Tetrahedron Vol 46, No 11, pp 4101-4108, 1990
Printed in Great Britain

0040-4020/90 $3.00+ 00

INVESTIGATION OF THE CONFORMATIONAL PROPERTIES OF CYCLODODECANONE BY ITERATIVE FORCE-FIELD CALCULATIONS

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(*Received in UK* 2 *March* 1990)

Abstract: Iterative force-field calculations show that the lowest energy conformation of Cyclododecanone (**1**) is the [3333]-2-one. Two conformational processes are needed to achieve pseudorotation of the [3333]-2-one conformation: one of these processes leads to time averaged C_2-symmetry in **1**, while the other results in time averaged C_s-symmetry in **1**.

Cyclododecanone (**1**) is a commercially available compound which is of importance as a synthetic intermediate.[1] It is the source of a wide variety of twelve-membered rings as well as of smaller and larger ring compounds.[2] Low-temperature x-ray data show that crystalline **1** has a disordered structure, and that it exists as a square [3333] conformation with the carbonyl group situated at a non-corner (side) position.[3] Similar conformations have been found for cyclododecanone oxime[4], 2,12-dibromocyclododecanone[5], and cyclododecane itself.[6,7] The ^1H and ^{13}C NMR spectra of **1** show dynamic NMR effects which are associated with a conformational barrier of 7.3-7.6 kcal/mol.[8] The ^1H NMR spectra of **1** have also been investigated in different solvents and in the presence of shift reagents, but this approach provides only very limited conformational information.[9] Hitherto, no force-field calculations on the conformations and conformational processes of **1** have been reported.

RESULTS AND DISCUSSION:

Force-field Calculations: Boyd's iterative computer program with modified parameters was employed for the force-field calculations of the conformations and conformational processes of Cyclododecanone.[10,11] Approximate coordinates for trial geometries were calculated by means of the program COORD[12] with torsional angles estimated from Dreiding-Fieser molecular models. Pseudorotation paths were explored by the migration of a specific carbon atom from a corner to an adjacent noncorner position (or sequences of such migrations).[11] As a result of the migration three torsional angles change by about 120° : One torsional angle passes through 0° and the other two pass through 120° in a sequential order (Figure 1). The appropriate torsional angles were changed by increments of 10-15°.

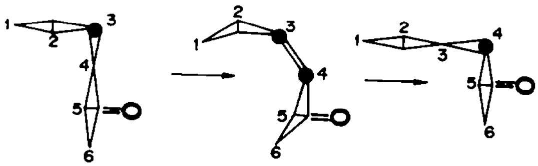

Figure 1. Migration of a carbon atom from a corner (black circle) to an adjacent non-corner (side) position.

The strain energies reported in this study correspond to molecules in a hypothetical motionless state at 0°K. However zero-point energy and vibrational enthalpy effects are expected to be similar for the different conformations of **1**. The present calculations will converge to either an energy minimum or maximum with respect to distortions corresponding to a normal mode of vibration. Hence the vibrational frequencies of all the conformations of **1** were calculated and in each case 3N-6 real vibrational frequencies were obtained, which indicates that each of these conformations corresponds to a true (local) energy minimum with respect to any small geometric distortion. For the conformational transition states of cyclododecanone 3N-7 real frequencies were obtained.The nomenclature used for the conformations of **1** has been previously described.[11,13]. Dale's "wedge" system has been employed to represent the three dimensional molecular conformations of **1**.[14] The magnitude and sign of each torsional angle are indicated alongside the respective carbon-carbon bond.

Conformations: The initial geometries required for the force-field calculations have been obtained by the replacement of methylene groups with cabonyl functions in molecular models of the known low energy conformations of cyclododecane (**2**).[6,14] This approach has been successfully employed in predicting the conformations of some medium-ring cycloalkanones from the known conformational properties of the corresponding cycloalkanes[11,15]. Theoretically the formal replacement in **2** of a CH_2 group by a CO group could give rise to changes in non-bonded (van der Waals), torsional and internal angle strains. Since the carbon-carbon bonds in both **1** and **2** are not far from being staggered changes in torsional strain should not be important; changes in internal angles should also have a small effect in these rings. The repulsive gauche proton-proton interactions in **2** should decrease when a methylene group is replaced by the smaller carbonyl function[16], provided that the methylene group is not at a corner position in the conformation of **2** under consideration.[11]

Altogether twentyone different conformations of cyclododecanone have been considered for calculations. These conformations can be formally derived from methylene - carbonyl group exchange in the three low energy conformations of Cyclododecane: [3333], [2334] and [2343].[6,14] Two conformations of **1** are derived from the square [3333] of **2**, while twelve and seven conformations of **1** can be derived from the [2334] and [2343] conformations of **2** respectively. The strain energies of the various conformations of **1** are listed in table 1.The lowest energy conformation is calculated to be the [3333]-2-one (Figure 2) in agreement with x-ray and NMR data on **1**. A comparison of the calculated torsional angles in cyclododecanone with those of the parent hydrocarbon cyclododecane (**2**)[6] and with torsional angles determined by x-ray diffraction analysis in cyclododecanone[3] and its oxime[4] and dibromo[5] derivatives (Table 2) shows strong similarities. Since **1** and its oxime have disordered structures, the data for these compounds are not very accurate and the differences between the calculated and observed torsional angles for **1** may not be very meaningful. Also, crystal lattice forces may distort the crystal conformation from that of an isolated molecule. 2,12-dibromocyclododecanone (Table 2) which is not disordered, actually has torsional angles close to those calculated for the parent ketone **1**. However, this could be a coincidence since the bromine atoms could modify the conformation somewhat. The change of a CH_2 group to a CO group results in comparatively small torsional angle changes in the [3333] conformation of cyclododecane (Table 2). The largest changes (ca. 15°) occur in torsional angles close to the CO group. The same situation occurs in the other energy minimum conformations of **1**, and therefore the torsional angles of these conformations are not listed.

The [3333]-2-one is the only conformation expected to be populated in **1** at low-temperatures, in agreement with ^1H and ^{13}C NMR data.[8] However, the force-field calculations indicate that the [3324]-2-one, [3423]-2-one, [4323]-3-one and [2334]-2-one have low strain energies (Table 1) relative to the [3333]-2-one, and may become

Table 1. Calculated Strain Energies (in kcal/mol) of Various Conformations of Cyclododecanone.

Conformation[a]	Relative Strain Energy[b]
[3333]-2-one	0.00
[3324]-2-one	1.24
[3423]-2-one	1.38
[4323]-3-one[d]	1.73
[2334]-2-one	1.86
[4233]-3-one	2.53
[3333]-1-one[c]	2.65
[4332]-2-one	2.67
[4323]-2-one	2.80
[3342]-2-one	2.81
[4233]-2-one	2.89
[2343]-2-one[d]	3.05
[3243]-2-one	3.28
[2433]-1-one	3.37
[3432]-2-one	3.56
[3243]-1-one	3.76
[3234]-2-one	3.77
[3324]-1-one	3.87
[2334]-1-one	3.93
[2343]-1-one	4.54
[3234]-1-one	5.05

[a] All conformations have C_1 symmetry except where otherwise stated.

[b] Strain-energy relative to [3333]-2-one which has a calculated total strain-energy of 7.90 kcal/mol.

[c] C_2 symmetry

[d] C_s symmetry

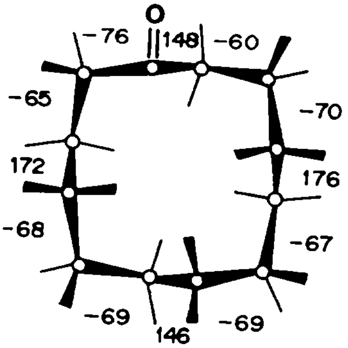

Figure 2. Calculated torsional angles of the [3333]-2-one conformation of cyclododecanone

Table 2. Experimental and Calculated Torsional Angles in Cyclododecanone and Related Compounds.

Compound[a]	ω_1	ω_2	ω_3	ω_4	ω_5	ω_6	ω_7	ω_8	ω_9	ω_{10}	ω_{11}	ω_{12}
$C_{12}H_{24}$[b]	69	-162	69	69	-159	69	69	-162	69	69	-159	69
$(CH_2)_{11}C{=}NOH$[c]	69	-164	69	73	-157	68	67	-164	75	75	-158	61
$(C_{11}H_{20}Br_2)C{=}O$[d]	79	-153	68	65	-171	63	73	-150	69	69	-172	62
$(CH_2)_{11}C{=}O$[e]	72	-159	68	71	-173	71	68	-159	72	64	-156	64
$(CH_2)_{11}C{=}O$[f]	76	-148	60	70	-176	67	69	-146	69	69	-172	65

[a] The torsional angle numbering is for the [3333] or [3333]-2-one conformation i.e. ω_1 is the bond adjacent to a corner position and to the carbonyl group if present.

[b] Calculated torsional angles of cyclododecane.[6]

[c] Experimentally determined torsional angles of cyclododecanone oxime.[4]

[d] Experimentally determined torsional angles of 2,12-dibromocyclododecanone.[5]

[e] Experimentally determined torsional angles of cyclododecanone.[3]

[f] Calculated torsional angles of cyclododecanone.

slightly populated near or above room temperature. All the conformations of **1** with calculated strain energies of 2 kcal/mol or more relative to the preferred conformation (Table 1) are not expected to be populated except at very high *temperatures. However, these conformations are important as intermediates and pseudorotation partners in the* pseudorotation of the lowest energy [3333]-2-one conformation.

Conformational Interconversions: There are two distinct types of pseudorotation in the [3333]-2-one conformation: one of these involves the [3333]-1-one as an intermediate and pseudorotation partner, and results in a time averaged C_2-symmetry for **1**; when the pseudorotation is fast. The other type of pseudorotation leads to time averaged C_s-symmetry for **1**. These two processes are designated as "C_2-pseudorotation" and "C_s pseudorotation" respectively and they both need to be fast for **1** to achieve time averaged C_{2v}-symmetry, and to fit the ^1H and ^{13}C NMR *spectra of* **1** *(Figure 3) in the fast exchange region (above about -100°C).*[8]

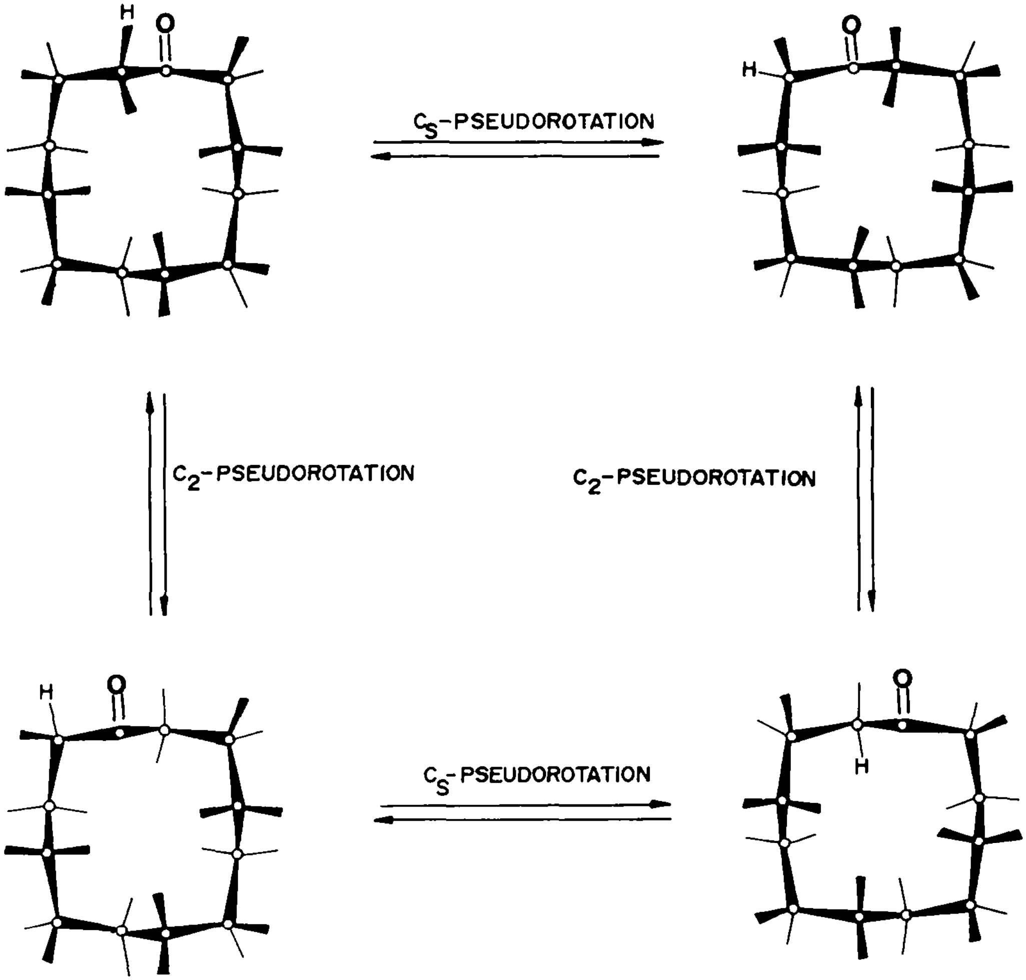

Figure 3. Effect of the C_2- and C_s-pseudorotation of the [3333]-2-one conformation. For clarity the position of only one specific α-proton is shown.

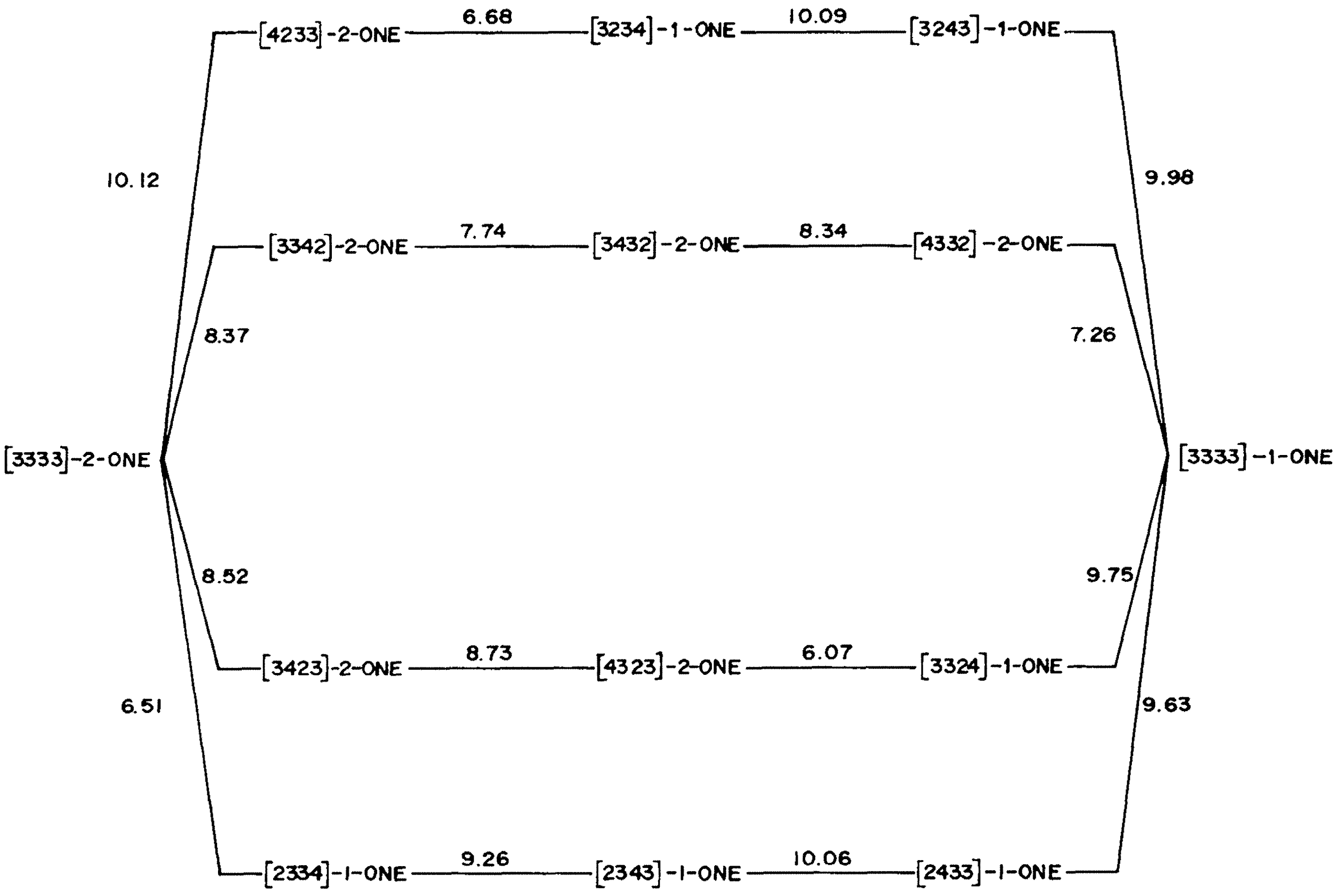

Figure 4. C_2-pseudorotation of the [3333]-2-one conformation. A number next to a line represents the strain energy (in kcal/mol) relative to the [3333]-2-one of the transition state for the conformational interconversion associated with that line.

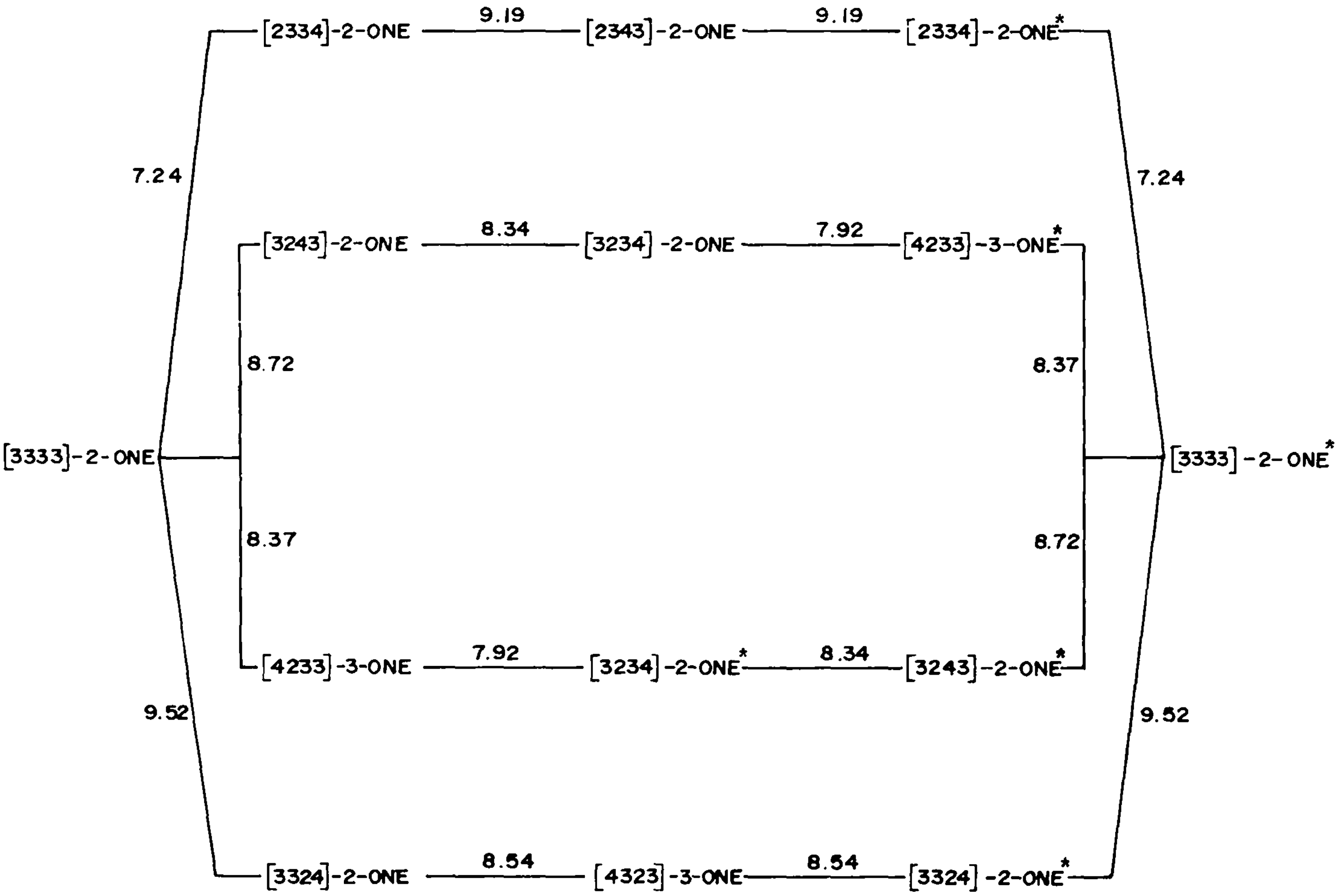

Figure 5. C_S-pseudorotation of the [3333]-2-one conformation (see figure 4). An asterix indicates the mirror image of an unlabelled conformation. The two sub-paths are mirror image of each other and together are considered to constitute one path.

The C_2-pseudorotation can proceed via four distinct paths (a total of eight if mirror image paths are included) as shown in Figure 4. The C_s-pseudorotation can take place via three paths (Figure 5): Two of these paths have plane-symmetrical pseudorotation partners of the [3333]-2-one. The third path has no symmetrical conformations and consist of two iso-energetic, but mirror image related, sub-paths which differ in the directions in which the intermediate conformations are traversed. Equal number of molecules will traverse each sub-path and thus the principle of microscopic reversibility is obeyed. Despite the absence of any plane symmetrical geometry along these two sub-paths, the resulting effect is exactly the same as if there were a plane symmetrical intermediate.

Force-field calculations have been carried out to obtain the strain energies of the conformational transition states associated with the paths shown in Figure 4 and 5, and are given in these figures. The best path for the C_2-pseudorotation has a calculated barrier of 8.3 kcal/mol (Figure 4). However, the other three possible paths for this process are calculated to have barriers which are 1.4, 1.6 and 1.7 kcal/mol higher in energy than the preferred path (Figure 4), and these values are within the expected margin of uncertainty in the calculations of conformational transition states. The best path for the C_s-pesudorotation has a calculated barrier of 8.7 kcal/mol and this is only 0.5 and 0.8 kcal/mol moe favorable than the other two possible paths for this process (Figure 5).[17]

Dynamic ^1H and ^{13}C NMR spectra of **1** show that the C_2- and C_s-pseudorotation processes of the [3333]-2-one conformation have virtually the same (free-energy) barrier of 7.5-7.7 kcal/mol. The calculated (strain-energy) barriers for these two pseuodorotation processes are 8.3 and 8.7 kcal/mol respectively, in reasonable agreement wih the NMR data.

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13. Nomenclature: The number of bonds on consecutive sides of a conformation are indicated within a square bracket starting with the side containing the carbonyl function. The direction of numbering around the ring is then dictated by the CO-group, and starts at the corner position nearest to this group. In cases where the CO function is symmetrically located on a side, the direction around the ring is chosen so as to have the second number the smallest possible. The position of the carbonyl group (from the nearest corner position) is indicated outside (after) the square bracket e.g. [4233]-3-one. This conformational labelling system should not be confused with the chemical labelling of Cyclododecanone, where 1 refers to the carbonyl carbon, 2 (or α) to the CH_2 next to the CO, etc.

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17. Our experience with the force-field calculations of medium-and large ring ketones is that the (energy minimum) conformations are accurate to within ±1 kcal/mol, while (energy maximum) conformational transition states are accurate to within ± 2 kcal/mol.

ACKNOWLEDGEMENT:

This work was supported by a grant (CY/FIEIDCAL/84) from King Fahd University of Petroleum and Minerals. We thank Dr. Frank A.L. Anet of the University of California, Los Angeles for his constructive discussions.