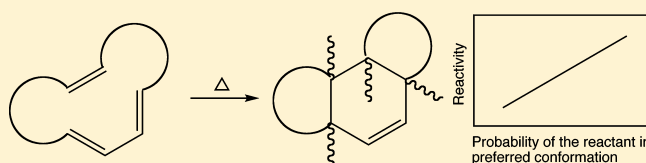# Transannular Diels−Alder Reactivities of 14-Membered Macrocylic Trienes and Their Relationship with the Conformational Preferences of the Reactants: A Combined Quantum Chemical and Molecular Dynamics Study

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S *Supporting Information*

ABSTRACT: Transannular Diels−Alder (TADA) reactions that occur between the diene and dienophile moieties located on a single macrocyclic triene molecule have been recognized as effective synthetic routes toward realizing complex tricyclic molecules in a single step. In this paper, we report a comprehensive study on the TADA reactions of 14-membered cyclic triene macrocycles to yield A.B.C[6.6.6] tricycles using quantum chemical methods and using classical molecular dynamics simulations. A benchmark study has been performed to examine the reliability of the commonly used ab initio methods and hybrid density functional levels of theory in comparison with results from CCSD(T) calculations to accurately model TADA reactions. The energy barriers obtained using the M06-2X functional were found to be in quantitative agreement with the CCSD(T) level of theory using a reasonably large basis set. Conformational properties of the reactants have been systematically studied using extensive molecular dynamics (MD) simulations. For this purpose, model systems were conceived, and force field parameters corresponding to the dihedral terms in the potential energy function were obtained. Linear relationship between the activation energies corresponding to the TADA reactions and the probability of finding the reactant in certain conformational states was obtained. A clustering method along with optimizations at the molecular mechanics and density functional M06-2X levels has been used to locate the most stable conformation of each of the trienes.

INTRODUCTION

The Diels−Alder reaction is considered to be one of the most effective methods in organic synthesis because of its wide applicability.[1−5] Transannular Diels−Alder (TADA) reactions occur in $(x + y + 2)$-membered triene macrocycles, which contain both the diene and the dienophile moieties, to form A.B.C$[x + 6 + y]$ type tricyclic compounds (Figure 1) having
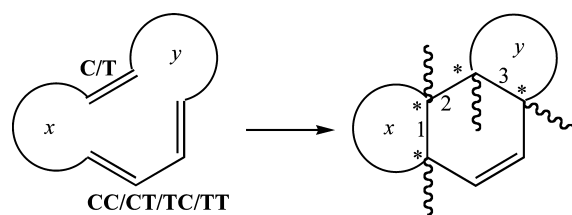

Figure 1. Schematic representation of a typical TADA reaction involving a $(x + y + 2)$-membered triene macrocycle yielding A.B.C[6.6.2] type tricyclic adduct. In the reactant, C and T refer to *cis* and *trans* configurations respectively. The chiral centers formed during the reaction are marked by * in the product.

four new stereogenic centers with a central double bond as first reported by Deslongchamps and co-workers.[1,6] TADA combines two most efficient chemical transformations in

synthetic organic chemistry, namely, Diels−Alder and intramolecular/transannular reactions.[1,6] Transannular reactions are energetically favorable because of the favorable entropic factor compared to reactions that occur between multiple species, and the Diels−Alder reactions are simple thermal reactions where the number of atoms is conserved during the process. During the TADA reactions, the sp[2] carbon atoms at the trienes are converted into four sp[3] carbon stereogenic centers at the site of cycloadduct formation.[7] Polycyclic structures with high degree of complexity and with varying degree of control of chemo-, regio-, and stereoselectivity at both the diastereo- and enantioselective levels have been synthesized using TADA reactions.[6,8−14] TADA reactions have been shown to usually occur with low activation energies especially when the formation of the *s-cisoid* form in the reactant is favored, because of the proximity of the diene and the dienophile moieties.[6] Also in a majority of the cases, the TADA reaction proceeds through endo transition states.[1] But by including a suitable conformational constraint, even an exo approach is favored.[15] Computational studies have played an instrumental role in understanding pericyclic reactions in general.[9,16−18]

Two different mechanisms were initially proposed for Diels–Alder reaction, namely, the concerted and stepwise pathways.[19−21] Stepwise pathway process proceeds via a diradical intermediate, while concerted pathway proceeds through a single transition state. Both DFT and ab initio calculations have been extensively used to study both these mechanisms.[22−28] The concerted pathway has been shown to be favored over the pathway involving a diradical intermediate in general. It has been shown that the level of theory employed and the quality of basis set used are critical for obtaining reliable results.[27−31] For example, Dinadayalane et al. have performed a systematic study on the Diels−Alder reactivity of butadiene and the cyclic five membered dienes with ethylene to examine the reliability of selected computational methods.[21]

During the past few years, total/biomimetic syntheses of several natural compounds, such as macquarimicins,[32] (−)-oblongolide,[6] (−)-spinosyn-A,[33] (+)-superstolide A,[8] and (+)-cassaine,[34] have been accomplished using the TADA reaction. While this approach seems powerful enough to be used seamlessly in the synthesis of stereochemically complex organic molecules, two primary issues curtail their synthetic utility.[13] First is the synthesis of the precursor triene macrocycle, and second is the difficulty in predicting and controlling the stereochemical course of the reaction.[6] The preparation of macrocyclic precursors has been addressed, and new synthetic methodologies have been proposed for the synthesis with relative ease. Methods like beta-ketoester alkylation,[35] Stille coupling,[36] and ring-contraction methodology[37] have been successfully used to macrocyclize **TTT** trienes (see Figure 1 for the nomenclature used). However, driving the TADA reactions toward a product with desirable stereochemistry is not straightforward. A recent study by Balskus and Jacobsen demonstrated the use of Lewis acid-based catalysis for asymmetric synthesis using TADA reactions.[38] A systematic study of this reaction to identify the structural and energetic determinants that influence the stereochemical course of the reaction is expected to further our understanding and, more importantly, to improve its synthetic utility in general. Dory and co-workers have studied TADA reactions in **CCC** and **TTC** systems using semiempirical AM1 and PM3 methods to explain their experimental results.[39] Out of all the possible configurations in the macrocyclic trienes, the **CCT** isomer was found not to undergo the TADA reaction because of its inefficiency in forming the boat conformation in its transition state in the central ring, which is considered to be one of the essential criteria for the TADA reaction to occur in macrocyclic trienes.[1]

In enzymatic and intramolecular reactions, the effect of proximity of the reacting moieties has been proposed to be crucial for their reactivities.[40,41] Bruice and co-workers have introduced the term "near attack conformation" to define the conformation of the reactant just necessary for it to enter into its transition state.[42] Menger and co-workers have proposed a spatial hypothesis that relates the distance between the reacting groups to the rate of the reaction.[43] They have carefully conceived several experiments to show that the spatiotemporal effect is highly relevant for intramolecular reactions. Koshland and co-workers have proposed the "orbital steering" theory, which emphasizes the importance of the overlap of the reactive cones of the two interacting orbitals along the reaction coordinates.[44] Here, we have examined the role of such spatiotemporal effects on the reactivities of the triene molecules.

In the present study, we have evaluated the performance of selected computational methods to accurately model the TADA reaction (Figure 2). Additionally, the TADA reactivities of all
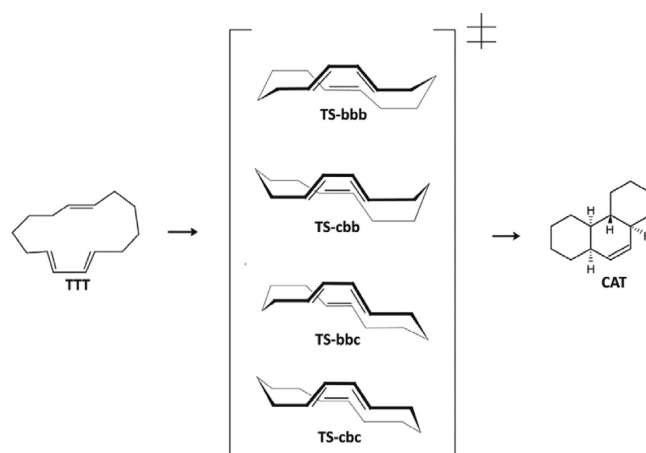

Figure 2. TADA reaction of the **TTT** triene macrocycle considered in this study. **TS**-cbc, **TS**-bbc, **TS**-cbb, and **TS**-bbb are the four possible conformationally different transition states during the reaction yielding the CAT tricyclic adduct.

possible (6 + 6 + 2)-membered macrocyclic trienes have been investigated. We attempt to find any correlation that exists between the geometric parameters of exclusively the reactants and their reactivities. Wolfe et al. have previously done conformational analysis using molecular mechanics and semi-empirical PM3 methods.[45] Molecular dynamics (MD) simulations are helpful in studying conformational properties of chemical and biological molecules in general.[46] In particular, replica exchange MD (REMD) simulation is the technique of choice for such studies since the sampling of conformational space of a given molecule is more efficient even with short time scale simulations.[47] The accuracy of the results obtained using MD simulations in general rely on the quality of the force field used.[48] In the present study, we have used the available CHARMM force field parameters optimized for alkanes and alkenes.[49] In addition, the torsion parameters have been validated in the context of the molecular systems under study using quantum mechanical calculations. Using this parameter set, we have employed several 1 μs long traditional MD and REMD simulations to investigate the conformational properties of six possible unsubstituted 14-membered macrocyclic triene molecules and obtained relationships between their conformational properties and TADA reactivities. Along with MD simulations, we also have employed density functional theory M06-2X method to identify several conformations of the reactants.

■ COMPUTATIONAL DETAILS

Quantum Chemical Calculations. The reactant, transition states and the product shown in Figure 2 were initially optimized at the ab initio MP2 and density functional theory (B3LYP,[50] M06,[51] and M06-2X[51]) levels using the 6-311G(d,p) basis set, and the nature of the stationary points were characterized using frequency calculations performed at each of these levels. The transition states studied here correspond to the concerted pathway of the Diels−Alder reaction, and it has been shown that the single determinant wave function-based methods model these transition states adequately.[31b] Additionally, single point energy calculations were performed at the MP3, MP4, CCSD, and CCSD(T) levels of theory using the 6-311G(d,p) basis set. For the single point energy calculations, B3LYP/6-311G(d,p) optimized structures were used. Further calculations on the modeling of all the reactions shown in Figure 3 were performed at the M06-2X level using the 6-311G(d,p) basis set. The relative energies reported for the species given in Figure 3 were calculated on the basis of the
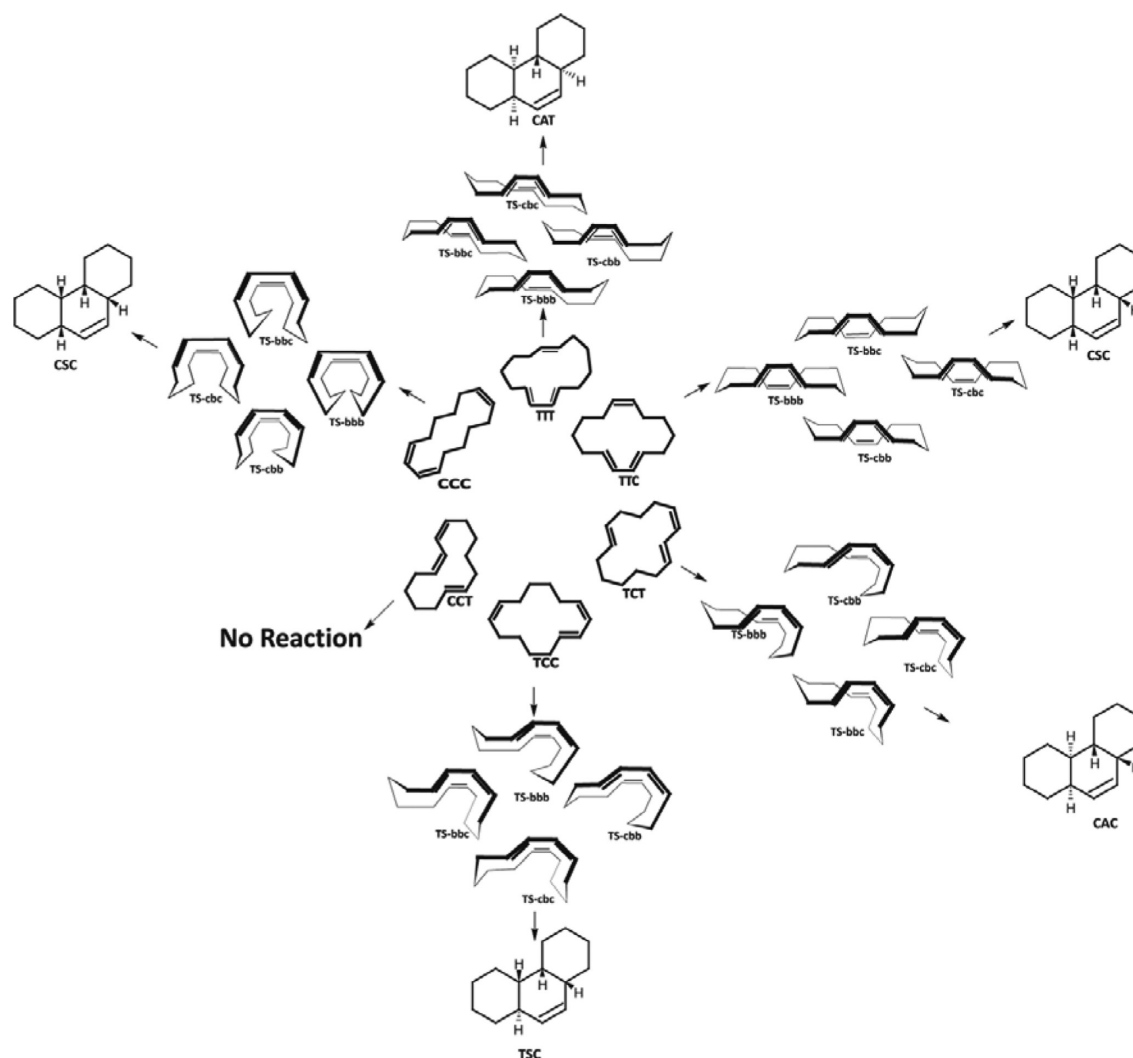
Figure 3. TADA reaction of all possible 14-membered triene macrocycles considered in this study. **TS-cbc**, **TS-bbc**, **TS-cbb**, and **TS-bbb** are the four conformationally different transition states during the reaction yielding the respective tricyclic adducts. No transition state could be located for the reaction of **CCT**.

zero point energy corrected electronic energies obtained at the M06-2X level. The root-mean-square deviation calculations to compare the change in geometries with respect to the level of theory used were performed using the analysis tools available in the VMD program.[52] All the ab initio and density functional theory calculations reported in the paper were performed using the Gaussian 03 and 09 programs.[53]

Force Field Parametrization. CHARMM all atom force field was used for the MD simulations.[54−56] In addition, we have obtained parameters for the dihedral terms in the potential energy function (see eq 1 in the Supporting Information) to accurately represent the macrocyclic trienes considered here. Quantum mechanical calculations related to force field parametrization were performed at the MP2 level using the 6-31G(d) basis set in conformity with previously published protocol.[54−56] After initial optimization of the model systems at the MP2/6-31G(d) level, potential energy curves corresponding to the rotation about the central bond in the model systems were obtained at the same level of theory. These were then used as the target data for further parameter optimization (see the Supporting Information for more details) for the dihedral terms.[54−56]

Molecular Dynamics Simulations. The molecular mechanics optimizations and MD simulations were performed using the CHARMM program.[57] The structures of the six macrocyclic trienes given in Figure 3 were obtained from optimizations at the MP2/6-31G(d) level, which

were then ported into the CHARMM program. The molecules were treated using the new dihedral parameters, along with the original bonded and nonbonded parameters (eq 1, Supporting Information). Initially the molecules were subjected to a 100-step adopted-basis Newton−Raphson (ABNR) optimization. This was followed by 1 μs long MD simulations using the Langevin dynamics[58,59] with a friction coefficient of 50 ps⁻¹. All the simulations were performed with infinite cutoff for the explicit calculation of nonbonded interactions, and the covalent bonds involving hydrogen atoms were constrained using the SHAKE algorithm.[60] Integration of 2 fs was used, and coordinates were saved every 10 ps, which were then used for analysis. Followed by the traditional MD simulations, all the six molecules were simulated using the replica exchange MD (REMD) simulations with eight replicas between 300 and 370 K. Exchange of replicas was attempted after every 100 integration time steps, and analysis was done on the trajectories obtained at 300 K. The MD simulation protocol used was the same as that used for the traditional MD simulations as given above. The probability distributions were obtained with a bin size of 0.2 Å for the lengths and 5° for the dihedral angles using python scripts, which were written in our lab. Unique conformations present in the trajectories obtained from REMD simulations were based on a clustering mechanism (see the Supporting Information).

Table 1. Relative Energies (kcal/mol) of the Transition States and the Product with Respect to the TTT Triene Reactant Obtained at Different Levels of Theory Using the 6-311G(d,p) Basis Set

	MP2	MP3	MP4 SDTQ	CCSD	CCSD(T)	B3LYP	M06	M06-2X
TTT	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
TS-cbc	6.3	21.0	11.9	21.5	16.1	19.5	16.6	16.5
TS-cbb	8.8	24.2	14.8	24.8	19.1	23.0	20.1	19.6
TS-bbc	9.1	24.4	15.0	24.9	19.3	22.6	20.3	20.0
TS-bbb	13.1	28.8	18.7	29.3	23.5	27.3	24.7	24.3
product-**CAT**	−53.0	−49.3	−49.7	−48.7	−48.3	−34.5	−45.2	−45.4

■ RESULTS AND DISCUSSION

Validation of Methods. The adequacy of various methods to quantitatively study TADA reactions was carried out by modeling the TADA reaction of **TTT** molecule, which yields the **CAT** tricycle as the product (Figure 2). Four conformationally different transition states that contain three six-membered rings are possible for this reaction. The central six-membered ring is in the boat form in all the four conformations since it is an essential geometric requirement for the Diels−Alder reaction to take place via the concerted pathway. Two other six-membered rings on either side may adopt a chair or boat form leading to four conformationally different transition states (Figure 2). The energies of the reactant, transition states, and the product corresponding to the TADA reaction of **TTT** (Figure 2) obtained at different levels of theory are tabulated below (Table 1). The data is pictorially represented as a graph and is given in the Supporting Information (Figure S1). The qualitative trends of the relative energies of the four transition states obtained at the various levels of theory are similar. However, magnitudes of the energy barriers vary quite significantly with respect to the wide range of methods used. This further demonstrates the importance of a validation study to recognize the reliability of the theoretical methodologies in modeling TADA reactions. Coupled cluster CCSD(T) method is the highest level of theory that is adopted in this study, and the energy barriers obtained using this are expected to be reliable.[18,61,62] Since it is not practical to perform CCSD(T) calculations on a regular basis on systems of this size, it is important to identify a method that is computationally less demanding, which can reproduce the CCSD(T) results. In the absence of experimental data on the energy barriers, the results from CCSD(T) were taken as the reference. Surprisingly, the MP2 method, which includes electron correlation, underestimates the reaction barriers substantially with respect to the energies obtained at the CCSD(T) level. Such a shortcoming of the MP2 level of theory trend has been observed before in conventional Diels−Alder reactions involving butadiene and other five-membered dienes with ethylene.[15,21,63] It has also been shown that MPx methods where $x > 2$ are essential for obtaining reasonable energy barriers of Diels−Alder reactions.[21,64−66] Single point calculations at the MP3 and MP4 (SDTQ) levels were performed to examine the change in energy barriers. Though not ideal, a marked improvement over the energy barriers is seen while going from MP2 to MP3 method. The energy barriers at MP4/SDTQ level are much lower compared to the CCSD(T) values. Remarkably, excellent agreement is observed between the transition state energies obtained at the M06-2X level, which utilizes only a fraction of the computational time, compared to the CCSD(T) calculation. The maximum difference between the energies obtained using these two levels is only 0.8 kcal/mol. Given that the transition state energies are the most
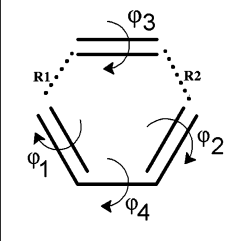
crucial determinants that control the outcome of the reaction, reactivity predictions of this class of reactions based on M06-2X calculations are deemed adequate. Reasonable agreement was observed between CCSD(T), and B3LYP and M06 levels of theory as well. Such a large dependence of the barrier heights with respect to the level of theory used may point to multireference nature of the wave function. The reaction energy (relative energy of the product, **CAT**) seems to be less dependent on the level of theory used (Table 1). Unlike the activation energies data, which is widely scattered with respect to the level of theory used, the reaction energies span a narrow range, and are less dependent on the level of theory used. The above observations indicate that M06-2X level is adequate enough for capturing the TADA reactivities quantitatively. The geometries obtained using the different levels of theory were compared by calculating pairwise root-mean-square deviations (Table S2 in the Supporting Information). The geometric parameters were found to be very similar with respect to the method used.

Relative Stabilities and TADA Reactivities of 14-Membered Macrocyclic Trienes. In this section, TADA reactivity of six different geometric isomers of the (6 + 6 + 2)-membered macrocycles, namely, **TTT**, **TTC**, **TCT**, **TCC**, **CCT**, and **CCC**, and their relative stabilities are discussed (see Figure 3). The reactant molecules are inherently flexible because of the presence of 11 rotatable bonds. We have performed replica exchange molecular dynamics simulations to identify all possible conformers of the reactants (see below). All unique conformers thus identified were then subjected to geometry optimization at the M06-2X/6-311G(d,p) level. The most stable conformations among the several conformers identified are presented here (Table 2).

Among the six reactant geometries, **TCT** isomer is the most stable, whereas **TTT** is the least stable isomer with a difference of about 5 kcal/mol as shown in Table 2. Molecules containing diene with two *trans*- or *cis*- moieties (**TTT**, **TTC**, **CCC**, and **CCT**) are less stable compared to those containing one *cis*- and one *trans*- double bonds in the diene (**TCT** and **TCC**). The sp^2 carbon centers of the diene part of the **TT** isomers substantially deviate from the planarity with respect to their connected atoms (Table 2). In the most stable conformers of **TTT** and **TTC**, dihedral angles φ_1 and φ_2 deviate from planarity by up to 20°. In all the other four isomers, the deviations of planarity of these sp^2 centers are negligible or marginal. In general, *s-cisoid* ($\varphi_4 = 0$) and *s-trans* ($\varphi_4 = 180°$) are expected to be more stable than the other conformations of a conjugated diene because of the stability contribution due to π-electron delocalization. The φ_4 dihedral angles in the CC isomers (**CCC** and **CCT**) indicate considerable deviation from planarity, which exhibit the inability of these isomers to form *s-cis* or *s-trans* conformation due to possible steric clashes. Such a distortion of the delocalization seems to make these two isomers less stable

Table 2. Relative Stabilities (ΔE) of the Trienes with Respect to the Most Stable TCT Triene along with the Dihedral Angles at the Diene and the Dienophile for All the Trienes at the M06-2X Level of Theory Using 6-311G(d,p) Basis Set

	ΔE	$\varphi 1$	$\varphi 2$	$\varphi 3$	$\varphi 4$
TTT	5.2	-165.8	-165.6	172.0	168.1
TTC	3.8	-164.1	-164.1	-0.4	161.4
TCT	0.0	179.1	-1.1	-177.6	179.7
TCC	0.2	-176.3	-1.4	-0.6	171.1
CCT	2.9	5.7	5.7	175.8	-148.3
CCC	1.2	-5.6	-5.6	2.9	156.8

than **TCT** and **TCC**. Within the same combination of *cis*- and *trans*- components in the diene part, *cis*- form is preferred over the *trans*- for the dienophile. For example, **TTC** is more stable than **TTT** isomer by about 1.5 kcal/mol. However, relative stabilities of the isomers **TCT** and **TCC** are comparable.

The relative energies of the transition states and the products with respect to the reactant geometries are given in Table 3.

Table 3. Relative Energies (kcal/mol) of the Transition States and the Products Corresponding to the TADA Reactions of the Five Triene Molecules Obtained at the Hybrid Density Functional M06-2X Level of Theory Using 6-311G(d,p) Basis Set[a]

	TTT	TTC	TCT	TCC	CCC
reactant	0.0	0.0	0.0	0.0	0.0
TS-cbc	**21.1**	**22.1**	34.9	**35.7**	48.8
TS-cbb	24.3	26.7	**34.1**	37.5	**47.1**
TS-bbc	24.6	26.7	37.1	39.0	50.1
TS-bbb	28.9	30.5	40.7	41.7	49.8
product	−40.7	−33.7	−28.8	−26.5	−27.7

[a]The relative energies were calculated on the basis of the most stable conformation of each of the reactants. The energies of the most stable TS corresponding to each reaction are given in bold.

While the transition states corresponding to the TADA reaction of **TTT**, **TTC**, **TCT**, **TCC**, and **CCC** were successfully located, several attempts to obtain transition state geometries for the reaction of **CCT** were futile. Notably, previous experimental studies have supported that **CCT** has very low or no TADA reactivity possibly because of the high build of strain in the geometry to form the transition state.[1] The products that are formed from the other five macrocyclic trienes are in good agreement with previous experimental studies.[1] Among the four conformationally different transition state geometries (**cbc**, **cbb**, **bbc**, and **bbb**) corresponding to each of the five reactions (Figure 3), the ones with two chair forms are more stable compared to the others in general. As predicted, the central ring of the macrocyclic triene should rearrange into boat-like conformation. But because of the restriction in stereochemistry, **CCT** triene cannot take the conformation in the central ring leading to the boat-like transition state due to geometric constraints that prevent the diene and the dienophile to come together during the course of the reaction. However, **cbc** and **cbb** transition states are similar in energy in the TADA reactions of **TCT** and **CCC**. It is expected that a six-membered ring in the chair form is more stable than when it is in boat form. However, it is possible that there is a competition between the preference of the chair form and the preference of a given conformer with less strain giving rise to comparable

energies for **cbc** and **cbb** in the reaction of **TCT** and **CCC**. Notably, the transition states with the conformation having two boat forms (**bbb**) are the least stable in all the cases. The most stable states for all the trienes under study are depicted below in Figure 4.

Further discussion on the TADA reactivities of the five macrocyclic trienes are based on the most stable transition state structures within each reaction given in Figure 3. The reaction energy profiles corresponding to the most stable transition state of the five TADA reactions are depicted in Figure 5. Previously reported experimental studies have shown that macrocyclic trienes containing **TT** diene (**TTT** and **TTC**) undergo TADA reaction in reasonably mild conditions (low temperatures).[6] Consistent with this observation, it is found that the activation energies corresponding to these two reactions are lower compared to the others. This is attributed to the facile formation of *s-cisoid* form and hence the transition state geometry. On the other hand, reactants containing **TC** and **CC** diene moiety were reported to require high temperature condition for the TADA reaction to take place. The results shown in Figure 5 capture these observations reasonably well. Formation of the *s-cisoid* form of the reactant molecules with one or two *cis*-double bonds (**TC** and **CC**) in the diene moiety would not be as preferred as compared to **TT** diene because of the steric clash. In the following sections, results from the MD simulations are presented.

Conformational Preferences of the Triene Macrocycles and TADA Reactivity. For a Diels−Alder reaction to take place, one of the primary requirements is that the diene part of the reactant has to adopt an *s-cisoid* like geometry. In addition, the reactive sites, namely, the diene and the dienophile have to be able to approach each other in order to form the transition state. The latter becomes especially crucial, when the two reacting species are part of a single molecule as is the case in TADA reactions. In the TADA reactions, the ease of approach between the diene and the dienophile moieties of the reactants is primarily controlled by their conformational properties. In this context, it is important to investigate the inherent conformational preferences of the triene molecules and their manifestation on their reactivities. Hence, the analysis of the MD trajectories focused on the two distances named R1 and R2 and on the dihedral angle (φ_4) corresponding to the diene moiety.

Traditional MD and REMD simulations were performed on the six macrocyclic trienes using the original CHARMM force field along with incorporating the dihedral parameters obtained in this study. Initially, the differences in the sampling of the conformation spaces of the triene molecules obtained from the MD compared to the REMD approach are compared. The probability distributions of the two distances put together that
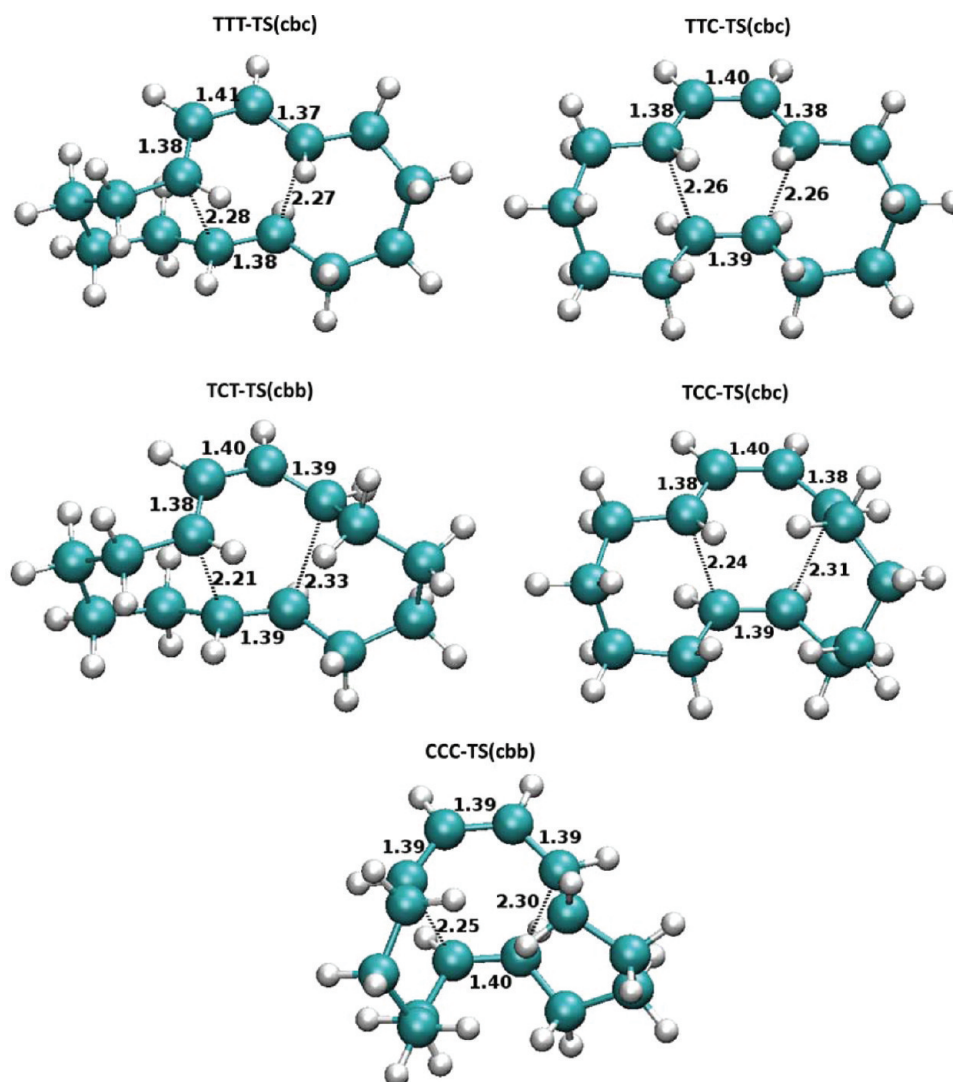
Figure 4. The most stable transition state for all the macrocyclic trienes at M06-2X/6-311G(d,p) level of theory along with the bond distances at the reaction center.
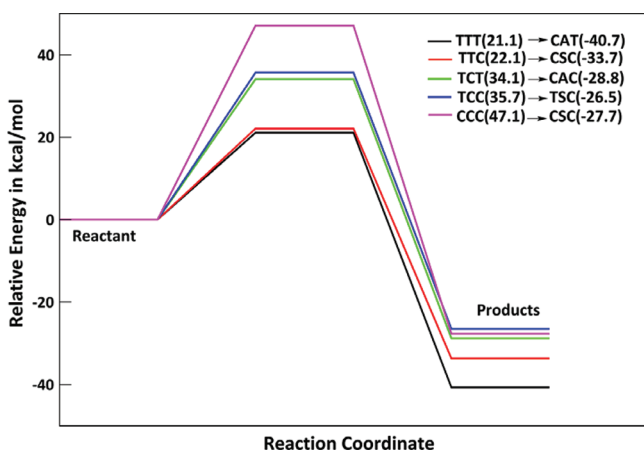

Figure 5. Energy profile diagrams of the macrocyclic trienes undergoing TADA reactions yielding respective tricycles at M06-2X/6-311G(d,p) level of theory. The most stable transition state among the four possibilities in each reaction is depicted here.

The corresponding distributions for the individual distances (R1 and R2) are given in Figures S6 and Figure S7 (Supporting Information). Additionally, the sampling of the diene dihedral angles in these molecules evaluated using the two methods are given in Figure S8 (Supporting Information). It is evident that the REMD simulations are efficient in sampling a larger conformational space compared to the traditional simulations at a similar simulation time scale. The range of distances and the dihedral angles adopted by the reactants are comparatively longer in case of the REMD simulations. For example, dihedral angles from −90 to 90° in **TTT**, **TTC**, **TCT**, and **TCC** are sampled well in the REMD simulations. In the traditional MD simulations, the molecule spent more time in the energetically favorable regions close to 180°, and the sampling of the energetically less favorable regions is relatively less since the molecules could not overcome the conformational energy barrier as often as in the REMD simulations. The discussion on the conformational properties of the triene macrocycles following this section are based on the results obtained from the REMD simulations.

The extent to which the conformational preferences of the trienes allow for proximal approach of the diene and the
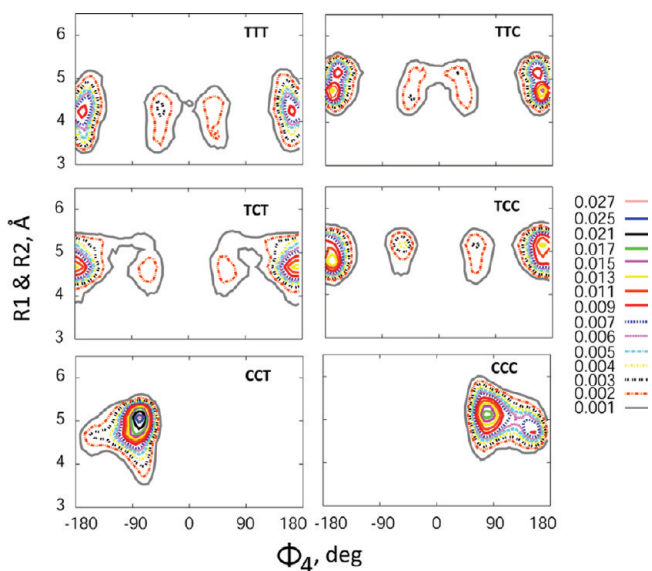
were obtained using the two approaches for the six molecules are depicted in Figure S5 (Supporting Information).

Figure 6. Probability contour plots corresponding to the diene dihedral angle (φ_4) and the distance (R1 and R2) obtained for the six macrocyclic trienes.

dienophile moieties was examined on the basis of the probability contours corresponding to the distances R1 and R2 (Figure S9, Supporting Information). The only triene that samples conformational space for either distances (R1 and R2) less than 4 Å is **TTT**. The probability of finding the other systems with R1 or R2 less than 4.5 Å are almost zero. Interestingly the most reactive triene to undergo TADA reaction has been shown to be the **TTT** isomer. However the relative reactivities of the other five trienes could not be explained on the basis of the distance parameters. In addition to the distances, ability of the diene to form *s-cis* geometry is a crucial factor for a Diels−Alder reaction to take place. The probability contours for the R1 and R2 distances and the diene

dihedral angle (φ_4) are depicted in Figure 6. The probability contours with respect to the individual distances R1 and R2 and the dihedral angles are shown in the Supporting Information (Figure S10). They are very similar to each other, and hence the combined data are given in Figure 6. Qualitatively, there is a good correlation between the reactivities and the probabilities corresponding to the *s-cis* form. In the discussion above, we have showed that the order of reactivity of trienes is **TT > TC > CC**. Figure 6 indicates that **TT** containing trienes sample the largest number of conformations corresponding to $\varphi_4 = -30$ to 30. **CCT** and **CCC** do not sample this region, and previous experiments have shown that the TADA reactivities of these tricycles are less.

The role of the conformational preferences on the reactivity was further quantified by correlating the transition state energy barriers obtained using DFT calculations with the overall probability of finding the reactants in certain conformational states. The transition state energies versus the probability of finding the conformer distances less than R1 and R2 < 4−5.5 Å with 0.5 Å intervals are given in Figure 7A. No systematic correlation between the two was obtained both at shorter and longer distances. However, the most reactive **TTT** isomer has the largest probability, and least reactive **CCC** isomer has the smallest probability. Similar analysis was done on the dihedral angle, φ_4 (Figure 7B). The probabilities corresponding to the combination of the distance criteria (R1 and R2) and existence of *s-cisoid* were computed on the basis of the contours shown in Figure 6. These cumulative probabilities were then correlated with the activation energy barriers and shown in Figure 7C. Very good correlation between the energy barriers and the probability of finding the system with $\varphi = -x$ to $+x$ ($x = 50-60°$). The correlation coefficients obtained for the linear fits of the plots are close to 1 (Figure 7C). It is tempting to conclude that the geometric features of the reactants dictate the rate of the intramolecular reactions, but it needs further verification on a large set of reactions.[40,43] A clustering method based on the all the dihedral angles in the macrocycles was used, followed by
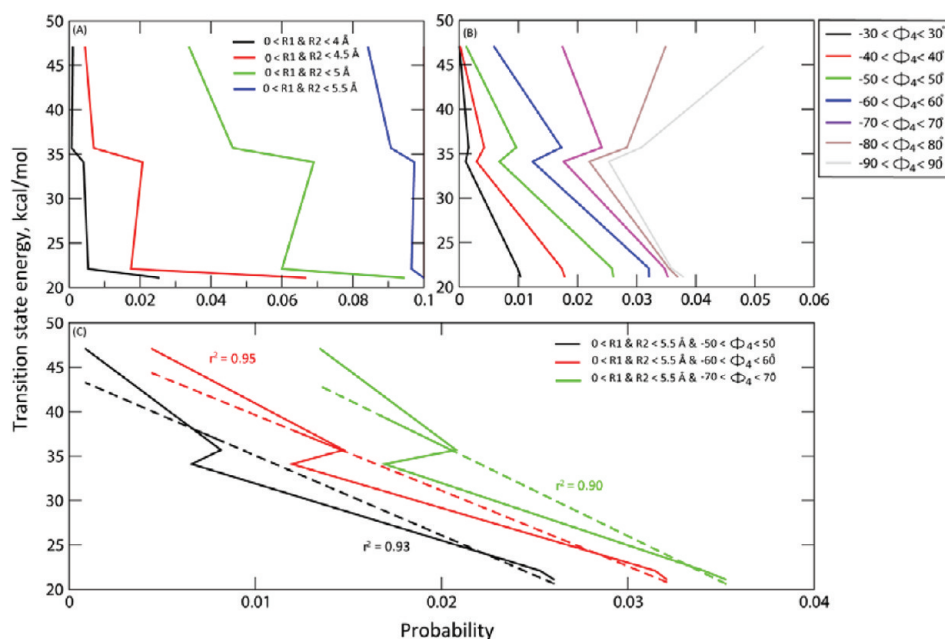

Figure 7. Transition state energy barrier versus (A) probability of finding the system where the distances R1 and R2 are < 4 Å, < 4.5 Å, < 5 Å, < 5.5 Å; (B) probability of finding the system where the diene dihedral angles satisfies $-x < \varphi < +x$ ($x = 30, 40, 50, 60, 70, 80, 90°$); (C) probability of finding the system where R1 and R2 < 5.5 Å and where $-x < \varphi < +x$ ($x = 50, 60$, and $70°$).
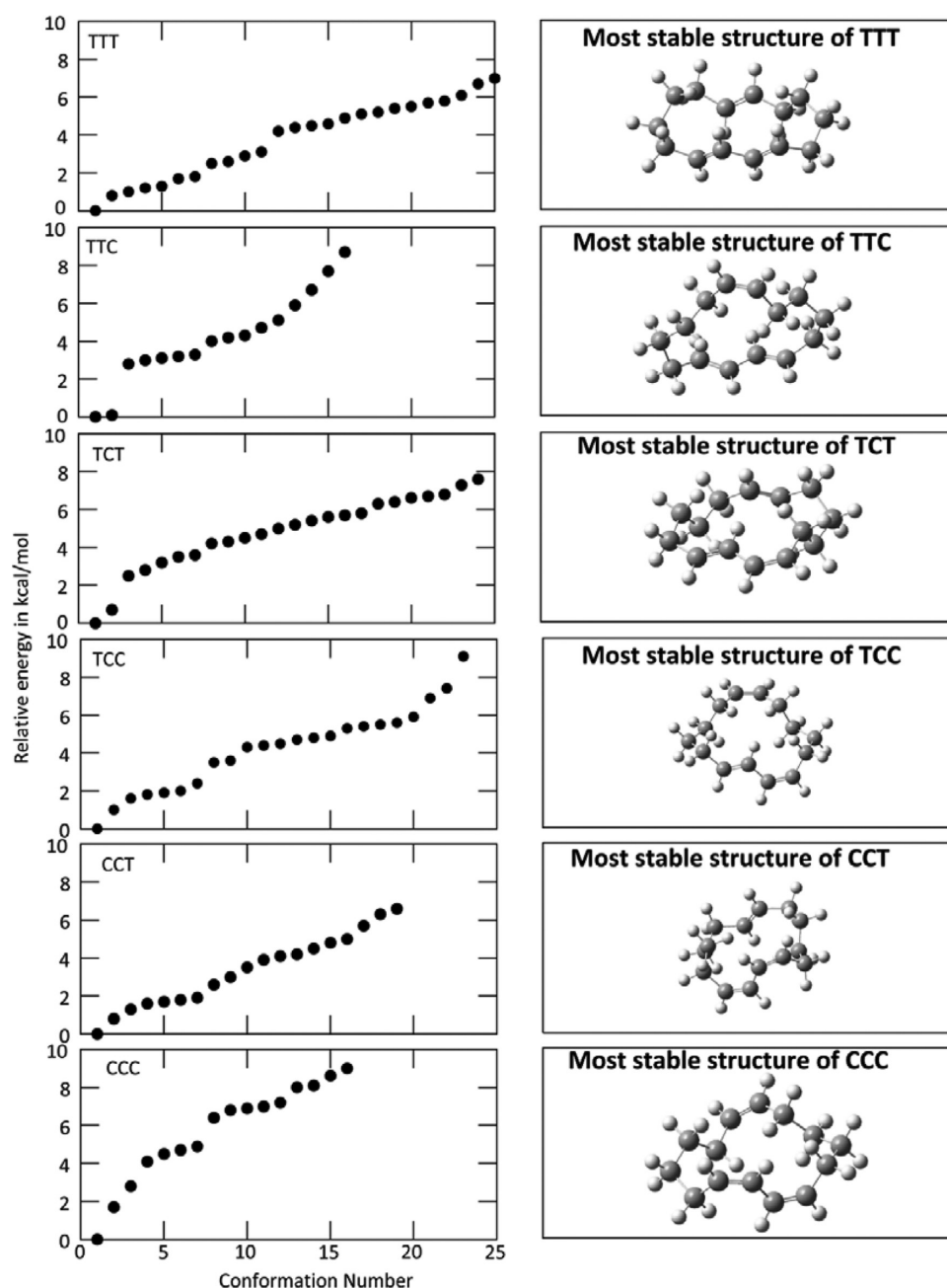
Figure 8. The energies of all the unique conformations of the six reactants obtained using the M06-2X/6-311G(d,p) level of theory. The most stable conformation of each of the six isomers are depicted.

geometry optimization, to obtain various conformers for each of the reactant molecules (Figure 8), more information of which can be found in the Supporting Information.

■ CONCLUSIONS

The current study presents a comprehensive examination of the TADA reactivities of 14-membered macrocyclic trienes and their relationship with the conformational preferences of the reactants. A benchmark study was undertaken to identify a computational approach that will accurately model the TADA reactions by taking CCSD(T) level as the standard. Data from the hybrid density functional M06-2X level of theory with a triple-ζ basis set are in quantitative agreement with those from the CCSD(T) calculations. MP2 level, which takes into account the electronic correlation, performs poorly in terms of the

prediction of the reaction energy barriers of the TADA reactions. The relative stabilities of six-triene macrocyclic trienes and their TADA reactivities were studied at the M06-2X level using the 6-311G(d,p) basis set. The macrocycles containing the **TC** dienes were found to be more stable compared the others. The **TT** diene-containing isomers were found to be less stable because of the nonplanar sp^2 centers, and the **CC** diene-containing isomers are less stable because of the lack of delocalization in the conjugated double bonds. Consistent with experimental studies,[1,6,39,67] **TTT** macrocycle was found to be the most reactive of the six trienes considered here. The **TC** diene-containing macrocycles (**TCT** and **TCC**) were found to be less reactive than the **TT** diene-contaning macrocycles. The **CC** diene-containing isomers were found to be the least reactive in agreement with previous experiments.[1,6,39,67]

An attempt was made to examine the relationship between the geometric parameters of the reactants and their TADA reactivities. Force field parameters for the dihedral terms involved in the potential energy of few model systems were obtained to match MP2 target data. Conventional and replica exchange MD simulations were performed to investigate the conformational preferences of these molecules. Along with the MD simulations, hybrid density functional M06-2X level was used to identify all conformations. Linear correlation between the activation energy barriers and the probability of finding the reactants in certain conformational states (close to *s-cis* form and short distance between the reactive sites). Most reactive **TTT** isomer has the largest probability of sampling such regions, and the least reactive **CCT** was found to have the smallest probability. A systematic quantum mechanical and molecular dynamics study of substituted macrocyclic trienes is expected to further our understanding of TADA reactivity in general. Moreover, the possibility of modulating the transition state barriers using substitutions will help to drive TADA reactions via a given transition state to form desired products, which will enhance the synthetic applications of this class of reactions. Studies on a larger number of test cases of intramolecular reactions to test the validity of the correlation are in progress.

ASSOCIATED CONTENT

Ⓢ Supporting Information

The parameter optimization details, full citations of reference 53, electronic energies, rmsd values, bond lengths for **TTT**, four **TS**, and the **CAT** adduct, the force field parameters of the modeled system for macrocyclic triene, probability distribution of distances, R1 and R2 obtained at conventional and replica exchange MD simulations, R1 histogram for all isomers, R2 histogram for all isomers, probability distribution of diene dihedral angle for the six isomers obtained using conventional and replica exchange MD simulations, probability contours with respect to the distances, R1 and R2 of the six triene molecules obtained using ReMD simulations, coupled probability between diene dihedral angle and distance between reactive sites and the Cartesian coordinates for the **TTT**, four **TS**, and the **CAT** adduct at the M06-2X/6-311G(d,p), M06/6-311G(d,p), B3LYP/6-311G(d,p), MP2/6-311G(d,p) levels of theory, followed by the Cartesian coordinates for the **TTC**, **TCT**, **TCC**, and **CCC** trienes along with their four possible **TS** and respective adducts at M06-2X/6-311G(d,p) level of theory. This material is available free of charge via the Internet at http://pubs.acs.org/.

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Notes
The authors declare no competing financial interest.

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DEDICATION

Dedicated to Professor Eluvathingal D. Jemmis on the occasion of his 60th birthday.

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