

Computational Study of Inversion-topomerization Pathways in 1,3-Dimethylcyclohexane and 1,4-Dimethylcyclohexane: Ab Initio Conformational Analysis

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Abstract: This work concerns the typical conformational behaviors for di-substituted cyclohexanes that inherently depend on spatial orientations of side chains in flexible cyclic ring. The 1,3-dimethylcyclohexane and 1,4-dimethylcyclohexane in both cis- and trans-configurations were focused here to unravel their conformational inversion-topomerization mechanisms. Full geometry optimizations were performed at B3LYP/6-311++G(d,p) level of theory to explicitly identify all distinguishable molecular structures, and thus explore potential energy surfaces (PES) of the complete interconversion routes for two stereoisomers of 1,3-dimethylcyclohexane and 1,4-dimethylcyclohexane. Additional quantum calculations were carried out by separately applying MP2/6-311++G(d,p), G4, and CCSD(T)/6-311++G(d,p) methods to further refine all PES' stationary points. With respect to quantum results, the conformational analysis was conducted to gain insight into the determination, thermodynamic stabilities, and relative energies of distinct molecular geometric structures. On base of highly biased conformational equilibria, the temperature-dependent populations of stable local minima for four studied dimethylcyclohexanes were obtained by utilizing Boltzmann distribution within 300-2500 K. Moreover, two unique interconversion processes for them, including inversion and topomerization, were fully investigated, and their potential energy surfaces were illustrated with the rigorous descriptions in two or three-dimensional schemes for clarify.

Keywords: Cycloalkanes; Conformational analysis; Dimethylcyclohexane; Inversion-topomerization; Boltzmann distribution;

1. Introduction

As the study of cycloalkanes, focusing on their molecular preferences, conformational behaviors, and relative energies, has long been a topic of interest for chemistry and some interrelated application, they have been investigated by theoretical calculations and experimental measurement.¹⁻¹³ The adopted experimental

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methods briefly include X-ray diffraction, Raman, infrared, NMR spectrum detection^{9,10,14-16}, and theoretical approaches contain ab initio, molecular force field, and dynamical density functional theory^{4,8,17-20}. These previous studies usually cover two mainly aspects: (1) conformational determination of the simple neutral cycloalkane compounds from three-membered ring to the larger ones, like cyclohexane, cyclooctane, and cyclotridecane²¹⁻²³; (2) conformational changing investigation of cyclohexane and its substitution derivatives^{8,15,24-27}. Since cyclohexane has a fluxional and most symmetrical structure, it serves as the archetype molecule to understanding the energetics and conformational preferences for other related cycloalkanes and yielded derivatives.²⁰ According to the prior researches^{9,10,20,28,29}, the distortion of cyclohexane ring typically generates four distinct steric molecular configurations, i.e. chair, twist-boat, half-chair, and boat conformers, and they could accomplish interconversion via inversion-topomerization process. As such, its detailed information plays an essential role in development of stereochemistry and organic chemistry, and particularly for conformational analysis.

With respect to this, the ongoing researches have been devoted to exploring the substituted cyclohexanes in terms of the determination of conformational preference, the relative energies of various conformers, thermodynamic stability and equilibrium, axial/equatorial reversal and ratios, and interconversion mechanism. Ribeiro et al.³⁰ presented the evidence that the hyper-conjugative interactions plays a significant role in controlling the conformational behaviors for a series of methyl-substituted six-membered rings. Their work was promoted by the findings reported by Wiberg et al.³¹ that the syn axial interaction has no obvious impact on determination of conformational energies for methylcyclohexane (MCH). Moreover, Wiberg et al.^{24,31} also experimentally and computationally obtained the conformational free energies, entropies, and enthalpies of ethyl-, isopropyl-, phenyl-, and 1-methyl-1-phenylcyclohexanes, and computed the equilibrium constants by measuring the ratios of axial/equatorial conformers. Durig et al.¹⁵ looked into the influence of mono-substitution on cyclohexane, resulting in the formation of both equatorial and axial forms by Raman spectra and quantum chemical calculations. And they reported the conformational stabilities of MCH conformers regarding to r_0 structural parameters, vibrational assignment, and ab initio results. Antúnez et al.³² studied the conformational equilibrium between axial and equatorial preferences for tert-butylcyclohexane by molecular mechanics computations.

As for the interconversion mechanisms of cycloalkanes, there have been limited studies aiming to

characterize transition states accessible to conformation, and particularly for their complete potential energy surfaces for inversion-topomerization pathways that have been rarely concerned and given in detail.^{8,16,18,33} Recently, Fernández-Alonso et al.^{8,19} theoretically studied the inversion and topomerization routes for oxane, thiane, and methylcyclohexane by utilizing ab initio methods. It was based on the original conversion pathways for cyclohexane from Kolossvary et al.³⁴ Stortz³³ applied ab initio and DFT calculations to obtain the conformational equilibria for cyclohexane and its mono-substituted derivatives, i.e. methyl-, hydroxyl-, fluoro-, chloro-, and t-butylcyclohexane, and then search for their conformational routes presented with the global three-dimensional hypersurfaces. Bain et al.¹⁶ reported a quantitative interconversion picture between two chair forms for trans-1,4-dibromodicyanocyclohexane by high-level electronic structure computations, in which two transition states and one intermediate involved were identified. They proposed that their experimental findings from NMR spectra support such quantum results. More recently, Bian et al.³⁵ elucidated the detailed inversion-topomerization pathways for ethylcyclohexane (ECH) and 1,2-dimethylcyclohexane (1,2-DMCH) in both cis- and trans-configurations by applying ab initio methods. Based on this work, furthermore, they uncovered that the conformational changing reaction mechanisms of ethylcyclohexyl radicals exhibit a profound effect on distribution of these radicals and subsequently influence the decomposition products at combustion conditions.⁶ And they also found that the initial decomposition, especially for intermolecular H-migration, of cis-1,2-dimethylcyclohexyl radicals are certainly affected by various conformational structures by theoretical calculations.⁷

Moreover, one thing should be emphasized that the explorations of distinguishable geometric structures and interconversion mechanisms for substituted cycloalkanes are of great importance in organic and combustion chemistries demonstrated by the proceeding studies.^{1,2,36-38} Supported by conformational analysis, Yang et al.^{1,36} gained insight into the role of steric structures for several cycloalkanes in their low temperature oxidation chemistry by ab initio calculations and ignition experiment in a motored engine. They proposed that the important 1,4 and 1,5 H-migrations show strongly structure dependence on such distinct conformers by inhibiting or triggering chain branching. Furthermore, Kang et al.² revealed that the reactivity of ethylcyclohexane is higher than its isomers 1,2-DMCH and 1,3-DMCH, caused by its conformational structures are more viable for 1,5 H-migration in a modified CFR engine. Davis et al.³⁷ computed the kinetic parameters for 1,2 to 1,6 H-migrations originated from various conformers of methyl- and ethylcyclohexyl

radicals. In addition, Yu et al.³⁸ figured out 22, 9, and 4 conformers respective for 2-cyclohexyl-ethyl, 2-ethylcyclohexyl, and transition states, and thus to acquire the accurate thermal rate constants of 1,4 H-migration by using multiple variational transition state theory (MP-VTST). This method can better deal with the low-frequency modes in cyclic ring by fully considering all conformational preferences, and thereby gain the reliable partition functions and kinetic predictions for cycloalkanes. Accordingly, as concerned in these former studies, there is an urgent need to further investigate the conformational features of substituted cyclohexanes, particularly ones with two side chains, since they play an essential role in application for several important branches of chemistry.

In this work, *cis*- and *trans*-stereoisomers of 1,3-dimethylcyclohexane (1,3-DMCH) and 1,4-dimethylcyclohexane (1,4-DMCH) were chose as the target molecules to characterize their conformational structures and look into inversion-topomerization mechanisms by utilizing the accurate *ab initio* computations. This is based on the prior one focusing on conformational behaviors of ECH and 1,2-DMCH.³⁵ All accessible steric molecular structures for these four dimethylcyclohexanes were carefully determined, and the factors mainly influencing the formations of various conformers were revealed. Afterwards, the thermodynamic stabilities and relative energies of all conformers were considered in conformational analysis. Moreover, Boltzmann distribution was applied to calculate the temperature-dependent populations for all local energy minima over 300-2500 K. Finally, the whole inversion and topomerization changing pathways were presented with two or three-dimensional schemes of potential energy surfaces. This study can have an important application for deeply revealing the conformational behaviors for di-substituted cyclohexanes, and be fruitfully applied to other related cyclic ring systems.

2. Computational Details

Full geometry optimizations for all stationary points studied in this work and associated with the conformational inversion-topomerization processes were studied by utilizing Gaussian 09 program.³⁹ The B3LYP density functional with the 6-311++G(d,p) basis set was employed to optimize the equilibrium geometries and obtain the rotational-vibrational frequencies for all discernible conformers for 1,3-DMCH and 1,4-DMCH in *cis*- and *trans*-configurations.⁴⁰ The local energy minima were confirmed with all positive frequencies by applying vibrational analysis at B3LYP/6-311++G(d,p) level of theory, whereas the other conformers corresponding to conformational transition states were ensured with solely one imaginary

frequency. Subsequently, the vibrational mode animations for transition states were to verify them involved in the desired reaction coordinate for inversion or topomerization. Afterwards, the intrinsic reaction coordinate (IRC) analysis was further carried out to guarantee transition state correctly connecting to the designated product and reactant, and thus depict the whole potential energy surface for conformational changing reactions.

To refine the energies for all stationary points, MP2/6-311++G(d,p), CCSD(T)/6-311++G(d,p), and G4 methods were separately utilized to acquire high level evaluations for single point energies, which was on base of the preliminary geometries optimized. Note that zero-point vibrational energies obtained from B3LYP/6-311++G(d,p) frequency analysis were included into the energies calculated by both MP2/6-311++G(d,p) and CCSD(T)/6-311++G(d,p) methods. As for the composite method G4⁴¹, it uses B3LYP/6-31G(2d,p) method to optimize geometries, which are for a series of single point energy computations at the higher levels of theory. Moreover, as for the internal rotation retaining in distinguishable side chain for each conformer, its potential energy surface was computed by employing B3LYP/6-311++G(d,p) method with an increment of 10°.

3. Results and discussion

Based on the former work for ECH and 1,2-DMCH³⁵, this current work serves as a continuation to further investigate the conformational behaviors of cis- and trans-stereoisomers for 1,3-DMCH and 1,4-DMCH. For the sake of clarity, they are separately indicated by a combination of uppercase and number in the following discussions, like C₁₃ for cis-1,3-dimethylcyclohexane in Table 1. Fig. 1 briefly depicts the schematic structures and numbering on carbon atoms of global energy minima for these four dimethylcyclohexanes. As proposed in the preceding studies^{31,35}, cyclohexane has two stable cyclic ring structures, i.e. chair and twist-boat, that are labeled by C and T, respectively. With regarding to both of them, there are severally two (equatorial and axial) and three (pseudo-equatorial, pseudo-axial, and isoclinal) specific positions available for side chains occupying. Thereupon, the lowercases (e, a, or i) added are to demonstrate the orientations of methyl group in cyclohexane ring. Herein, C₁₃Tea presents cyclic ring in twist-boat form with the equatorial and axial methyl groups for cis-1,3-dimethylcyclohexane. Under some particular situations, the superscript E would be included after to mark one enantiomer in a mirror image pairs, like C₁₃Tea^E and C₁₃Tea. As for the conformer regarded as transition state, half-chair and boat ones for four dimethylcyclohexanes are simply

described by uppercases H and B followed by number, for instance C₁₃H₂.

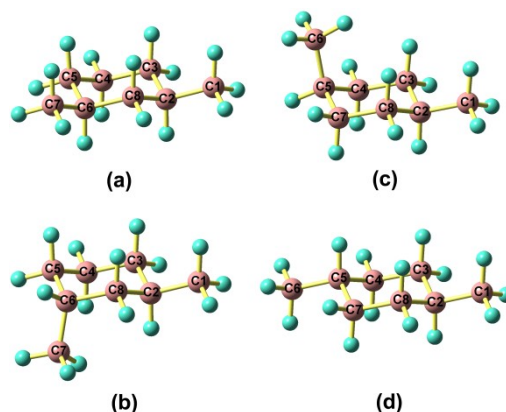


Figure 1. Numbering schemes for 1,3-dimethylcyclohexane (a and b) and 1,4-dimethylcyclohexane (c and d) in both cis- and trans-configurations.

The zero-point inclusive energies for all different conformers for 1,3-DMCH and 1,4-DMCH in both cis- and trans-configurations are referred to their global energy minima at 0 K, which are separately listed in Tables 1 and 2. As mentioned before, these energies were computed by MP2/6-311++G(d,p)//B3LYP/6-311++G(d,p), CCSD(T)/6-311++G(d,p)//B3LYP/6-311++G(d,p), and G4 quantum methods. It can be obviously noticed that the disparities in energies among three methods for stable conformers are less than 0.5 kcal/mol, while the energy deviations for conformational transition states are within 0.7 kcal/mol. This phenomenon explicates that the quantum results obtained by these above methods are of good consistency, which also agrees well the conclusions from previous studies.^{7,35} Moreover, in line with the former, the zero-point corrected CCSD(T)/6-311++G(d,p)//B3LYP/6-311++G(d,p) energies are used in subsequent discussions. In addition, Cartesian coordinates, vibrational frequencies, and rotational constants of the optimized structures for all studied conformers are provided in *Supplemental Material*.

3.1 Conformational analysis

3.1.1 Cis- and trans-1,3-dimethylcyclohexanes

As proposed in previous studies^{8,29,35}, cyclohexane is a fluxional, highly symmetrical, and almost strain-free molecule, of which the stable chair and twist-boat conformers have D_{3d} and D₂ symmetries, respectively. Their structural characteristics determine that there are two and three discernible types of positions available for substituents occupying, as noted above. When the alkyl groups selectively locate at cyclohexane ring, their numbers and relative dispositions would certainly induce quite different conformational behaviors. For 1,3-

DMCH, two methyl groups are to situate in meta-positions on same or opposite sides of cyclohexane ring. It results in cis-1,3-DMCH having two chairs (Cee and Caa) and three twist-boats (Tea, Tei, and Tai), and trans-isomer encompassing one chair (Cea) and four twist-boats (Tee, Tei, Tai, and Taa), of which the steric structures are presented in Fig. 2. These are fairly different from the numbers and conformational preferences for cis- and trans-1,2-DMCH reported in former one.³⁵ Moreover, it is noteworthy that these distinct conformers are generated by the pseudorotation retained in six-membered ring, of which the chain or carbon atom in skeleton of carbon ring alters its spatial position and thereupon leads to the distortion of ring proposed by Weiser et al.⁴²

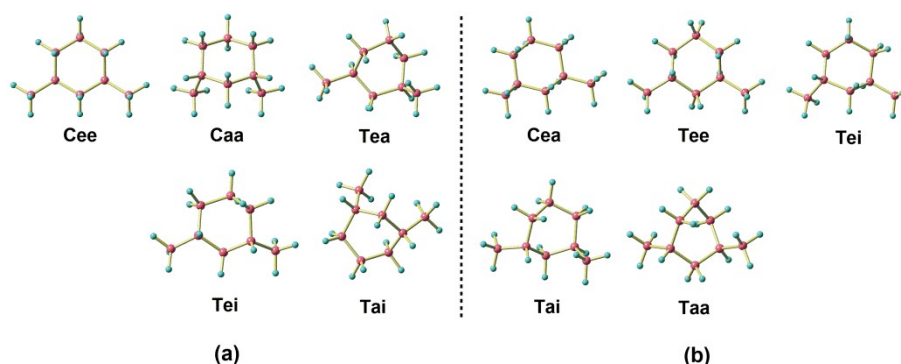


Figure 2. Steric structures for diverse conformers in (a) cis- and (b) trans-1,3-dimethylcyclohexanes obtained at B3LYP/6-311++g(d,p) level.

As depicted in Fig. 3, the internal rotations of two methyl groups have no contributions to yield the distinguishing torsional conformers, which are caused by their three-fold symmetries. This shows good accordance with the ignorable role of side chain in the formations of various conformers for 1,2-DMCH and MCH.^{31,35} However, one thing should be mentioned that torsional potential energy profiles for the pseudo-equatorial and pseudo-axial methyl groups separately in C_{13} Tea and C_{13} Tai are not symmetrical three-fold in Fig. 3(a), as well as one for the isoclinal side chain in T_{13} Tai in Fig. 3(b). When the pseudo-equatorial methyl group in C_{13} Tea rotates along C-C bond, it causes the ring deformation to relocate at pseudo-equatorial position in C_{13} Tei. And the same situation happens to the pseudo-axial methyl group in C_{13} Tai, it would change to pseudo-axial one in C_{13} Tea, as illustrated in Fig. 3(a). But for T_{13} Tai in Fig. 3(b), its isoclinal side chain becomes pseudo-equatorial one in T_{13} Tei through internal rotation. These phenomena could be explained by the fact that there exists the strong steric repulsion for these three rotation modes, and such interaction prefers to induce the distortion of ring structure and then alters the relative positions for two

methyl groups. In addition, the rotational energy barriers for side chains in chairs are generally smaller than ones in twist-boats for 1,3-DMCH in cis- and trans-preferences. The reason for this might result from non-planar ring of twist-boat giving rise to the larger steric repulsive force. Of particular interest is to observe that the torsional barrier for equatorial methyl group in $C_{13}Cee$ is higher than that for axial one in $C_{13}Caa$. And one can obviously notice that the axial side chain in $T_{13}Cea$ is more easily to undergo rotation than the equatorial one, as demonstrated in Fig. 3(b). These drive us to conclude that the side chain is more close to or even in the planar of six-member ring, it would have the higher rotational barrier height in general.

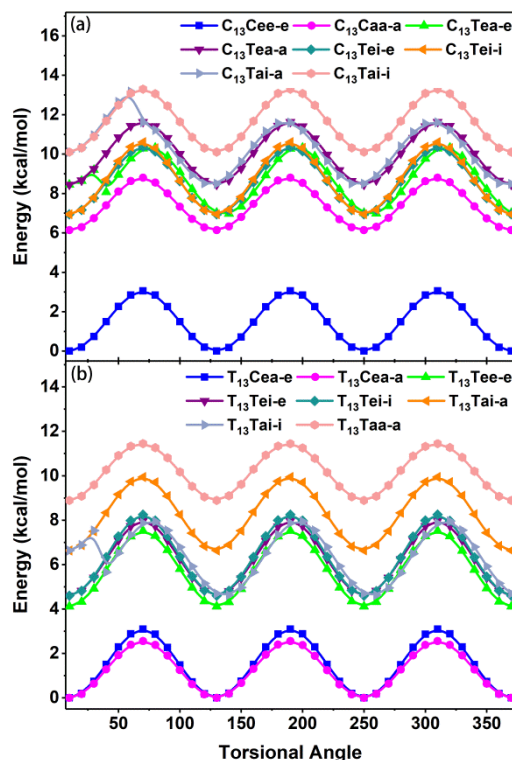


Figure 3. Potential energy changes for the internal rotations of methyl groups that separately occupy axial, equatorial, and isoclinal positions in distinct conformers for (a) cis- and (b) trans-1,3-dimethylcyclohexanes by MP2/6-311++G(d,p) method.

The prior studies^{31,35,42} reported that the molecular structures adopted in different ring forms, particularly with special orientations of side chains, would induce different structural constrains. These constrains may force diverse conformers to have entirely different energies. As listed in Table 1, the zero-point inclusive energies for five stable conformers of cis-1,3-DMCH are within 0-9.2 kcal/mol, whereas these for ones in trans-forms vary from 0 to 8.6 kcal/mol computed by CCSD(T)/6-311++G(d,p)//B3LYP/6-311++G(d,p) method. Note that $C_{13}Cee$ is global energy minimum with two equatorial methyl groups. The other chair $C_{13}Caa$ has 5.2 kcal/mol higher energy than $C_{13}Cee$. This certainly gives the evidence that the side chain in

chair is more likely to situate at equatorial position, which is consistent with the findings for MCH^{8,31}, ECH^{2,31,35}, cyclohexylperoxy radical¹, and cis-1,2-DMCH³⁵. In addition, two chairs for cis-isomer has the smaller energies than three twist-boats with 7.7-9.2 kcal/mol, and one chair T₁₃Cea are apparently lower than four relevant twist-boats having 4.3-8.6 kcal/mol. Not surprisingly, chair conformers have more stable molecular structures, mainly contributed by this special six-member ring form. Basically, this phenomenon commonly exists in some studied peroxy group and alkyl-substituted cyclohexanes.^{2,31,35,36} For twist-boats in both cis- and trans-configurations, there is no obvious difference in their ring structures, as provided in *Supplemental Material*. As such, the deviations in their energies are predominantly controlled by the spatial orientations of side chains. Seen from Table 1, the relative energy ranking for four twist-boats in trans-form is: T₁₃Taa > T₁₃Tai > T₁₃Tei > T₁₃Tee. It indicates that the pseudo-equatorial and pseudo-axial positions are most conducive and unfavorable to side chain to occupy, respectively. This rule applies similarly to cis-isomers for 1,3-DMCH. Note that C₁₃Tai and T₁₃Taa have the highest energies, which are same to C₁₂Tai and T₁₂Taa remaining largest steric repulsion.³⁵

Table 1. Relative energies of various conformers in cis- and trans-1,3-dimethylcyclohexanes at 0 K in kcal/mol by MP2/6-311++G(d,p)//B3LYP/6-311++G(d,p), CCSD(T)/6-311++G(d,p)//B3LYP/6-311++G(d,p), and G4 methods, respectively. Energies are relative to most stable conformers (C₁₃Cee and T₁₃Cea), respectively.

Species	MP2	G4	CCSD(T)	Species	MP2	G4	CCSD(T)
Cis-conformers (C ₁₃)				Trans-conformers (T ₁₃)			
C ₁₃ Cee	0	0	0	T ₁₃ Cea	0	0	0
C ₁₃ Caa	5.6	5.1	5.2	T ₁₃ Tee	4.3	4.4	4.3
C ₁₃ Tea	8.0	7.7	7.7	T ₁₃ Tei	4.6	4.7	4.6
C ₁₃ Tei	6.5	6.3	6.3	T ₁₃ Tai	6.6	6.5	6.4
C ₁₃ Tai	9.7	9.3	9.2	T ₁₃ Taa	9.0	8.7	8.6
TSs				TSs			
C ₁₃ H1	12.2	11.5	11.6	T ₁₃ H1	10.9	10.9	10.5
C ₁₃ H2	14.5	13.4	13.7	T ₁₃ H2	11.8	11.7	11.3
C ₁₃ B3	8.5	7.8	8.1	T ₁₃ B3	5.8	5.8	5.8
C ₁₃ B4	11.6	10.6	11.1	T ₁₃ B4	7.1	6.8	6.8
C ₁₃ B5	8.3	7.3	8.1	T ₁₃ B5	10.4	10.1	10.0
C ₁₃ B6	11.3	10.0	11.3				

According to the preceding studies^{6,7,31,32,38,42}, the conformational equilibria, equilibrium constant, and ratio of axial/equatorial or cis/trans-isomers for substituted cyclohexanes are concentrated on, which could gain the detailed information insight to fully evaluate the conformers' contribution to entropy and partition

function, and their significant role in reaction mechanism. Therefore, with regarding to zero-point inclusive energies from CCSD(T)/6-311++G(d,p)//B3LYP/6-311++G(d,p) method listed in Table 1, this work applied to Boltzmann distribution to calculate the temperature-dependent population of distinct conformers for cis- and trans-stereoisomers for 1,3-DMCH in a temperature range of 300-2500 K. As presented in Fig. 4, $C_{13}Cee$ and $T_{13}Cea$, severing as the global energy minima, overwhelmingly dominate the conformational populations for cis- and trans-isomers over the studies temperatures, respectively. Since the thermal distribution highly depends on the relative energies of various conformers, $C_{13}Cee$ has larger contents than $T_{13}Cea$ under the same condition. One noticed that the fraction of $C_{13}Cee$ is 99.2% at 500 K, and thus becomes 70.6% at 1500 K and 50% at 2500 K, whereas one for $T_{13}Cea$ is 97.5% at 500 K, and then decreases to 61.6% at 1500 K and 44.1% at 2500 K. These downward trends bring into correspondence with ones reported for ECH, 1,2-DMCH, and their radicals in both cis- and trans-configurations.^{6,7,35} However, twist-boats with the higher energies demonstrate the opposition changing trends in their proportions. They become more important in thermodynamics at high temperature end. It is of particular interest to point out that twist-boat conformers even play a more essential role in some structure-dependent chemical reactions than chairs to some extent, as suggested by the prior articles studying the combustion properties of cycloalkanes.^{2,6,7}

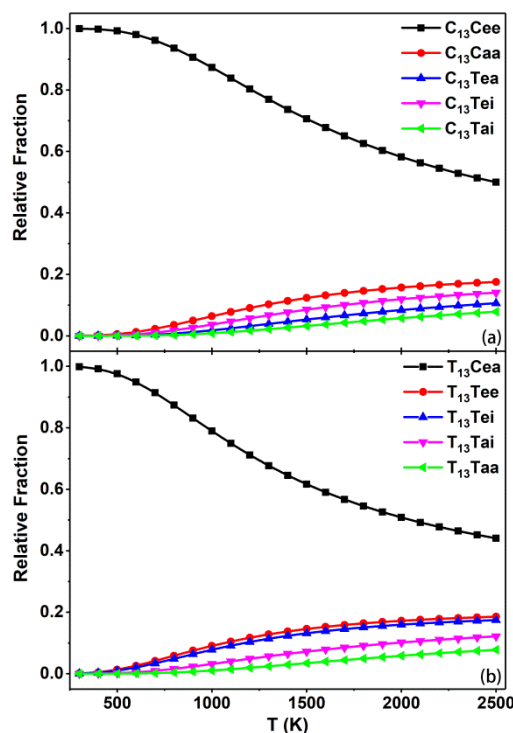


Figure 4. Boltzmann distribution of various conformers for (a) cis- and (b) trans-1,3-dimethylcyclohexanes over

3.1.2 Cis- and trans-1,4-dimethylcyclohexanes

As the stereoisomers of 1,2-DMCH and 1,3-DMCH, 1,4-DMCH in cis- and trans-configurations have three and four stable conformers with two methyl groups situated in para-positions, respectively, as demonstrated in Fig. 5. The numbers of these conformers in both cis- and trans-preferences are obvious less than the corresponding ones for 1,2-DMCH and 1,3-DMCH. According to the former discussions³⁵, the internal rotation in methyl group would not generate the distinguishable conformers, and the same phenomenon is also found for these rotation modes retained in 1,4-DMCH displayed in Fig. 6. So thus, the formations of different conformers for 1,4-DMCH are also attributed to the pseudorotation in cyclic ring and particularly for the special orientations of two methyl groups. It agrees well with the conclusions for 1,2-DMCH and 1,3-DMCH. Note that the cyclohexane ring in chair form has D_{3d} symmetry, and it individually situates two methyl groups within its symmetry plane to yield cis-conformer ($C_{14}Cea$) with C_s symmetry and trans-conformers ($T_{14}Cee$ and $T_{14}Caa$) with C_{2h} symmetry due to two identical side chains. As for twist-boats, $C_{14}Tee$, $C_{14}Tii$, and $T_{14}Tii$ are all the C_2 symmetrical molecules, while $T_{14}Tea$ has non-symmetry (i.e. C_1) facilitated by two methyl groups separately occupying pseudo-equatorial and pseudo-axial positions. One thing should be mentioned that there are only two twist-boats (i.e. $C_{14}Tee$ and $C_{14}Tii$) in cis-configuration, and one twist-boat ($C_{14}Taa$) with both two methyl groups in pseudo-axial positions cannot stable exist. The reason could be explained by the fact that the high repulsion energy raised by two pseudo-axial side chains is more likely to induce the distortion of cyclic ring to convert to $C_{14}Tee$ or $C_{14}Tii$.

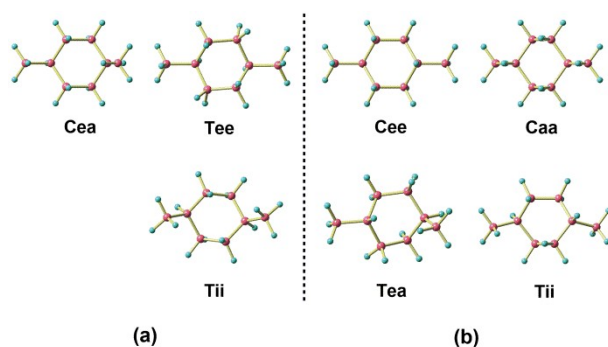


Figure 5. Steric structures for diverse conformers in (a) cis- and (b) trans-1,4-dimethylcyclohexanes obtained at B3LYP/6-311++g(d,p) level.

Table 2 presents the relative energies of various conformers for 1,4-DMCH, which are separately referred to the most stable conformers C₁₄Cea and T₁₄Cee obtained from three quantum chemical methods. It can be noticeably observed that the variation tendencies in these energies for conformers generally demonstrate a consistent association with the quantum results for ECH, 1,2-DMCH and 1,3-DMCH.³⁵ That is, chair conformers in cis- or trans-configuration certainly have the lower energies than the related twist-boats because of their more stable structural preferences, as shown in Table 2. Furthermore, these twist-boats would give rise to the larger hindrance force for the rotations in methyl groups by compared to ones involved in chairs, as depicted in Fig. 6. Among five types of side chains, the axial and pseudo-axial ones have the lower rotation barriers than others, which demonstrates the very similar behaviors to the findings in those for 1,3-DMCH. Taking the influence of the axial methyl group into account, T₁₄Caa has 3.8 kcal/mol higher energy than T₁₄Cee. It can be also found that the energy of T₁₄Tea is slightly larger than that of T₁₄Tii. These phenomena may be mainly ascribed to the presence of pseudo-axial side chain. Moreover, one can notice that C₁₄Tee is more stable than C₁₄Tii, since the pseudo-equatorial position is more available for substituents occupying. Of particular interest is to find that the energy deviations (0-4.9 kcal/mol) among three conformers for cis-1,4-DMCH are comparatively smaller than the related ones (0-7.9 and 0-9.2 kcal/mol) within those respective for cis-1,2-DMCH and cis-1,3-DMCH. And the same situation happens to distinct conformers for trans-1,4-DMCH that their energy disparities are slightly more modest with a range of 0-8.1 kcal/mol. These phenomena are reasonable to conclude that the para-position in cyclic ring is more favorable to locate two methyl groups by direct comparison with ortho- and meta-positions.

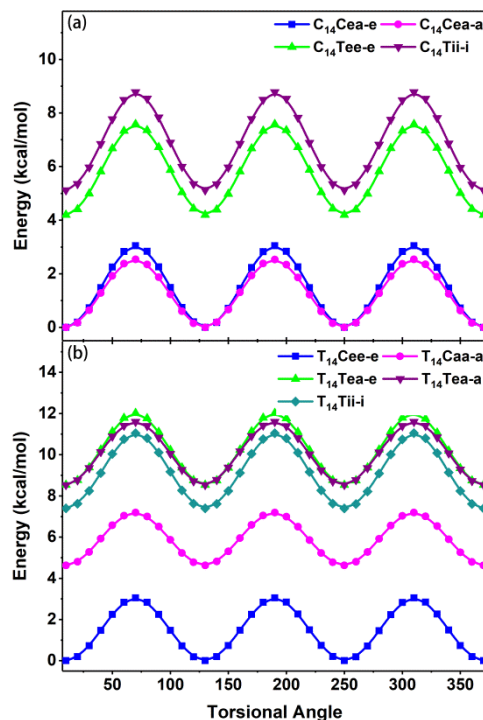


Figure 6. Potential energy changes for the internal rotations of methyl groups that separately occupy axial, equatorial, or isoclinal position in distinct conformers for (a) cis- and (b) trans-1,4-dimethylcyclohexanes by MP2/6-311++G(d,p) method.

Table 2. Relative energies of various conformers in cis- and trans-1,4-dimethylcyclohexanes at 0 K in kcal/mol by MP2/6-311++G(d,p)//B3LYP/6-311++G(d,p), CCSD(T)/6-311++G(d,p)//B3LYP/6-311++G(d,p), and G4 methods, respectively. Energies are relative to most stable conformers for C₁₄Cea and T₁₄Cee, respectively.

Species	MP2	G4	CCSD(T)	Species	MP2	G4	CCSD(T)
Cis-conformers (C ₁₄)				Trans-conformers (T ₁₄)			
C ₁₄ Cea	0	0	0	T ₁₄ Cee	0	0	0
C ₁₄ Tee	4.5	4.6	4.4	T ₁₄ Caa	4.2	3.9	3.8
C ₁₄ Tii	5.0	5.0	4.9	T ₁₄ Tea	8.4	8.3	8.1
TSs				T ₁₄ Tii	7.1	7.0	6.9
C ₁₄ H1	11.0	11.0	10.6	TSs			
C ₁₄ B2	5.5	5.6	5.6	T ₁₄ H1	12.9	12.7	12.2
C ₁₄ B3	6.4	6.3	6.2	T ₁₄ H2	14.1	13.9	13.4
				T ₁₄ B3	11.1	10.9	10.8
				T ₁₄ B4	9.2	8.9	8.8

Considering the significant role of conformational structure in thermodynamics, the conformational populations of three and four stable conformers for cis- and trans-stereoisomers in 1,4-DMCH are obtained by applying Boltzmann distribution. As displayed in Fig. 7, the global energy minima C₁₄Cea and T₁₄Cee are

respective the most abundant components within 300-2500 K. With the temperature increasing, they exhibit the similar decreasing trends in their contents. Note that the proportion for C₁₄Cea (T₁₄Cee) is lowered from 98.1% (97.7%) at 500 K to 70.3% (69.2%) at 1500 K, and 56% (52.3%) at 2500 K. However, the other conformers in cis- or trans-configuration remain on the upward tendencies in proportions over the studied temperature range. Among them, the other chair T₁₄Caa especially has a sharp increasing in population and its content is roughly 20% at 1500 K shown in Fig. 7(b), which is in line with ones for T₁₂Caa.³⁵ For four dimethylcyclohexanes studied in this work, the most stable chairs reveal the very similar conformational behaviors in reducing contents, and the total proportions of the other conformers can fairly compare to those for global minima at high temperature end. It indicates that the conformers with higher energies make a greater contribution to thermodynamics in terms of entropy and partition function. Additionally, this conclusion is also supported by quantum chemical results for 1,2-DMCH in cis- and trans-forms.³⁵

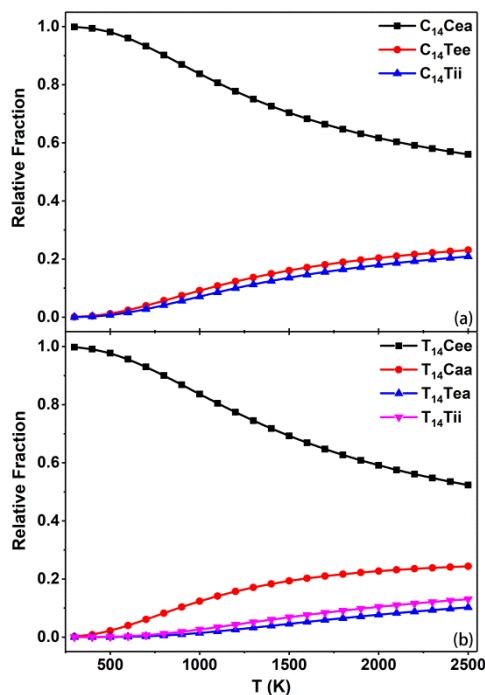


Figure 7. Boltzmann distribution of conformers for (a) cis- and (b) trans-1,4-dimethylcyclohexanes over 300-2500 K.

3.2 Inversion-topomerization process

3.2.1 Cis-1,3-dimethylcyclohexane

Fig. 8 gives a rigorous description of conformational inversion and topomerization pathways for cis-1,3-DMCH, of which the discussion would be conducted upon two stable chairs (Cee and Caa). Note that they

locate two methyl groups at same equatorial or axial positions in cyclic ring with D_{3d} symmetry, leading to them having C_s symmetrical structures. For Cee, when the $-CH_2-$ moiety marked by C4 on symmetry plane goes up to the plane formed by C2, C3, C5, and C6, as indicated in Fig. 1, it would proceed the first conversion step to generate half-chair transition state H1 with C_s symmetry and a 11.1 kcal/mol barrier, and thereby produce twist-boat Tei and its enantiomer Tei^E. H1 is identified by solely one imaginary frequency - 214.38 cm^{-1} that maintain C4 group upward and downward the mentioned quasi-planar, as provide in *Supplemental Material*. For the other beginning for inversion, the C3 or C5 moiety in Caa goes up to the quasi-planar characterized by C2, C4, C5, and C8 (or C3, C4, C6, and C8), resulting in the formations of two specular symmetric isomers H2 and H2^E that have the higher barrier (i.e. 13.7 kcal/mol) and -155.03 cm^{-1} imaginary frequency. H2 and H2^E transitions states individually serve to connect Caa to Tea and Tea^E. Note that, compared with the half-chair transition states retained in cis- and trans-1,2-DMCH³⁵, H2 and H2^E have the largest activation energies that could result from high steric repulsion. Such interaction force is facilitated by their two methyl groups occupying the quasi-axial positions on same side of cyclic ring.

Figure 8. Conformational inversion-topomerization process of cis-1,3-dimethylcyclohexane. Zero-point-inclusive

energies of various conformers and transition states are relative to Cee at 0 K in kcal/mol at

$$\text{CCSD(T)/6-311++G(d,p)//B3LYP/6-311++G(d,p)}.$$

Moreover, boat transition state B3 is to accomplish the conversion between Tea and Tei. During this process, the pseudo-axial side chain in Tea relocates at isoclinal position to form Tei. The other pseudo-equatorial methyl group in Tea also can transfer to the isoclinal one, and thus generate Tai conformer by going through B4 transition state. It is of great interesting to point out such topomerization that allows two side chains to alter the relative positions has a complete mirror conformational process, i.e. $\text{Tei}^{\text{E}}\text{-B3}^{\text{E}}\text{-Tea}^{\text{E}}\text{-B4}^{\text{E}}\text{-Tai}^{\text{E}}$. These two pathways can establish a topomerization circuit, i.e. $\text{Tei-B3-Tea-B4-Tai-B6-Tai}^{\text{E}}\text{-B4}^{\text{E}}\text{-Tea}^{\text{E}}\text{-B3}^{\text{E}}\text{-Tei}^{\text{E}}\text{-B5-Tei}$, contributed by transition states B5 and B6 with Cs symmetry. This phenomenon exhibits the same conformational behavior to cis-1,2-DMCH.³⁵ For four diacritical boats, B3 and B5 have 8.1 kcal/mol barrier heights that are smaller than B4 and B6 separately having 11.1 and 11.3 kcal/mol. This is caused by the higher repulsion interaction between side chains in B4 and B6. And their imaginary frequencies vary within -50.173 to -79.10 cm^{-1} given in *Supplement Material*. Seen from Fig. 8 and *Supplemental Material*, the energies and imaginary frequencies for boats are still lower than these for half-chairs H1 and H2. It implies that the inversion pathways for cis-1,3-DMCH dominate the whole conformation process, which brings into correspondence with the former results for substituted cyclohexanes.^{8,33,35} Differing from the multistep inversion processes for MCH⁸ and ECH³⁵, this studied process briefly includes two steps accomplished by B3 transition state, and follows the sequence Cee-H1-Tei-B3-Tea-H2-Caa. In addition, the group triggers such conformation reaction is $-\text{CH}_2-$ moiety labeled by C3, C4, and C5 for cis-1,3-DMCH in current work, not $-\text{CH}-$ moiety occupied by side chain in MCH⁸, ECH³⁵, and 1,2-DMCH in cis- and trans-configurations³⁵. One thing should be mentioned that two mirror processes existing in both inversion and topomerization are attributed to Cs symmetrical structures for Cee, Caa, H1, B5, and B6 presented in Fig. 8 and Supplemental Material.

3.2.2 Trans-1,3-dimethylcyclohexane

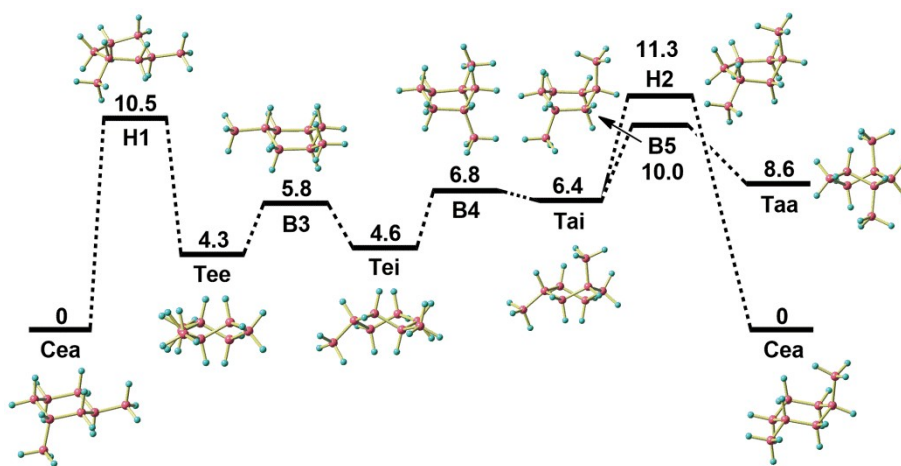


Figure 9. Conformational inversion-topomerization process of trans-1,3-dimethylcyclohexane. Zero-point-inclusive energies of various conformers and transition states are relative to Ce at 0 K in kcal/mol at CCSD(T)/6-311++G(d,p)//B3LYP/6-311++G(d,p).

Trans-1,3-DMCH has two meta methyl groups separately located on two opposite sides of six-membered ring, leading to the entirely different conformational behavior from that for its cis-isomer. As depicted in Fig. 9, it can be noticeably observed that there is no the topomerization circuit and mirror conformational changing process. Moreover, the whole inversion pathway for trans-1,3-DMCH is to achieve the ring flip between Cea itself. Thus, the conformational discussion would start with Cea according to potential energy surface illustrated in two-dimensional scheme in Fig. 9. As shown in Fig. 1(b), when $-\text{CH}_2-$ moiety indicated with C5 in Cea goes down to the quasi-planar formed by C3, C4, C6, and C8, the half-chair transition state H1 is generated with a 10.5 kcal/mol barrier and -150.53 cm^{-1} imaginary frequency. Afterwards, the C5 moiety in H1 continues to go further below the planar aforementioned, H1 will transform into Tee with C_2 symmetry. Moreover, C3 moiety in Cea changes its relative spatial position into the plane formed by C4, C5, C8, and C2, resulting in the formation of H2 with 11.3 kcal/mol energy and -192.71 cm^{-1} imaginary frequency. Its energy release would subsequently yield twist-boat Tai. The transformation between Tee and Tai must undergo two-steps topomerization reactions (i.e. Tee-B3-Tei-B4-Tai), which can properly connect the above two inversion routes, as clearly presented in Fig. 9.

As for the topomerization routes for trans-1,3-DMCH, there are four stable twist-boats to exchange their side chains among three specific pseudo-equatorial, pseudo-axial, and isoclinal orientations through three boat transition states. As displayed in Fig. 9, Tee transfers to Tei via B3, during which one pseudo-equatorial side

chain in Tee becomes the isoclinal one in Tei. Afterwards, the pseudo-equatorial and isoclinal groups in Tei would correspondingly change to the isoclinal and pseudo-axial ones in Tai by going through B4 transition state, respectively. Furthermore, Tai can convert to Taa via B5, of which the isoclinal side chain alters its location in pseudo-axial position. Of particular interest is to mention that methyl group, moving along the frame of twist boat ring to alter the relative position, must adhere to the principle: pseudo-equatorial \leftrightarrow isoclinal \leftrightarrow pseudo-axial. This demonstrates the pseudo-equatorial side chain cannot directly change to pseudo-axial one. Consequently, the inversion and topomerization pathways for trans-1,3-DMCH follow the sequences: Cea-H1-Tee-B3-Tei-B4-Tai-H2-Cea and Tee-B3-Tei-B4-Tai-B5-Taa. Proposed by Fernández-Alonso et al.⁸, the inversion and topomerization are two unique and independent processes, even when some twist-boats serve as the common intermediates involved in both conformational events. The findings for conformational behavior of trans-1,3-DMCH revealed herein dovetails with this former conclusion. Additionally, in line with the prior results^{8,33,35}, half-chairs H1 and H2 have the higher energies and larger imaginary frequencies than those with 4.3-10.0 kcal/mol and -60.40 to -80.67 cm⁻¹ for boats. Among half chairs or boats, the ones, dissipating their energies to transform into stable conformers with the higher energies, have the larger activation energies. One can notice that B5, connecting to Tai and Taa, has the largest barrier height in comparisons with B3 and B4.

3.2.3 Cis-1,4-dimethylcyclohexane

Cis-1,4-DMCH situates two methyl groups in para-position on same side of cyclohexane ring, of which the conformational inversion-topomerization mechanism is given with two-dimensional scheme in Fig. 10. It has four identifiable energy maximum structures (i.e. one half-chair and three boats) and five distinct energy minimum structures (i.e. one chair and four twist-boats) are determined on its conformational potential energy surface. Among them, one thing should be mentioned that there are two and one pairs of specular isomers figured out for stable and transition state conformers, respectively. Same to cis- and trans-stereoisomers in 1,3-DMCH studied above, the whole conformational path for cis-1,4-DMCH should be explored with the global energy minimum (i.e. Cea) with Cs symmetry. With regard to the numbering scheme in Fig. 1(c), when the axial methyl group promotes its occupying -CH- moiety (signed by C5) into the plane by C3, C4, C7, and C8, giving rise to the generation of H1 with 10.6 kcal/mol and Cs symmetry. And H1 releases its energy to

convert to twist-boat conformers Tee and Tee^E. The vibration mode of C5 group in H1 is featured by -129.72 cm⁻¹ imaginary frequency, of which the detailed information is provided in *Supplemental Material*.

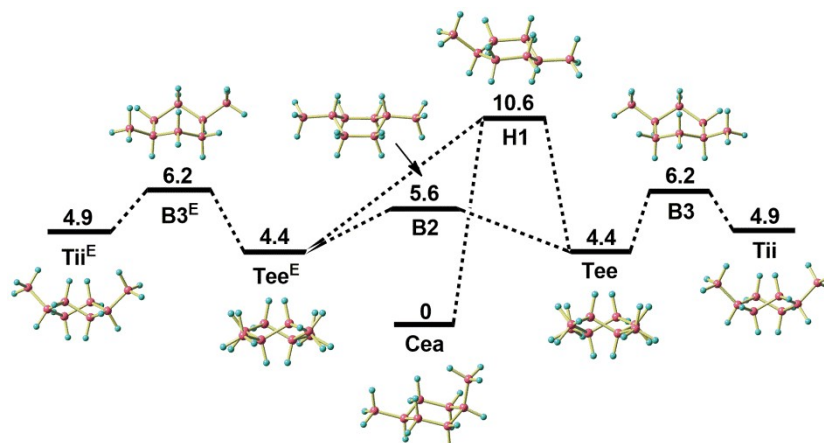


Figure 10. Conformational inversion-topomerization process of cis-1,4-dimethylcyclohexane. Zero-point-inclusive energies of various conformers and transition states are relative to Cea at 0 K in kcal/mol at CCSD(T)/6-311++G(d,p)//B3LYP/6-311++G(d,p).

Subsequently, Tee will carry on topomerization to yield twist-boat Tii via a boat B3, which has a 6.2 kcal/mol energy barrier and -61.25 cm⁻¹ imaginary frequency. Same to cis-1,3-DMCH, there exists a mirror process for this described topomerization route that is Tee^E-B3^E-Tii^E. Boat transition state B2 is responsible for the connection of these two paths. Note that B2 has D_{2h} symmetry for two methyl groups maintaining a cis-type relationship on boat structure, and it has 5.6 kcal/mol energy barrier and -103.09 cm⁻¹ imaginary frequency. Accordingly, with a view to the overall situation, the whole inversion-topomerization process for cis-1,4-DMCH could be reasonable simplified as Cea-H1-Tee-B3-Tii, which includes one inversion and one topomerization in brief. One thing should be pointed out that, same to Tee and Tii aforementioned, B3 also happens with the C₂ symmetry that is contributed by the para methyl groups in boat ring with C_{2v} symmetry.

3.2.4 Trans-1,4-dimethylcyclohexane

Compared with cis-1,4-DMCH, the trans-isomer is to locate two methyl group on opposite sides of cyclic ring, which certainly has the quite different conformational paths. Trans-1,4-DMCH has two stable chairs, i.e. Cee and Caa, with C_{2h} symmetry that are considered as the original structures for inversion pathways. Thereby, on base of two-dimensional potential energy surface illustrated in Fig. 11, the detailed explication on its inversion-topomerization mechanism is expanded by regarding them. For Cee, due to its C_{2h} symmetrical

structure shown in Fig. 1(d), no matter C3, C4, C7, or C8 intends to go the other side of cyclic ring, the half-chair H1 with C_2 symmetry would be formed with a 12.2 kcal/mol energy and -193.46 cm^{-1} imaginary frequency. Moreover, H1 connects to Tii by dissipating energy remaining in ring structure. As for Caa, the C2 or C5 moiety with methyl group situated alters its relative position into the plane comprised by C3, C4, C7, and C8, bringing into generation of H2 with C_s symmetry. And H2 can further transform into a pair of enantiomers Tea and Tea^E. Note that H2 has a slight higher energy (i.e. 13.4 kcal/mol) than H1, and it is identified by a -193.46 cm^{-1} imaginary frequency, as listed in *Supplemental Material*.

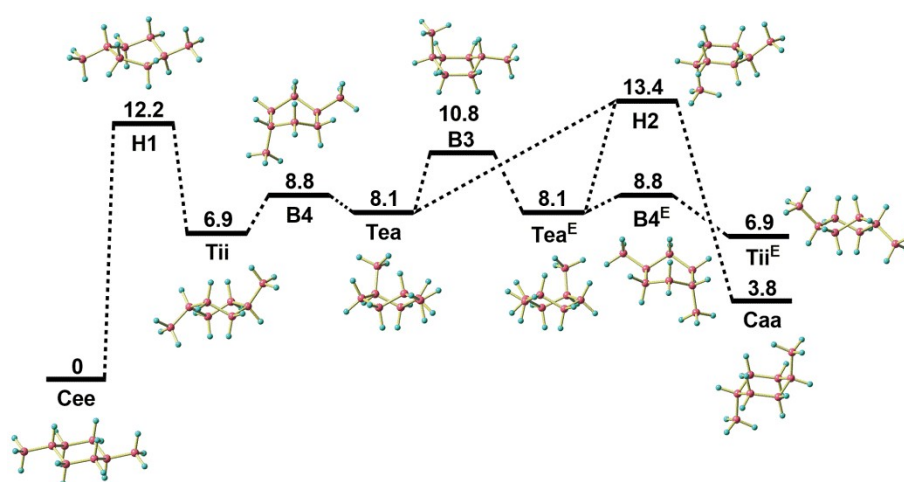


Figure 11. Conformational inversion-topomerization process of trans-1,4-dimethylcyclohexane. Zero-point-inclusive energies of various conformers and transition states are relative to Cee at 0 K in kcal/mol at

$$\text{CCSD(T)/6-311++G(d,p)//B3LYP/6-311++G(d,p)}.$$

Furthermore, for twist-boats, two methyl groups can change their relative positions through boat transition states by proceeding topomerization. It is of great interest to reveal that there also exists two mirror processes among four twist-boats and three boats, i.e. Tii-B4-Tea-B3-Tea^E-B4^E-Tii^E. This phenomenon is extremely same to the quantum results for cis-1,4-DMCH. However, different from B2 for cis-1,4-DMCH, B3 for trans-one linking these two mirror processes has the higher activation energy than the other boats. It may result from that B3 is amenable to convert Tea and Tea^E with the particular pseudo-axial side chain. Moreover, regarding to conformational paths in Fig. 11, the inversion process can simply undergo the multiple steps, i.e. Cee-H1-Tii-B4-Tea-H2-Caa, to accomplish the ring flip between Cee and Caa. As a consequence, the quantum result for trans-1,4-DMCH are in keeping with the findings for three other dimethylcyclohexanes studied in this work. One can easily notice that the inversion reaction controls the

whole conformational mechanism, of which the half-chair transition states have the larger energies and imaginary frequencies than these boats, as evidently presented in Fig. 11 and *Supplemental Material*.

4. Conclusions

In summary, this current study gains insight into the conformational behaviors of 1,3-DMCH and 1,4-DMCH in both cis- and trans-configurations, and presents a global picture of their inversion-topomerization pathways in detail. The theory of B3LYP/6-311++G(d,p) method was utilized to carefully characterize all distinguishing molecular preferences for stationary points on conformational potential energy surfaces, and then three accurate quantum chemical methods were to refine the energies. With respect to quantum results, the temperature-dependent populations of diverse stable conformers for each dimethylcyclohexane were obtained by applying Boltzmann distribution, which was based on highly biased conformational equilibria among them. Subsequently, the inversion-topomerization mechanisms for four dimethylcyclohexanes were explicitly investigated to further uncover their conformational properties. Conformational analysis finds that the determination of various structures is primarily dominated by pseudorotation in cyclohexane ring and the relative locations of two methyl groups. For all conformers existing in one dimethylcyclohexane, chairs are generally more stable than twist-boats, and half-chairs linking chair to twist-boat have the higher energies than boats. This indicates that chairs make a greater contribution to thermodynamics because of their abundant components within 300-2500 K, and twist-boats become more important at high temperature end.

For chairs, the side chain prefers to situate in equatorial position rather than the axial one, and the location ranking of twist-boats that are in favour of side chain occupying is: pseudo-equatorial > isoclinal > pseudo-axial. Additionally, inversion is to accomplish the ring flip between chairs by passing through boat and twist-boat, and topomerization allows side chains altering their locations in twist-boat frame that follows the regularity: pseudo-equatorial \leftrightarrow isoclinal \leftrightarrow pseudo-axial. Furthermore, inversion dominates in whole conformational mechanism for cis- and trans-stereoisomers in 1,3-DMCH and 1,4-DMCH. One thing should be mentioned that although there exists some common characteristics in conformational behaviors of four dimethylcyclohexanes, the specific orientations of two methyl groups contribute to the significant differences in aspects of number, steric structures, and relative energies of conformers, and their inversion-topomerization paths. Note that only cis-1,3-DMCH has a topomerization circuit, and trans-1,3-DMCH is a special one

without the mirror topomerization process. Consequently, this work understanding of conformational behaviors for di-substituted cyclohexanes has involved the perspective from stereochemistry and organic chemistry, in particular for their practical applications in combustion chemistry. We feel that the findings and methods could be fruitfully applied to other systems with the similar structures, and strengthen the awareness of various conformational structures and analysis in determining rate coefficients and constructing the combustion kinetic modeling.

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Supplementary Material

Supplemental Material for the optimized geometries for cis- and trans-stereoisomers for 1,3-DMCH and 1,4-DMCH is provided.

