

## **Electronic Supporting Information**

### **Origins in the substituent effects in the aldol condensation of axially chiral thiohydantoins: a computational study**

Nazli Goksel Carpa,<sup>‡</sup> Zekihan Ozerdem,<sup>‡</sup> Ilknur Dogan, Zeynep Pinar Haslak\* and Viktorya Aviyente\*

Department of Chemistry, Bogazici University, Bebek, Istanbul 34342, Turkey

<sup>‡</sup>These authors contributed equally.

**Benchmark Study on the Choice of Methodology:**

For the benchmarking study of the DFT method, we have modeled the rate determining step (TS2), the second step in which benzaldehyde adds to the enolate, by using M06-2X/6-311+G(d,p), B3LYP/6-311+G(d,p) and B3LYP-D3/6-311+G(d,p) // B3LYP/6-311+G(d,p) level of theories in conjunction with CPCM implicit solvation method. We have calculated the isomeric proportions (%) of synthesized aldol adducts by both considering the activation free energies ( $\Delta G^\ddagger$ ) and the relative stabilities of the hydrolyzed products ( $\Delta G_{\text{rxn}}$ ) using the Boltzmann distribution function. According to the results presented in **Table S1**, none of the methodologies can provide the experimental distribution when the calculations were performed with  $\Delta G^\ddagger$  since the latter are quite low and do not control the stereochemistry of the reaction while all the methodologies satisfied the general tendency of stereoselectivity when the calculations were performed with  $\Delta G_{\text{rxn}}$ . The most accurate results were obtained when M06-2X/6-311+G(d,p) level of theory was used for modeling the aldol addition reaction. Thus, the results presented in this study are reported based on the M06-2X calculations.

**Table S1.** Comparison of experimentally determined and calculated isomeric proportions (%) of synthesized aldol adducts. The calculated values are based on relative hydrolyzed product Gibbs free energies ( $\Delta G_{\text{rxn}}$ ), whereas the calculated values in parentheses are based on activation free energies ( $\Delta G^\ddagger$ ).

Compound	Isomer	ee % <sup>a</sup> (Experimental)	ee % (M06-2X)	ee % (B3LYP)	ee % (B3LYP-D3// B3LYP)
I	RMS*+RMR*	80	100 (36)	76 (26)	99 (21)
	SMS*+SMR*	20	0 (64)	24 (74)	1 (79)
II	RPS*+RPR*	23	12 (19)	34 (61)	2 (69)
	SPS*+SPR*	77	88 (81)	66 (39)	98 (31)
III	RMS*+RMR*	47	49 (93)	24 (19)	40 (52)
	SMS*+SMR*	53	51 (7)	76 (81)	60 (48)
IV	RMS*+RMR*	100	100 (95)	88 (92)	100 (98)
	SMS*+SMR*	0	0 (5)	12 (8)	0 (2)

<sup>a</sup> without any purification.

ee: enantiomeric excess

**Table S2.** Calculated thermodynamic parameters (*kcal/mol*) and kinetics (*M<sup>-1</sup>s<sup>-1</sup>*) for the enolization reactions of **SM** and **RM** isomers of 4 thiohydantoin derivatives as precursor of aldol adducts (M06-2X/6-311+G(d,p) / CPCM(THF), 195 K).

reactant	product	$\Delta G_{\text{rxn}}$	$\Delta G_f^\ddagger$	$k_f$	$\Delta G_r^\ddagger$	$k_r$
SM- <i>pre</i> -I	M-I-Li-enolate	-27.3	2.0	$2.5 \times 10^{10}$	29.2	$6.6 \times 10^{-21}$
RM- <i>pre</i> -I	M-I-Li-enolate	-27.6	2.9	$2.2 \times 10^9$	30.5	$2.6 \times 10^{-22}$
SM- <i>pre</i> -II	M-II-Li-enolate	-27.2	2.6	$4.7 \times 10^9$	29.8	$1.5 \times 10^{-21}$
RM- <i>pre</i> -II	M-II-Li-enolate	-26.1	4.4	$5.1 \times 10^7$	30.5	$2.4 \times 10^{-22}$
SM- <i>pre</i> -III	M-III-Li-enolate	-27.8	3.4	$7.8 \times 10^{10}$	29.3	$9.4 \times 10^{-21}$
RM- <i>pre</i> -III	M-III-Li-enolate	-25.6	1.5	$5.5 \times 10^8$	29.1	$5.0 \times 10^{-21}$
SM- <i>pre</i> -IV	M-IV-Li-enolate	-29.0	-1.8	$4.5 \times 10^{14}$	27.2	$1.3 \times 10^{-18}$
RM- <i>pre</i> -IV	M-IV-Li-enolate	-28.3	-1.0	$6.0 \times 10^{13}$	27.3	$1.0 \times 10^{-18}$

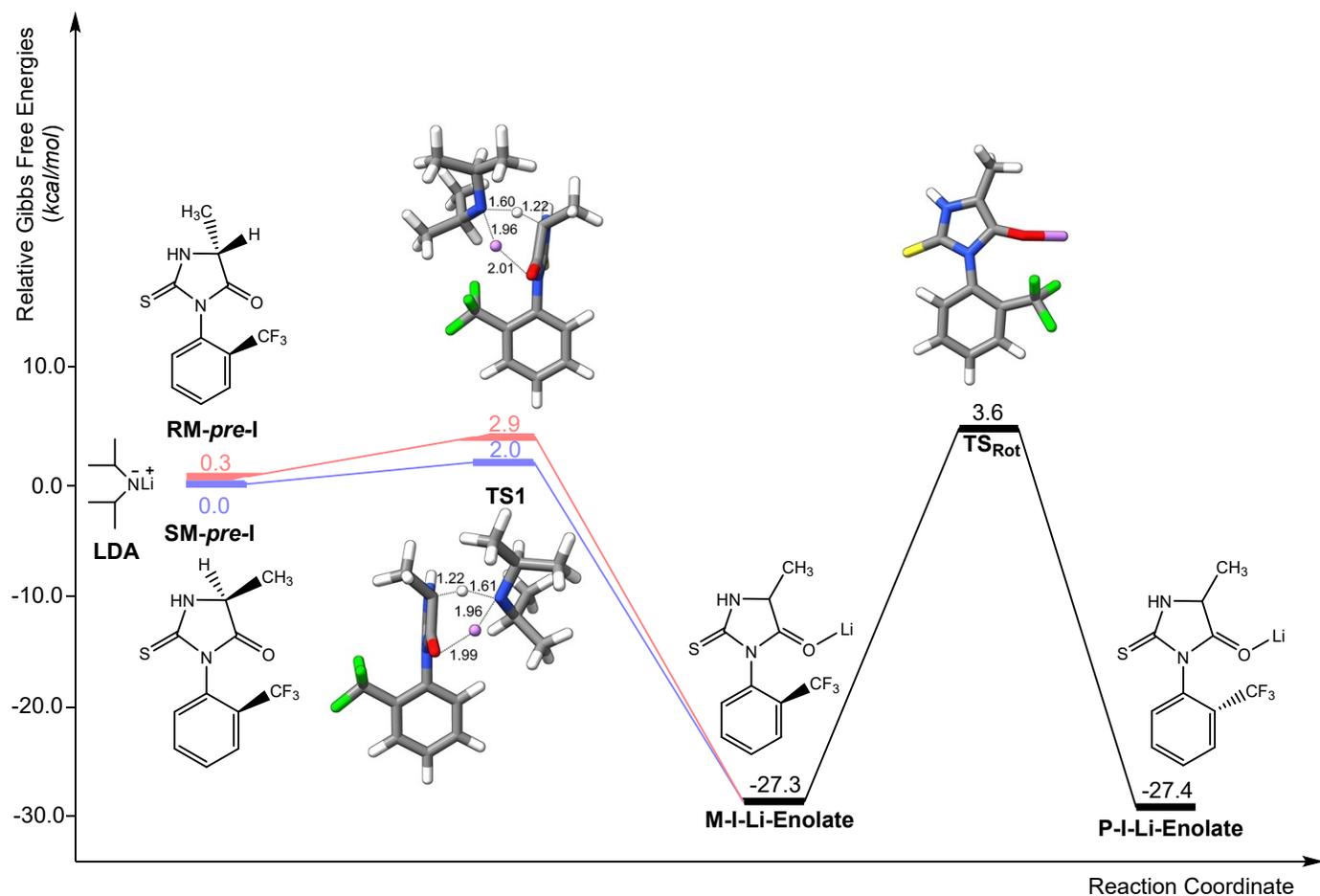
$\Delta G_{\text{rxn}}$ : Reaction Gibbs free energies (kcal/mol)

$\Delta G_f^\ddagger$ : Gibbs free energy of activation of the forward reaction (kcal/mol)

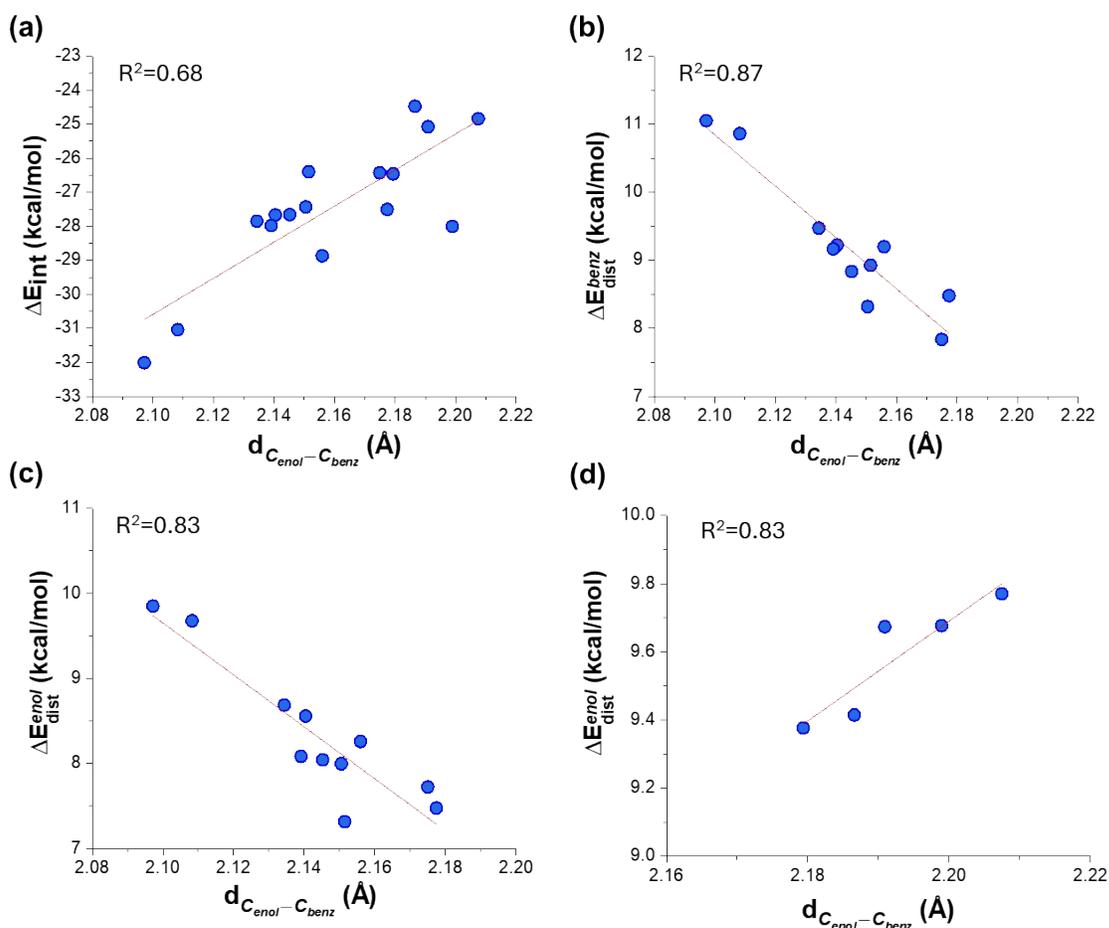
$k_f$ : calculated rate constant of the forward reaction ( $M^{-1}s^{-1}$ )

$\Delta G_r^\ddagger$ : Gibbs free energy of activation of the reverse reaction (kcal/mol)

$k_r$ : calculated rate constant of the reverse reaction ( $s^{-1}$ )

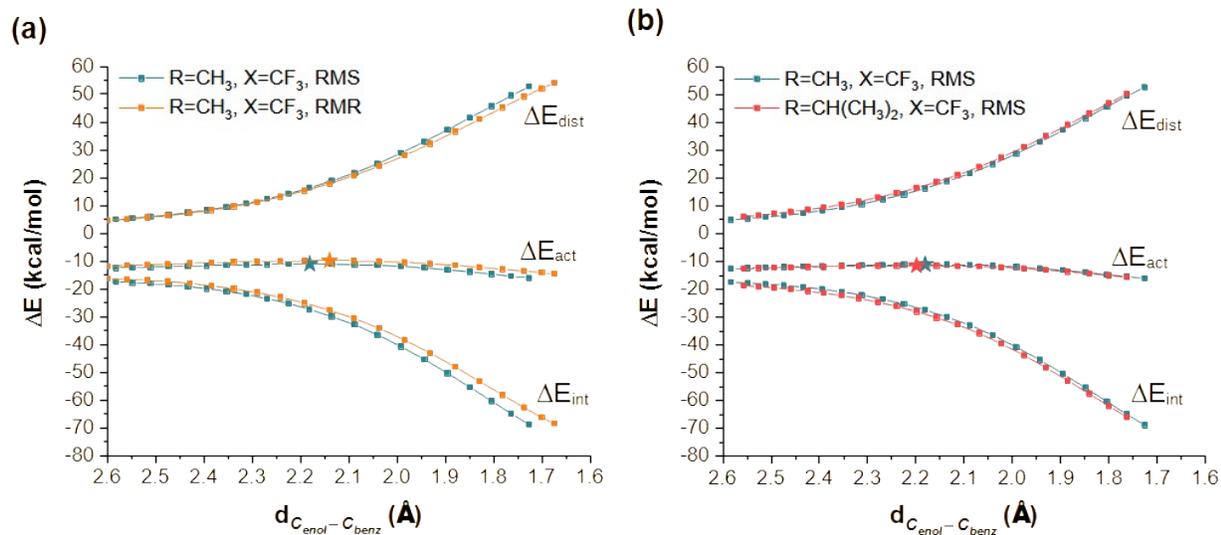


**Figure S1.** Free energy profile for the enolization of **SM-*pre-I*** and **RM-*pre-I*** (R=CH<sub>3</sub> and X=CF<sub>3</sub>) in the presence of LDA, with respect to the most stable geometries of the isolated reactants.



**Figure S2.** Plots of

- interaction energy ( $\Delta E_{int}$ ) vs forming bond distances between C5 of Li-enolate and C(=O) of benzaldehyde ( $d_{C_{enol}-C_{benz}}$ ),
- distortion energy of benzaldehyde ( $\Delta E_{dist}^{benz}$ ) vs  $d_{C_{enol}-C_{benz}}$  for compounds **RMS\*-I, II, III, RMR\*-I, II, III, IV** and **SMS\*-I, II, III, IV**,
- distortion energy of Li-enolate ( $\Delta E_{dist}^{enol}$ ) vs  $d_{C_{enol}-C_{benz}}$  for compounds **RMS\*-I, II, III, RMR\*-I, II, III, IV** and **SMS\*-I, II, III, IV**,
- distortion energy of Li-enolate ( $\Delta E_{dist}^{enol}$ ) vs  $d_{C_{enol}-C_{benz}}$  for compounds **SMR\*-I, II, III, IV** and **RMS\*-IV** in TS2.



**Figure S3.** The activation energy ( $\Delta E_{act}$ ), the total distortion energy ( $\Delta E_{dist}$ ) and the interaction energy ( $\Delta E_{int}$ ) between benzaldehyde and Li-enolate of **RMS\*-I** and **RMR\*-I** (a), **RMS\*-I** and **RMS\*-IV** (b) as a function of forming  $C_{enol}-C_{benz}$  bond length along the aldol addition reaction. The location of the TS is represented by stars.