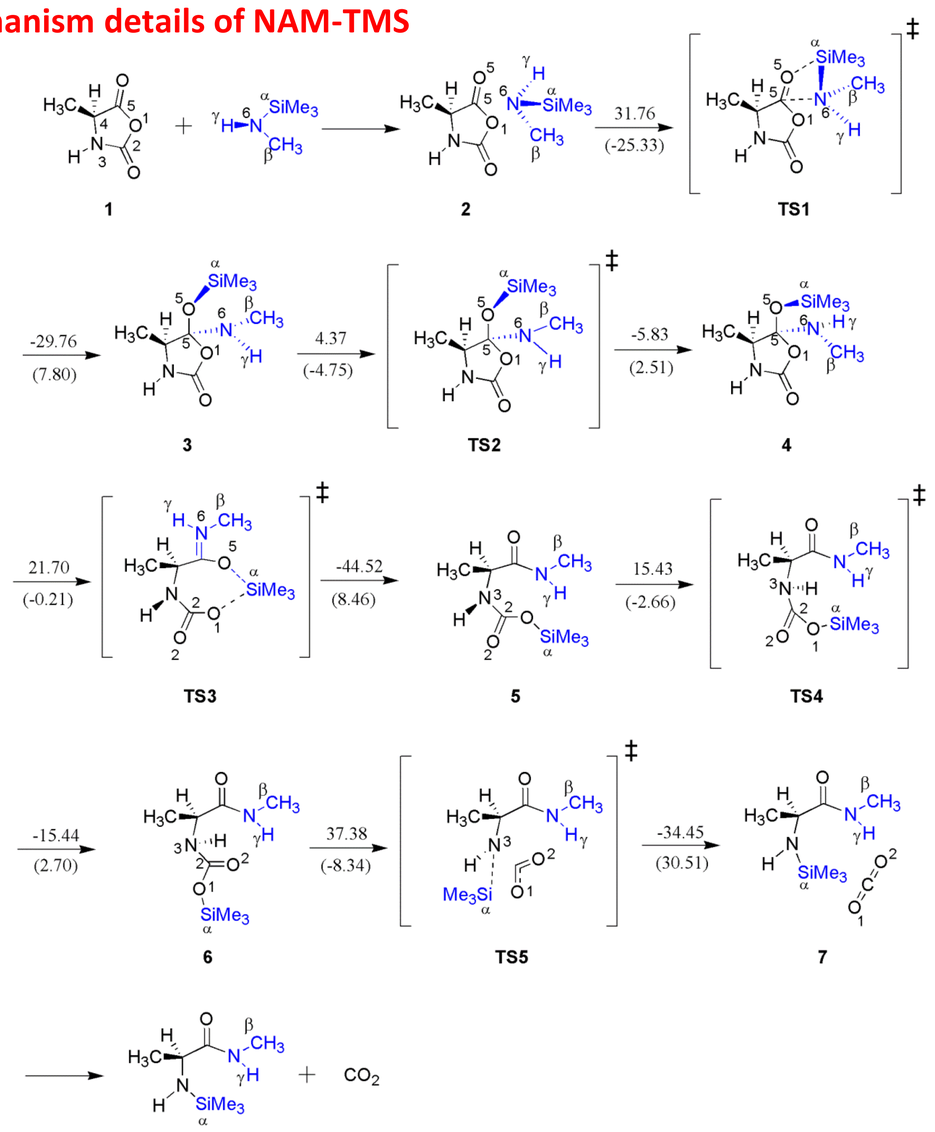


Fig. 6. DFT calculated ring-opening mechanism of L-Alanine-NCA initiated by MeNHTMS with ΔG (kcal·mol^{-1}) energies and ΔS (cal·mol^{-1}·K^{-1}) in parentheses.

Conclusions

We propose a NAM-TMS of ROP of Ala-NCA and Sar-NCA initiated by MeNHTMS by means of DFT calculation, and confirm that TMS is a more efficient transfer group than proton. The rate-determining step of NAM-TMS is decarboxylation step, which suggests that both removal of CO_2 and application of polar solvent accelerate NCA polymerization rate. This work encourages alternative design of transfer group to improve the syntheses of polypeptides and polypeptoids.

Acknowledgement

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References

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