Cyclization of lapachol in acidic aqueous media: regioselectivity and interconversion mechanism study

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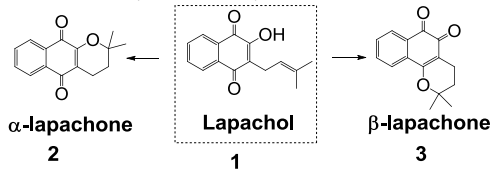
INTRODUCTION

Intramolecular cyclization reactions of lapachol can produce α- and β-lapachone which have value as potentially cytotoxic quinone compounds. The lapachones are selectively obtained by use of either diluted or concentrated acidic media, and the interconversion equilibrium between these isomers can also be controlled using different acid concentrations (Scheme 1).



Entry	Solvent	α : β	Yield
1	HCl	1 : 0	70%[1]
2	H_2SO_4	0 : 1	80%[1]

Scheme 1. Experimental conditions for preparation of α- and β lapachones.

DFT calculations were employed to compute the pathway connecting lapachol to the lapachones considering the effect of the acid strength in aqueous solution.

METHODS

Geometry optimizations and vibrational frequency calculations were carried out with Gaussian 09 using B3LYP/6-31++g(d,p) and the continuum solvent model (PCM) with water as solvent together with explicit solvation. Basicity (-ΔG) and protonic affinity (-ΔH) of lapachol were calculated to evaluate the preferential protonation sites in acidic media. Energy parameters for cyclization reaction were also calculated.

RESULTS AND DISCUSSION

Di-protonated and tri-protonated lapachol may be formed in HCl and H_2SO_4 depending on the different acid concentration. Di-protonated lapachol affords mainly α-lapachone by kinetic control (**Figure 1** – **A**). Tri-protonated lapachol affords exclusively β-lapachone derivative by thermodynamic control (**Figure 1** – **B**), once the reverse process is feasible.

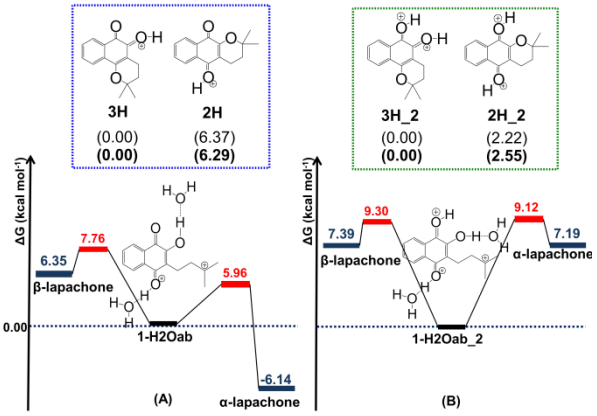


Figure 1. Variation of Gibbs free energy for di- (**A**) and tri-protonated (**B**) lapachol cyclization. All values are in kcal mol^{-1}.

CONCLUSIONS

Activation barriers for cyclization are all below 10 kcal mol^{-1}. Regioselective formation of α- and β-lapachone derivatives is dominated by kinetic and thermodynamic control via cyclization of the di- and tri-protonated forms of lapachol, respectively.

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