Theoretical Evaluation of the Conformations of Previtamin D₃

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The ground-state conformational equilibrium of previtamin D₃ (Pre₃) was modeled by means of MMP2 calculations on a suitable molecule (Pre) in which the side chain was substituted by a methyl group. Independent calculations were carried out on each of the two possible conformations of the A ring with the OH group either pseudoaxial (Pre$_a$) or pseudoequatorial (Pre$_e$). The torsional angles around C6–C7–C8–C9 and C10–C5–C6–C7 were varied in a systematic fashion within each series. The calculated energies of the various geometries form an energy surface with respect to the two above-defined torsional angles in each series. The analysis of the data located four minima in each case, corresponding to two cZc conformations and two tZc forms each, differing only in the relative helicity of the triene moiety. The (+)tZ(−)c form with a pseudoequatorial OH group was identified as the global minimum. Comparison of the theoretical treatment with experimental observations is discussed.

Introduction

The chemistry of previtamin D₃ (Pre₃) is well known and all products, derived by either photochemical or thermal reaction, are characterized. The photochemical formation of three products is observed: lumisterol D₃ (L₃), provitamin D₃ (Pro₃), and tachysterol D₃ (T₃). The thermal rearrangement produces vitamin D₃ (Vit₃) (Scheme I).

The formation of the different products is believed to occur from different ground-state conformations of Pre₃.[2] Of interest here are primarily the conformations that arise from rotations around the single bonds (C5–C6 and C7–C8) within the triene moiety. In the above scheme are shown representations of the two main groups of conformations. The central double bond in Pre₃ is always in the cis or *Z* configuration. Depending on the orientation of the single bonds with respect to the neighboring double bonds we distinguish between s–cis,s–cis conformations (cZc) and s–trans,s–cis conformations (tZc). These also include twisted conformations, s–cis incorporates a possible ±89° deviation of planarity, the conformations with a dihedral angle of ±91° to ±180° are therefore called s–trans (a ±90° angle would lead to an orthogonal arrangement).

The experimental data pertaining to the conformational equilibrium of Pre₃ do not lead to an unequivocal prediction as to the most stable conformation of Pre₃. For example, the finding of the preferred formation of T₃ upon irradiation of Pre₃ led Pfoertner[3] to suggest that a planr tZc conformation was the most stable, followed by two cZc conformations with the A ring above and below the plane of the C,D rings, which were viewed as the precursors of the corresponding ring closed products L₃ and Pro₃. Different model reaction pathways for the photoreactions of Pre₃ have been proposed by the Havinga group.[4] In their first model it was assumed that the double bond in ring A was almost perpendicular to the plane of the remaining diene system. More recently, it was suggested that the entire triene system is flexible and the maximum energy was reached at the planar cZc conformation.[5] Within this framework, the molecule could adopt a number of

spatially different forms that are not separated by substantial energy barriers, leading to a broad energy minimum between 80° and 300° rotation around the C5–C6 single bond. Within this broad minimum, distinction was given between two nonplanar cZc conformations, i.e. (+) and (−) forms with the C19 methyl group below and above the plane of the C,D rings, and two tZc-conformations. From this analysis, it was not clear which conformations were actually predominant.

In order to clarify this picture, a theoretical investigation of the ground-state conformations of Pre₃ was undertaken.

MMP2 Calculations for a Model Compound of Previtamin D₃.

To accomplish this task with such a large molecule only force field calculations can be used. The chosen force field was MMP2, which incorporates the latest MM2 force field of Allinger, together with a π-system treatment.[6]

In order to find the global minimum, a mapping of the ground-state surface of Pre₃ was essential. To make the calculation easier, the side chain in Pre₃ was substituted by a methyl group (R would be CH₃ in the above scheme). It is obvious, that this side chain can adopt multiple conformations, for which there would be no complement in the investigated model. Nevertheless, these conformations play no role in the above discussed reactions, as can be seen by the formation of similar products upon irradiation in the vitamin D₂ series.[7] Thus, so far as calculations are concerned, "Pre" refers to the molecule with a side chain of only a methyl group.

Possible different conformations of the A and/or the C,D rings in Pre₃ influence the spatial arrangement of the triene moiety. The A ring in Pre₃ is expected to be conformational mobile and to adopt two half-chair conformations with the OH group in pseudoequatorial and pseudoaxial positions, respectively.[8a] This was confirmed by a thorough analysis of 3,4-dimethylcyclohex-3-en-1-ol (equivalent to the A ring in Pre₃ with the rest of the molecule substituted by a methyl group) with the MacroModel package of Still.[9] Indeed, only two low energy half-chair conformations can be found, the next possible conformation is in the boat form and was calculated to be

(1) Recipient of a Feodor-Lynen fellowship of the Alexander von Humboldt-Stiftung, 1986–1987.

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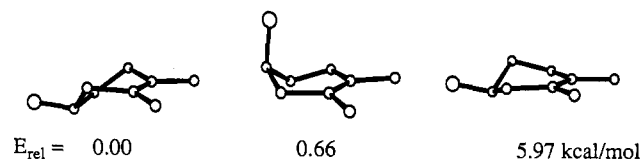
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5.97 kcal/mol higher in energy.

E_{rel} =   0.00   0.66   5.97 kcal/mol

The trans-fused C,D rings give rise to a fairly rigid system, the double bond in ring C and the trans ring junction in connection with the cis-positioned methyl groups impose enough constriction to achieve an almost rigid system. This could be confirmed with MacroModel calculations.

It is clear, that the conformational change in the A ring has an influence on the total energy of the molecule. Upon ring-flip in the A ring the energy of the whole molecule should change in the same order of magnitude as it would in the A ring alone. Therefore, the above located boat conformation for the A ring was not considered in the further calculations, because this would lead to geometries too high in energy. Thus, only the two half-chair conformations of the A ring in Pre have to be dealt with and consequently two surface maps have to be calculated to picture the conformational properties of this molecule.

In order to obtain a complete three-dimensional ground-state map of the two A-ring conformers of P_3 mentioned above, the torsional angle driver option in MMP2 was employed. The torsional angles C10–C5–C6–C7 and C6–C7–C8–C9 in Pre were systematically changed in 10° steps to cover all possible combinations. This provided a 36×36 data matrix for each of the ground-state surfaces. The starting geometry for each of these points was identical at the beginning.

The graphical representations of the final results are shown in Figures 1 and 2. Pre_a refers to Pre with the OH group in the pseudoaxial position, Pre_e to that with the OH in pseudoequatorial position. As can be seen, within a reasonable energy range, four minima can be located in each case. In both cases only the cZc and tZc forms contribute to the ground-state conformations of Pre. The data are given in numerical form in Tables I and II, including ORTEP plots of the minimized geometries. There is an interesting difference between Pre_a and Pre_e. In Pre_a, the global minimum is (–)cZ(–)c, whereas in Pre_e, it is (+)tZ(–)c.

The direct comparison of the four energy minima obtained in each series (Table III) reveals that the cZc forms in both cases are calculated to be in the same relative order. Such is not the case for the tZc forms. The energy difference between the cZc systems with pseudoaxial and pseudoequatorial OH groups is about the same as it would be in the A ring alone, the pseudoequatorial form being the more stable one.

This conformational relationship is understandable when one examines the ORTEP plots of their geometries in Tables I and II. The part of the A ring, which changes upon the ring-flip, i.e. C2–C3–C4, is fairly remote from the triene moiety, therefore its influence on their arrangement and on the energy of molecule as a whole is rather small. The situation is different, when one considers the tZc forms. The changing part of the A ring is now close to the C,D rings, the 4α- and 4β-H are interacting with the 9-H. This interaction in the Pre_a series has to be made responsible for putting the tZc forms higher in energy than the cZc forms, which have only the weaker 19-H,9-H interactions. In Dreiding models, built after the calculated geometries, it becomes quite clear that the latter interaction can well be less than the 4-H,9-H interaction, due to
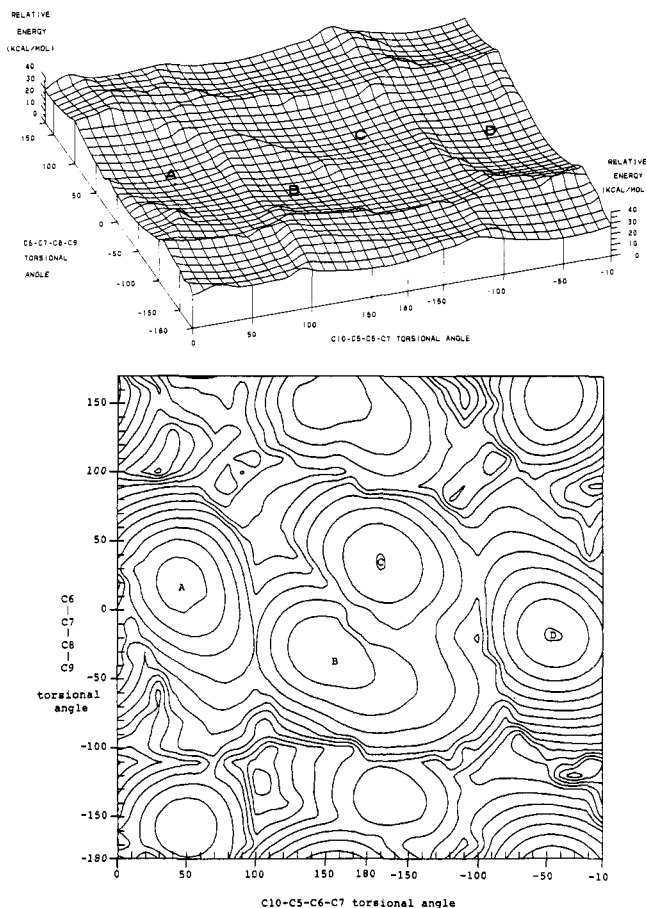

Figure 1. 3D plot (a, top) and contour map (b, bottom) of the ground state surface of Pre_a. Key: A, (+)cZ(+)c; B, (+)tZ(–)c; , (–)tZ(+)c; D, (–)cZ(–)c.

the twist around the C5–C6 single bond in the cZc forms. But it is surprising that the (+)tZ(–)c form with an pseudoaxial OH group becomes on ring-flip the most stable form in the Pre_e series, in fact, the global minimum. This can be attributed to the steric interaction of 4β-H with 9-H in the pseudoaxial form, which is relieved upon ring-flip. Nevertheless, the magnitude of this effect could not have been foreseen.

According to these results the conformational equilibrium of Pre is very complicated. To give a qualitative idea what the distributions between cZc and tZc forms will be, the possible "pure" equilibria in each series have been calculated with the enthalpies of formation as calculated by MMP2, assuming a Boltzmann distribution and no entropy effects (Table IV).[11] Also included is the distribution as it would be for both Pre_a and Pre_e together. The calculated distributions do not take into account the

(11) This assumption may be incorrect. The shallow valleys in the surface maps suggest a very flexible molecule; therefore, entropy will be important for the free energy of the particular conformation. On the other hand, we are dealing with relative energies, thus, eliminating the entropy term.

(12) This value, based on a Boltzmann distribution, is almost identical with the one obtained upon inclusion of the entropy of mixing.[8b] With the equations $H = \sum N_i H_i$ and $S = -R\sum(N_i \ln N_i)$, N_i being the mole fraction of the ith conformer, the calculated enthalpies and entropies for Pre_a and Pre_e were $H_a = -37.43$ kcal/mol, $S_a = 1.28$ cal/K mol, $H_e = -38.20$ kcal/mol and $S_e = 2.09$ cal/K mol. This corresponds, at 298 K, to $G_a = -37.81$ kcal/mol and $G_e = -38.82$ kcal/mol, respectively. The difference in free energy of 1.0 kcal/mol leads to a mixture with 85% of the molecules having the OH group in pseudoequatorial position. Taking into account the different contributions of the cZc and tZc forms, one obtains overall that 45% of Pre should be in cZc forms and 55% in tZc forms.

Table I. Calculated Properties of the Four Lowest Energy Minima in the Pre_a Series (the Sign of the Torsional Angle Follows the Rules of Klyne and Prelog[10])
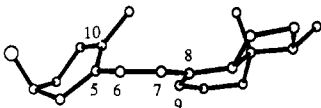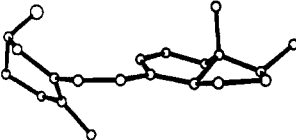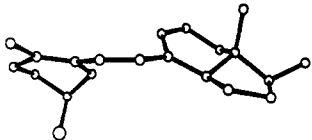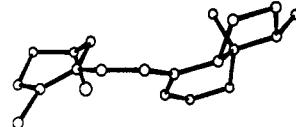
	geometry	torsional angle, deg 10–5–6–7	5–6–7–8	steric energy	enthalpy of formation
	(−)cZ(−)c	−46	−16	39.27	−37.68
	(+)cZ(+)c	48	16	40.73	−36.68
	(−)tZ(+)c	−173	37	41.16	−35.67
	(+)tZ(−)c	153	−31	41.34	−35.53

Table II. Calculated Properties of the Four Lowest Energy Minima in the Pre_e Series (the Sign of the Torsional Angle Follows the Rules of Klyne and Prelog[10])
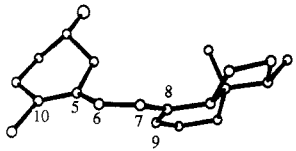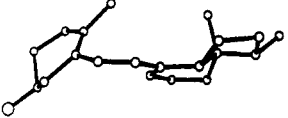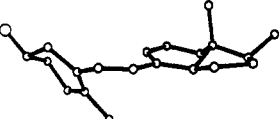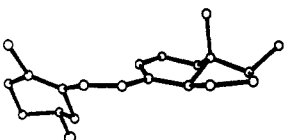
	geometry	torsional angle, deg 10–5–6–7	5–6–7–8	steric energy	enthalpy of formation
	(+)tZ(−)c	168	−17	38.41	−38.50
	(−)cZ(−)c	−37	−9	39.33	−38.04
	(+)cZ(+)c	34	9	39.94	−37.53
	(−)tZ(+)c	−159	10	39.88	−37.03

Table III. Comparison of the Calculated Enthalpies of Formation for the Energy Minima of Pre_a and Pre_e (kcal/mol) Based on the (+)tZ(−)c Form of Pre_e as 0.0 kcal/mol

conformer geometry	energy in Pre_a series	conformer geometry	energy in Pre_e series
(−)cZ(−)c	0.8	(+)tZ(−)c	0.0
(+)cZ(+)c	1.8	(−)cZ(−)c	0.5
(−)tZ(+)c	2.8	(+)cZ(+)c	1.0
(+)tZ(−)c	3.0	(−)tZ(+)c	1.5

surroundings of the molecule. The relative stability of the conformations in Pre_a and Pre_e can easily be changed by solvents, due to their influence upon the axial–equatorial equilibrium. Consequently, the distribution of the con-

formers of Pre and in turn of Pre_3 in solution cannot be predicted at this time.

It can be seen on the surface maps that the minima are relatively shallow. It can be expected that there is a large amount of movement around the C5–C6 and C7–C8 bonds possible, without having the molecule leave the particular valley. There are also barriers between these valleys shown, and their height can be determined. But these heights are quite low for some processes, and this can be attributed to a limitation in the performed calculations. The description of the ground state of Pre_3 with only two variables is an approximation that incorporates the assumption that the dihedral angle around the C6–C7 double bond plays no role in the investigated problem. But this
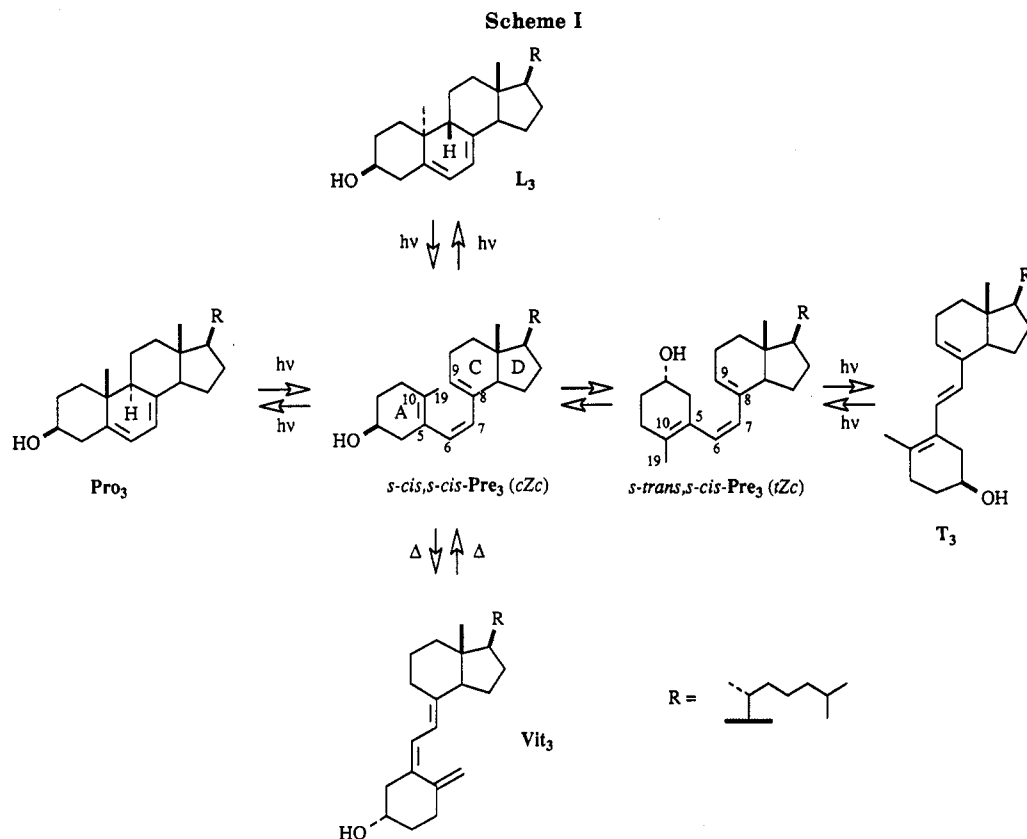
Scheme I

Table IV. Percentage of Abundance of the Calculated Conformers According to a Boltzmann Distribution at 298 K

	(−)cZ(−)c	(+)cZ(+)c	$\sum$cZc	(+)tZ(−)c	(−)tZ(+)c	$\sum$tZc
only Pre$_a$	80	15	95	2	3	5
only Pre$_e$	25	11	36	59	5	64
both[12]	34	12	46	50	5	54

assumption breaks down if the molecule tries to adopt planarity in our calculations.

If one turns with the help of the *driver* the C5–C6 and C7–C8 bonds to approach, for example, 0° as it is necessary for the interconversion of (+)cZ(+)c and (−)cZ(−)c forms the C6–C7 bond becomes largely twisted by the program to avoid the considerable steric interactions of C ring and the C19 methyl group. Therefore, starting out from either (+)cZ(+)c or (−)cZ(−)c, one obtains geometries with opposite twist in the central double bond. Obviously, this does not correspond to a saddlepoint, because these geometries are not directly interconvertible. Similar problems arise with the (+)tZ(−)c and (−)tZ(+)c forms. For a complete description, one has therefore to include the dihedral angle C6–C7, but this would lead to a four-dimensional problem, which cannot be handled properly. In addition, it is not possible with MMP2 to drive more than two angles. Fortunately, this represents only a problem for the estimation of conformational barriers, the shape of the valleys and the detected minimum conformations are still valid.

In order to obtain reasonable barriers for the interconversion between our calculated minimum conformations, one has to apply certain restrictions on the minimization, which go further than the use of the *driver* (see the Experimental Section). Therefore, the calculated values for the interconversion of cZc and tZc forms are only approximate—even within the limits of the program.

The calculated barriers in each series are shown in Figure 3, the values obtained directly from the corresponding surface map are given for comparison and except for one value there is good agreement (see the Experi-

mental Section). In the analysis, one has to keep in mind that molecular mechanics does not always give good results for rotational barriers. In general, the calculated values tend to be too low.[13] Nevertheless, the presented values may give an idea about the possible interconversions. Obviously, there will be no direct interconversion of the cZc forms into each other. The calculated barriers are much too high for these processes to occur. All other pathways seem to be possible, and the corresponding barriers can be easily surmounted at room temperature. Therefore, it can be said that in Pre$_a$ for the interconversion of (+)cZ(+)c into (−)cZ(−)c forms to occur one has to go through (+)tZ(−)c and (−)tZ(+)c; in Pre$_e$ this is also true, but because (+)tZ(−)c is the most stable, the interconversions will start there.

Comparison of Theoretical with Experimental Data. The structure of Pre$_3$ has not been investigated by direct methods. There is no X-ray structure of Pre$_3$ (or its analogues) reported in the literature. Therefore, other spectroscopic or chemical evidence was sought. Some conclusions were drawn from the formation of Vit$_3$,[15,16] from UV and CD data,[4,5,18] and from the amounts of

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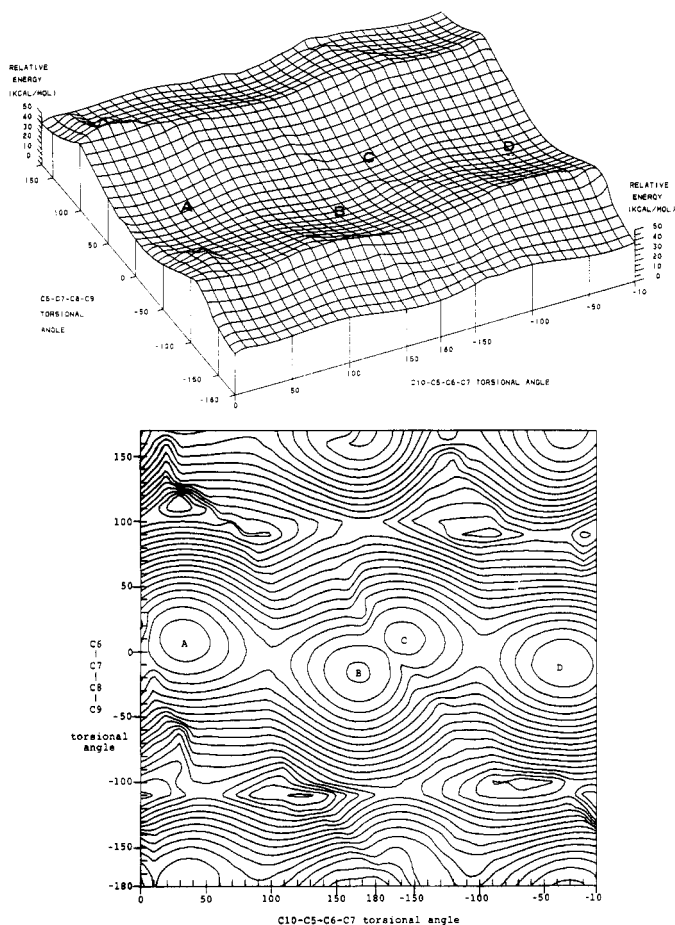(18) Maessen, P. A. Thesis, Leiden, 1983.

Figure 2. 3D plot (a, top) and contour map (b, bottom) of the ground-state surface of Pre_e. Key: A, $(+)cZ(+)c$; B, $(+)tZ(-)c$; C, $(-)tZ(+)c$; D, $(-)cZ(-)c$.

Figure 3. Schematic representation of the rotational barriers, (a, top) for Pre_a, (b, bottom) for Pre_e. Given are the relative enthalpies of formation in kilocalories/mole (the values in parentheses are obtained by analysis of the corresponding calculated surface).

various photoproducts formed upon irradiation.[5,18] There is only one study in which NMR spectroscopy was used to evaluate the conformation of Pre_3.[18] The results of these various studies can now be compared with the present calculation results.

The formation of different photoproducts was taken as evidence for the relative stability of the various conformers of Pre_3.[3] Not regarding the formation T_3, one has to explain why Pro_3 and L_3 are not formed in equal amounts. Under the assumption that the $(-)cZ(-)c$ forms should exclusively cyclize to form Pro_3 and the $(+)cZ(+)c$ conformations correspondingly to L_3, one would assume, based on the calculated distribution of their precursors, that Pro_3 is formed in greater amounts than L_3, assuming comparable efficiency in the photocyclization. The concept of ground-state population control has been shown to parallel, roughly, the percentage of the various conformations. However, if the quantum yields are not of comparable efficiency, and indeed, the quantum yield for the formation of L_3 is about twice that for Pro_3,[14] quantitative prediction cannot be expected.

Mazur[15,16] has reported that the formation of Vit_3 occurs predominantly from Pre_3 in the $(+)cZ(+)c$ conformation and from such a result it has been inferred that this conformation is the more stable one.[5] The cZc conformation is required for the reaction, and in either the Pre_a or Pre_e series, the present calculations show that the $(-)cZ(-)c$ is the more stable of the two conformations in each series. Clearly, this thermal reaction cannot be used to indicate relative ground-state conformational stabilities since product ratios need not be related to starting material conformation ratios (Curtin Hammett Principle[8c]). How-
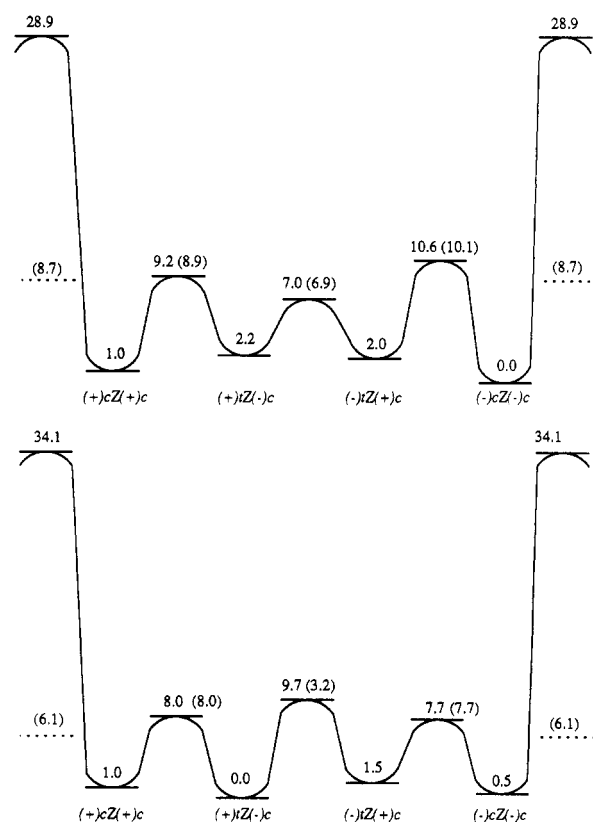
ever, one possible explanation for this preferred thermal reaction stereochemistry could be that the $(+)cZ(+)$ conformation reacts faster than the $(-)cZ(-)c$ conformation. Support for this argument can be found in the recent kinetic study of the [1,7] hydrogen shift in analogues of *cis*-isotachysterol by Okamura,[17] which showed that the shift is 3–7 times faster when the HO group is syn-facial to the antarafacial migrating hydrogen. In the Pre_3 case, such an orientation would indicate that $(+)cZ(+)c$ reacts faster than $(-)cZ(-)c$.

UV and CD spectra are sensitive to conformational changes in the chromophore being studied. Consequently, the UV spectrum of Pre_3 was thoroughly analyzed[4] and it was concluded that the room temperature UV spectrum mainly results by the absorption of a conformation with more or less a planar cisoid C6–C7–C8–C9 diene moiety with the C5–C10 double bond in a plane perpendicular to the plane of the s-*cis*-diene. The low-temperature UV and CD spectra have been determined,[15] and the red shift of the maxima was attributed to a tendency of the chromophore to become planar.

The influence of solvent and temperature on the UV and CD spectra of Pre_3 recently has been reinvestigated,[18] and it was concluded that lower temperatures and increased solvent polarity shift the conformational equilibrium of Pre_3 toward the skew cZc forms. The conclusions of these studies are contradictory, but the shift of the conformational equilibrium toward nonplanar conformations is in agreement with the present reported calculations.

NMR methods also have been used to investigate the conformational equilibrium of Pre_3, and the conformation of the A ring was determined by studying the coupling pattern of the 3α-H.[18] The result was that the pseudoequatorial form predominants in polar solvents, whereas the

pseudoaxial position of the OH group is favored in nonpolar solvents. Next it was tried to find the most abundant conformation with NOE measurements at different temperatures. Upon irradiation of the 9-H (solvent: CD_3OD), an enhancement of only one signal was observed which was assigned as 4-H. It was therefore concluded that a tZc form must exist in solution even at lower temperatures. Upon closer examination of these data, one can see that the observed signal is centered at δ 2.2. The 4α-H was assigned at 2.43, the 4β-H at 2.15. Thus, the enhanced signal can be assigned to the 4β-H. This is exactly the proton that would be closest to 9-H in our global minimum, the (+)tZ(-)c conformation with the OH in pseudoequatorial position (4α-H $\leftrightarrow$ 9-H; 3.0 Å; 4β-H $\leftrightarrow$ 9-H, 2.1 Å). In all cZc forms, the distance between 19-H and 9-H is smaller than the 4-H,9-H distance; therefore, it should have been detected.

The ring-closure photochemistry of Pre₃ also has been interpreted as being partially dependent upon properties of the ground-state conformation of the compound. From the ratio ($\sim$4:1) of the quantum yields for the formation of L₃ and Pro₃, respectively, it has been inferred that the (+)cZ(+)c conformations are the more stable.[5,18] In such a conformation it was assumed that the reacting centers C-9 and C-10 are closer together than in the (-)cZ(-)c conformation, and thus, the higher quantum yield for L₃ formation would be expected.[5] The cZc conformation is required for the reaction, and, as mentioned earlier, the present calculation indicated that in the Preₐ and Preₑ series, the (-)cZ(-)c is the more stable of the two cZc conformations in each series. Also, the calculated torsional angles of the triene chromophore are almost identical in both the (+) and (-) conformations, indicating that ground state geometry, per se, should play no dominant role in the photochemistry. However, as suggested by the Leiden group,[5,18] the difference in the relaxation pattern in the excited state of the two cZc conformations would be important.

Summary

The presented molecular mechanics investigation gave the first quantitative insight into the conformational variety of Pre₃. A more detailed picture could not be drawn, due to the number of conformations involved. The tZc forms contribute more to the ground state of Pre₃ than previously ancipitated. The rotation of the A ring is restricted by distinct energy barriers between the calculated energy minima.

Experimental Section

All MMP2 calculations were performed on a VAX station II. The 3D-surfaces were drawn with the CATIA program (version 2, release 2.0) implemented on an IBM 3090 mainframe with an IBM 5080 graphics workstation.

The quoted energy differences are based on the calculated heat of formation as given by the program. We regard these values as more informative than the steric energy. The steric energy predicts the same relative order of conformations, but the corresponding values are of course different. It has to be kept in mind that the accuracy of MMP2 for heats of formation calculations is about ±0.84 kcal/mol.[6]

Every calculation with the driver function was performed by starting from the same geometry, i.e. the minimized (-)cZ(-)c form with the OH either pseudoaxial or -equatorial position. It was thought that this approach would avoid the difficulties that often occur with the use of the driver in a continuous fashion.[19] Unfortunately, this was not the case. The calculated energies were sometimes very high with respect to the surroundings, and they represented a discontinuity in the slope of the surface. This feature does not correspond to the physical reality.[19b] Often simple recalculation of these values, i.e. with the geometry obtained in the first calculation as input for a second calculation with the same torsional angles, gave a reasonable result. Sometimes this had to be repeated several times. In the few cases, where this approach did not give a smooth slope, the neighboring geometries were used as input to calculate the energy of the particular torsional angle combination. With this method; satisfactorily results were obtained in all cases.

The reason for these calculational problems is probably poor geometries generated by the dihedral driver. The driver alters, prior to the calculation, the torsional angles in question. This may lead to severe steric strain in some starting geometries, which cannot be resolved in a single calculation.

The calculation of the conformational barriers was performed under the assumption that the interconversion between the two cZc forms and the two tZc forms passes through a planar transition state. It was not possible to find another pathway that could, for instance, involve a rotation of the C,D ring piece to allow the A ring to rotate freely.

In order to achieve reasonable geometries for the transition states, it was necessary in the above mentioned cases to constrain the motion of the atoms C19 (in the case of the cZc forms), C10, C5, C6, and C7 in all space directions and to apply the driver to the angles C5–C6–C7–C8 and C6–C7–C8–C9, both fixed to the desired angles. This latter constraint was dictated by the fact that in modeling the barrier high energy transannular interactions develop that in some cases can cause a change in the structure of the model. This needed constraint leads to a better barrier value than that of a surface map.[19]

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(19) (a) Burkert, U.; Allinger, N. L. *J. Comp. Chem.* **1982**, *3*, 40. (b) Ôsawa, E. *J. Comput. Chem.* **1982**, *3*, 400.