

DFT Study on the Possible Intramolecular Rearrangement of Four Monocyclic Monoterpenes

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ABSTRACT: As the basis and preliminary work of future experimental study on PAHs formation under high temperature, theoretical computations on the intramolecular rearrangement reactions of sylvestrene (1-methyl-3-vinylcyclohexene) and 1,4-dimethyl-4-vinylcyclohexene are conducted and reveal that they may be transformed to themselves. The conversion between Dipentene and 2,4-dimethyl-4-vinylcyclohexene is also predicted. All the reactions proceed along concerted paths through a single *cis-endo* transition state with relatively high energy barrier (~200 kJ/mol) and presumably occur when alkenes burn. These possible Cope rearrangement reactions have some characters of stepwise Diels-Alder cycloadditions during which diene and dienophile are replaced by each other and may suggest the complexity of cyclic hydrocarbons formation.

KEYWORDS: Cope rearrangement; Diels-Alder reaction; Monocyclic monoterpenes; Intramolecular cyclization.

INTRODUCTION

With respect to occurrence in nature, the monoterpenes represent the best-investigated class of terpenic compounds which have many laboratories- as well as industrial-scale applications. Due to their nature (odor, taste, chirality), they serve as important synthetic building blocks for the production of flavors, fragrances, pharmaceuticals, and nutraceuticals. Their derivatives are widely applied in enantioselective reactions as ligands or auxiliaries [1]. Additionally, they are the major components of the unsaturated gaseous hydrocarbons present in tobacco and tobacco smoke. It had been proposed that the terpene components of tobacco (such as solanesol) can decompose into isoprene [2] and pyrosynthesize into larger polycyclic aromatic hydrocarbons (PAHs) [3],

including benzo[a]pyrene which is a widespread environmental pollutant and carcinogen. Therefore the experimental and theoretical researches of isoprene are of great significance for organic materials, energy and chemical industry and environmental protection.

Besides these practical applications, the chemistry of terpenes is interesting from both theoretical and mechanistic viewpoints. The wide structural diversity and possibility for internal C-C linkage offer the opportunity of performing rearrangement reactions in the gaseous, liquid, and supercritical phase. In our previous work, we have studied the pathway of the Diels-Alder reaction between two isoprenes which may produce four monocyclic monoterpenes, such as sylvestrene,

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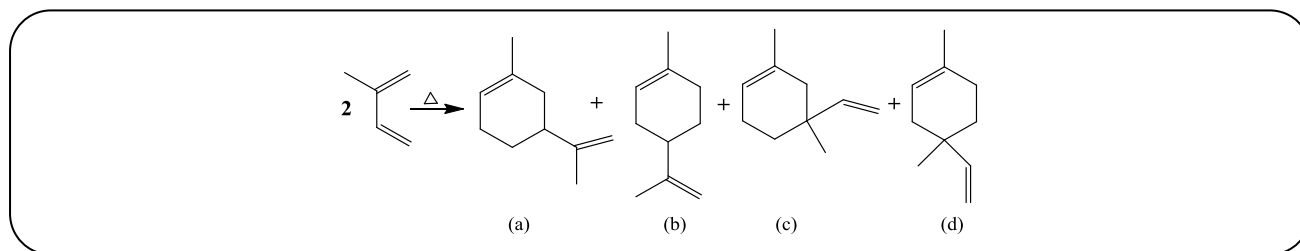


Fig. 1: Dimers of cycloadditions from two isoprenes.

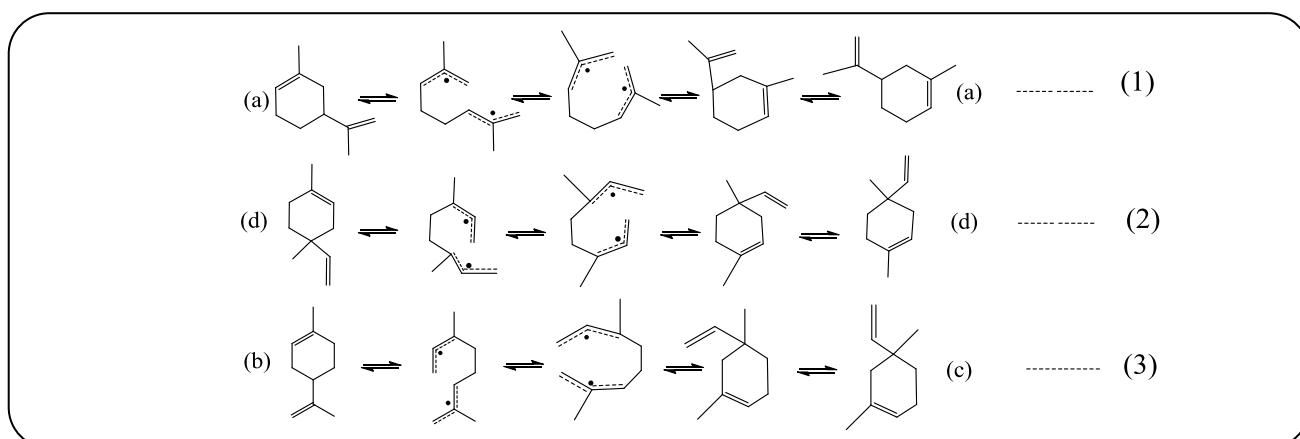


Fig. 2: Three possible intramolecular rearrangement pathways of monocyclic monoterpenes *a*, *b*, *c*, and *d*.

dipentene, 2,4-dimethyl-4-vinylcyclohexene and 1,4-dimethyl-4-vinylcyclohexene (**a**, **b**, **c** and **d** in Fig. 1, respectively) [4]. Besides the theoretical concerted and stepwise mechanisms of the isoprene dimerization, we also found a novel transition state (TS_{b-c}) connected the monoterpenes **b** and **c** according to our calculations [5]. Here we will address a more comprehensive theoretical study further on the possible intramolecular rearrangement of monocyclic monoterpenes **a** and **d**. We suggest that these works may provide more interesting examples of pericyclic reaction researches and be the foundation of our future experimental study on PAHs formation under high temperature.

COMPUTATIONAL METHODS

The reactants, products and Transition States (TSs) are fully optimized and characterized by vibrational frequency calculations using B3LYP (Becke's three-parameter-hybrid functional combined with the correlation function of Lee *et al.*) with 6-311⁺⁺G(d,p) basis set [6-8]. All minima and transition structures are confirmed to have none or only one imaginary frequency, respectively. The Intrinsic Reaction Coordinate (IRC) analyses [9]

are followed to determine the connections between the transition structures and the minima. All calculations are performed with the Linux version of Gaussian 09 [10].

RESULTS AND DISCUSSION

Three Rearrangement Reaction Pathways

According to our calculations, we found three pathways in Fig. 2. The products of the first two reactions are the reactants themselves (**a** or **d**), that is, the compounds lay at both ends of the reactions are identical rather than two isomers. Compound **b** and **c** convert to each other in the third reaction. All the three reactions could be described clearly with the examples of the Cope rearrangement [11], such as the degenerate rearrangement of 1,5-hexadiene which is the simplest but controversial case. On the other hand, the reactions are also very similar to the [4+2] Diels-Alder cycloaddition [12] to some degree. Having two double bonds each, the two isoprene monomers can act as either diene or dienophile when they dimerize into compounds **a**, **b**, **c**, and **d**. We use two colors (green/grey, or light/dark in black and white version) and a non-traditional label method to help us recognize the two isoprene monomers (Fig. 3). In Fig. 3a,

C1-C1' bond and C4-C2' bond of the reactants can be seen as the σ bonds formed by cycloaddition of two isoprenes in which the "green" monomer is the diene, while C1-C1' and C4'-C2 bond of the products may be regarded as the cycloaddition results in which the "green" monomer is the dienophile. When C4-C2' bond breaks and C1-C1' bond still exists, the generated linear biradical is very similar to an intermediate of a stepwise Diels-Alder reaction. The original dienophile may become diene as long as the distance and the orientation is suitable. The similar phenomena are shown in Fig. 3b and 3c. It is very hard to distinguish the reactant and product of path (1) or (2) despite the atom arrangements of them are different indeed.

The dissociation of the original bonds and the formation of the new bonds take place at the coordinates just before and after the corresponding TSs, respectively. The distances between them and the corresponding TSs are approximately equal. The energy barriers of the forward and reverse pathways are almost equal, too. It is suggested that all the reactions are reversible despite the relatively high energy barriers.

Transition States Structures and Comparison with DA reactions

As a classic example of sigmatropic reaction, the nature of 1,5-hexadiene rearrangement has been converged upon a mechanism that it occurs by a single "aromatic" TS which is very similar with our calculated TSs in Fig. 4. We can see that the distances between C2-C4' and C4-C2' of the TS_{a-a} are exactly the same, so are the C1-C3' and C3-C1' of the TS_{d-d}. While the little difference of the distances between C1-C2' and C3-C4' for the TS_{b-c} makes the symmetry of path (3) is little weaker than path (1) and (2). The *cis* conformation (C₁₋₂₋₃₋₄ and C_{1'-2'-3'-4'}) of the two "isoprene monomers" in all the TSs provide them the equal opportunities to be either diene or dienophile in the reactions. These three TSs may be seen as the results of two isoprene's competition to become diene or dienophile. The bonding atoms approach each other via *endo* orientation, otherwise the re-cycloaddition may not occur. As we know that the dimerization of isoprene via Diels-Alder reaction gives mixtures of stereoisomer, i.e. dipentene (b) is the racemic limonene which contains (*R*)- and (*S*)- limonene, and only (*S*)-configuration of compounds can rearrangement through *cis-endo* TSs based on the TSs' geometries.

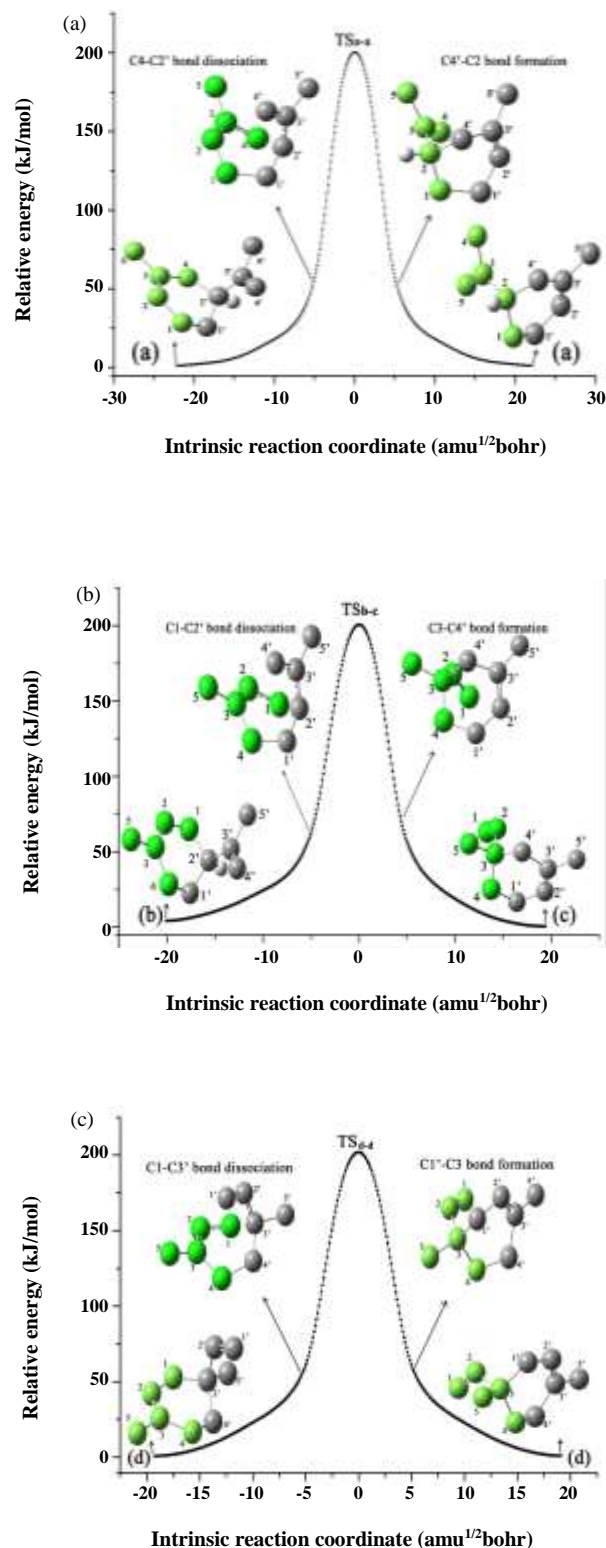


Fig. 3: Relative energy profiles along the intrinsic reaction coordinate for the three molecular rearrangement reactions and the geometries of selected points structures (hydrogen are not shown except that on the chiral atoms).

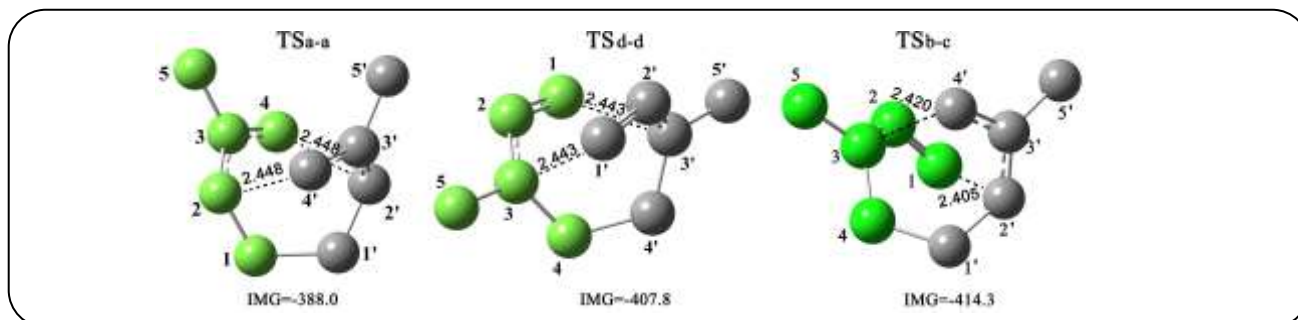


Fig. 4: Geometries and imaginary frequencies (IMG in cm^{-1}) of the transition states for the molecular rearrangement reactions (hydrogen not shown, distances in \AA).

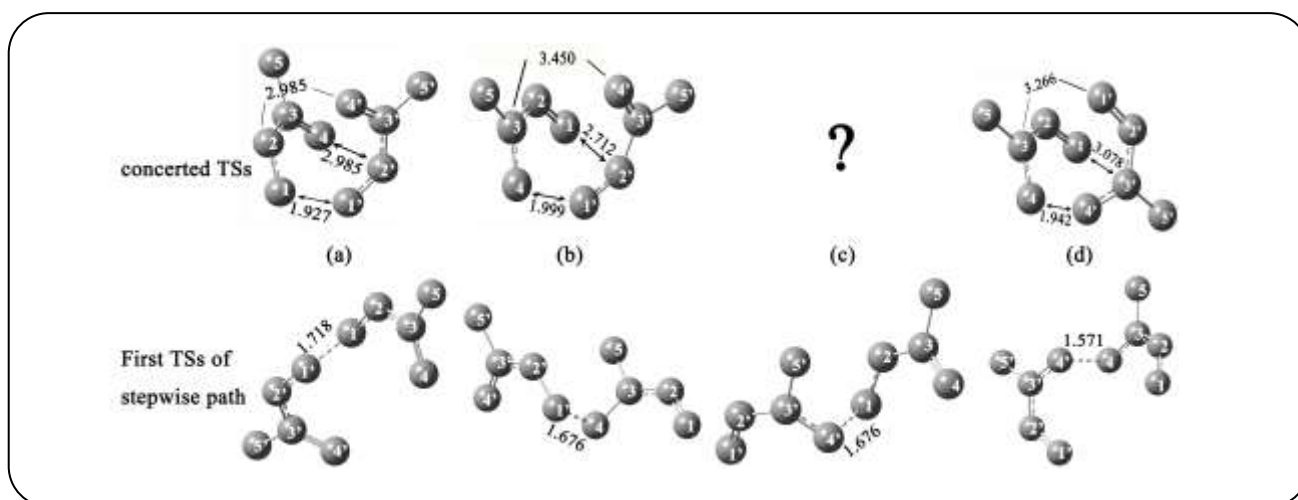


Fig. 5: Geometries of the concerted and stepwise transition states for the *cis_endo* DA reactions between two isoprenes (hydrogen are not shown, distances in \AA). The concerted TS of the DA reaction for the dimer (c) has not been identified according to our calculation.

To comprehend the rearrangement reactions further, we calculated the concerted and stepwise pathways of *cis_endo* DA reactions between two isoprenes (Fig. 5). The concerted TS for the dimer (c) had not been identified in our calculations and we suggest that the dimer (c) may be produced through the stepwise pathway. The structure and the orientations of the atoms of all the concerted TSs are similar to those of the rearrangement TSs except the distances between the bonding atoms. All the new bonds in the concerted TSs are not formed and the distances between the bonding atoms are longer than those of the rearrangement TSs. The difference between the rearrangement TSs and the first TSs of stepwise DA reactions is the latter may dissociate into two reactant monomers or become cyclic through the second TSs via the torsion of the first new σ bond from a liner biradical intermediate, and the former will form a new σ bond directly to become cyclic again.

CONCLUSIONS

Intramolecular cyclization are very important reactions for the synthesis of many natural and unnatural products such as terpenes [13]. Although all the possible intramolecular rearrangement reactions described in this paper could have high active barriers (about 200kJ/mol) according to our calculation (Table 1), we think they may take place under certain conditions such as high temperature. They presumably are the by-pass pathways when the liner intermediates of the stepwise DA reactions change their conformation to some appropriate location to form different products. The reactant and product are entirely the same molecules like a path (1) and (2) do not make the reactions meaningless. Special attention should be paid to decrease the infinite recurrence between the reactants and products. The introduction of some certain substituent at the appropriate site may provide more opportunity to produce more novel isomers and may make these reactions more viable and valuable.

Table 1: Energy differences (kJ/mol) of the transition states relative to each reactant.

product	DA reaction		Intramolecular rearrangement TS
	concerted TS	first TS of the stepwise path	
a			
b	97.9	123.1	199.7
c	102.4	118.2	197.8
d	—	122.4	
	108.8	120.5	201.8

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