Ring Strain Energies from ab Initio Calculations

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Received November 13, 1997. Revised Manuscript Received March 9, 1998

Abstract: A new approach employing ab initio calculations is suggested for evaluating the strain energy of ring molecules as well as for estimating the relative contribution of different sources of strain to the ring strain energy. The approach developed is calibrated by reproducing experimentally determined strain energies of mono- and bicyclohydrocarbons, cyclic ethers, and amines. It is then used to predict ring strain energies of cyclic phosphoesters, hydrogen fluoride cyclic clusters, and magnesium dialdehyde cyclic chelates. The usefulness of the method is demonstrated in disclosing the role of ring strain in the enhanced reactivity of a five-membered cyclic phosphate relative to its acyclic analogue and six-membered ring counterpart.

Introduction

The concept of ring strain, put forward by Baeyer[1] over 100 ago, has proven quite useful in understanding chemical properties, in particular, chemical reactivity of a number of biologically significant cyclic compounds. The ring strain concept has been widely applied in organic chemistry, biochemistry, and photochemistry.[2] In many cases ring strain energy (E_{RS}) has been postulated to be the main driving force behind the chemical transformations of ring systems. For example, ring strain was originally and commonly assumed to be the chief driving force for the enhanced reactivity of five-membered cyclic phosphate and phosphonate relative to their acyclic analogues.[3] Specifically, the rate acceleration of five-membered cyclic phosphoesters was attributed to relief of ring strain in the transition state of the rate-determining step.

Ring strain energy is a relative quantity. It is defined as an energy excess between the cyclic molecule and an appropriately chosen strain-free counterpart. Experimentally E_{RS} can be determined from the respective heats of formation (ΔH_f) by employing the group equivalent scheme. Group equivalents are enthalpic, strain-free quantities for specific chemical groupings such as CH_3, CH_2, CH, $-CH{=}CH_2$, etc., which have been evaluated from the heats of formation of a large number of noncyclic strainless molecules.[4−6] Thus, E_{RS} is obtained as a difference between the actual heat of formation measured for the ring compound, and the hypothetical strain-free ΔH_f calculated for the same molecule by summing up the group equivalents for the respective fragments.[4−7] Note that additivity and transferability of group parameters are assumed in implementing the group equivalent scheme.

If the group equivalents or the heat of formation of the molecule of interest are not available, the heats of appropriately chosen chemical reactions can be used instead. The ring strain energy is defined to be the reaction energy of a balanced chemical reaction in which the reactant and product differ by the presence of a ring. Various types of reactions have been proposed, such as isodesmic,[8] homodesmotic,[9] and group equivalent reactions.[10] Another method of estimating the ring strain of cyclic species is to compare the measured heat of hydrolysis of the ring molecule and that of the acyclic analogue.[11] This method has been applied to assess the ring strain of some cyclic phosphate and phosphonate esters.[11−13] In particular, the difference in the enthalpies of hydrolysis of cyclic and acyclic phosphate and phosphonate esters was found to be roughly 2 kcal/mol less than the difference in activation enthalpies, suggesting that ring strain provided most, but not all, of the contributions to the observed rate enhancement in cyclic five-membered phosphorus esters.[13]

The pioneering work of Westheimer laid the basis for the theoretical evaluation of ring strain energy, which was estimated from ring bond angles and ring bending force constants,[14] i.e.

$$E_{RS} = \sum_{i=1}^{N} k_i^{\theta}(\theta_i - \theta_i^{0})^2 \qquad (1)$$

In this expression k^{θ} is a diagonal ring bending force constant, θ is a ring bond angle, θ^0 is the respective reference angle in a molecule considered strain-free, and N is the number of ring bond angles. Equation 1 is attractive in its simplicity. It

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S0002-7863(97)03895-X CCC: $15.00

accounts for contributions from ring bond angle distortions, but neglects torsional strain and strain arising from nonbonded interactions, which are important for bigger cycles. Since k^{θ} in the ring molecule is assumed to be the same as that in the strain-free molecule, it is best suited for small variations of θ around the tetrahedral angle. Thus, eq 1 performs well for evaluating the ring bending strain for medium-size rings. Three- and four-membered rings with deviations from tetrahedral angle of about 50° and 20°, respectively, need special attention.[7,15,16] Equation 1 has been employed to show that there is relief of strain energy on going from a tetrahedral five-membered cyclic phosphate (preferred $\angle$OPO = 109.5°) to a transition state with a $\angle$OPO of 90°, in sharp contrast to the large increase in strain energy for a transition state with a preferred $\angle$OPO of 120°.[17] Thus, the ring strain calculations using eq 1 suggested a trigonal-bipyramidal (TBP) transition state with the five-membered ring joined in the basal−axial positions for the hydrolysis of cyclic phosphates, a prediction that has been confirmed by both experimental[18] and theoretical studies.[19,20]

Theoretical estimates of ring strain energy can also be obtained by using group equivalents to convert ab initio energies into reasonably accurate heats of formation,[21] which can subsequently be employed in the group equivalent scheme to determine E_{RS} (see above). Another means of estimating the ring strain energy from ab initio calculations has been applied to a five-membered cyclic phosphodiester relative to its six-membered counterpart using the following expression:[22]

$$E_{\mathrm{RS}} = (E_{5\mathrm{cyclo}} - E_{5\mathrm{acyclo}}) - (E_{6\mathrm{cyclo}} - E_{6\mathrm{acyclo}}) \qquad (2)$$

where $E_{i\mathrm{cyclo}}$ is the energy of the i-th membered ring, and $E_{i\mathrm{acyclo}}$, that of the respective acyclic counterpart. The double subtraction in eq 2 eliminates the necessity to account for the different number of atoms included in five- and six-membered rings. Ab initio calculations using eq 2 have confirmed the existence of strain in the five-membered-ring ground state. Ab initio calculations have also been employed in evaluating ring strain energies of various inorganic rings.[23−25] In these systems, the ring strain energy was calculated as an energy difference between the reactants and products of a homodesmotic chemical reaction which preserves both bond types and valence environment around each atom. For example, in evaluating the strain energy of homoatomic sulfur rings the following reaction was designed:[23]

$$\mathrm{S}_n(\mathrm{ring}) + n\mathrm{HS}_2\mathrm{H}(\mathrm{chain}) \rightarrow n\mathrm{HS}_3\mathrm{H}(\mathrm{chain}) \qquad (3)$$

The reaction energy released in opening the ring is considered to be the ring strain energy.

In this work, a straightforward method for calculating ring strain energy and the relative contributions of various internal coordinates to the ring strain energy is presented (see Methods). The validity of such an approach is assessed by comparing the computed and experimental ring strain energies of mono- and bicyclic hydrocarbons, cyclic ethers, and cyclic amines. This is described in Results, which also demonstrates the generality of the approach by using it to predict the ring strain energies of noncovalent ring systems such as cyclic hydrogen fluoride clusters and magnesium dialdehyde chelates, as well as cyclic phosphoesters. Experimental determination of ring strain for such systems may not be easy and, therefore, theoretical estimates of ring strain provide useful information. The advantages and limitations of our approach are highlighted in the Discussion, which also shows how the present results have served to test the hypothesized role of ring strain in the hydrolysis of five-membered cyclic phosphate esters.

Methods

Ring Strain Energy. This is part of the total energy of a cyclic molecule. The strain energy of a given ring molecule relative to another structurally related *cyclic* compound (reference) can be calculated by directly comparing the ab initio energies of the two molecules provided the energy of the fragment, by which the two species differ from each other, is known. In the series of mono- and bicyclic hydrocarbons, cyclic ethers, cyclic amines, cyclic magnesium dicarbonyl chelates, and cyclic phosphates and phosphonates, this fragment is $(-\mathrm{CH}_2)_n$, where $n \geq 1$, while in the series of cyclic hydrogen fluoride clusters the repeating unit is $(\cdots\mathrm{HF})_n$, where $n \geq 1$. Thus, the strain energy of an n-membered ring relative to a r-membered (reference) ring can be computed from

$$E_{\mathrm{RS}} = E_n - E_r - (n - r)E_X \qquad (4)$$

where X denotes the differential fragment in the series ($-\mathrm{CH}_2$ or $\cdots$HF). It is assumed that the energy of this fragment is additive in a given series. Note that E_X must be a strain-free quantity and, therefore, has to be evaluated from strainless molecules. The most appropriate candidates for evaluating $E_{-\mathrm{CH}_2}$ seem to be straight-chain *all-trans*-paraffins. Thus, the $E_{-\mathrm{CH}_2}$ term in eq 4 was obtained as a difference between the ab initio energy of *all-trans*-hexane and that of *all-trans*-pentane. For the cyclic hydrogen fluoride clusters, $E_{\cdots\mathrm{HF}}$ was determined from the energy difference between a HF linear dimer and a single HF molecule.

The strain energy of an organic molecule can also be calculated relative to its acyclic counterpart containing the same number of heavy atoms (C, N, O, P, etc.). In this case, E_{RS} is given by

$$E_{\mathrm{RS}} = E_{\mathrm{cyclo}} - E_{\mathrm{acyclo}} + mE_{2\mathrm{H}} \qquad (5)$$

where

$$E_{2\mathrm{H}} = 2E_{\mathrm{C-H}} - E_{\mathrm{C-C}} \qquad (6)$$

is a balancing term accounting for two more C−H bonds at both ends of the acyclic chain, and an additional C−C bond for closure of the ring in the cyclic species; m is the number of rings in the cyclic system ($m = 1$ for monocyclic molecules, $m = 2$ for bicyclic species, etc.). The two energy terms on the right-hand side of eq 6 were derived from ethane:

$$E_{\mathrm{C-H}} = E_{\mathrm{CH_3CH_3}} - E_{\mathrm{CH_3CH_2}\bullet} \qquad (7)$$

$$E_{\mathrm{C-C}} = E_{\mathrm{CH_3CH_3}} - 2E_{\mathrm{CH_3}\bullet} \qquad (8)$$

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Table 1. Fragment Energies (Hartrees)

fragment	HF/6-31+G*	MP2/6-31+G*
E_{-CH_2}	−39.035 00	−39.167 29
$E_{\cdots HF}$	−100.022 42	−100.211 80
E_{2H}	−1.153 33	−1.161 77

Ring Strain Parameters. The relative contribution of a given source of strain to the strain energy was estimated from ring strain parameters (RSP), defined by

$$\mathrm{RSP}(I) = \Delta E_{\mathrm{RS}}/\Delta I = (\Delta E_n/\Delta I) - (\Delta E_r/\Delta I) \quad (9)$$

for a cyclic reference molecule, and

$$\mathrm{RSP}(I) = \Delta E_{\mathrm{RS}}/\Delta I = (\Delta E_{\mathrm{cyclo}}/\Delta I) - (\Delta E_{\mathrm{acyclo}}/\Delta I) \quad (10)$$

for an acyclic reference molecule. In eqs 9 and 10 I is a ring internal coordinate (bond stretch, bond angle, or dihedral angle), and ΔI is a small change in I. A given internal coordinate is slightly distorted from its equilibrium value (say, by −0.02 Å for bond lengths and −3° for bond and dihedral angles; i.e., $\Delta I = -0.02$ Å and $\Delta I = -3°$, respectively) and is kept frozen during subsequent molecular geometry optimization. The distorted energies E_i^{dist} ($i = n$, r, cyclo, acyclo) are then compared with E_i^{o} obtained by full energy optimization to yield $\Delta E_i = E_i^{\mathrm{dist}} - E_i^{\mathrm{o}}$.

Calculations. Ring strain energies were computed for the following series of ring molecules; viz., (a) cycloalkanes (C_3−C_7), (b) cycloalkenes (C_3−C_7), (c) bicycloalkanes (C_5−C_8), (d) cyclic ethers (C_2−C_6), (e) cyclic amines (C_2−C_6), (f) cyclic hydrogen fluoride clusters $(HF)_n$ ($n = 3, 4, 5, 6$), (g) cyclic dicarbonylmagnesium chelates (five- to eight-membered rings), (h) cyclic phosphates (three- to seven-membered rings), and (i) cyclic phosphonates (three- to seven-membered rings). Ab initio energies were computed using the program Gaussian 94.[26] The molecular geometries were fully optimized at the HF/6-31+G* and MP2/6-31+G* levels for all the molecules treated. Only the total electronic energy was considered in the calculations. Zero-point energy has been reported to contribute about 0.5 kcal/mol[22] to the overall ring strain energy and, therefore, was neglected in the present study. Values of E_{-CH_2}, $E_{\cdots HF}$, and E_{2H} from HF/6-31+G* and MP2/6-31+G* ab initio calculations are summarized in Table 1.

Results

Cyclic Hydrocarbons, Ethers, and Amines. The calculated ring strain energies of these molecules are listed in Table 2. Two sets of E_{RS} are given: the first set is evaluated relative to the respective six-membered ring in the series, usually thought to be the least strained species, and the second set is calculated with respect to a strainless open-chain molecule depicted on the right-most side of the table. In the case of bicycloparaffins, the less strained bicyclo[2.2.2]octane served as a reference ring molecule. By definition, the ring strain energy of the reference molecule is zero. Experimentally determined strain energies, where available, are also listed for comparison in Table 2. These were derived from gas-phase measurements[5−7] and are, therefore, appropriate for calibrating our ab initio results.

The E_{RS} values relative to a reference ring molecule in Table 2 show very good agreement (in trends of changes and absolute values) between the calculated and experimental ring strain energies. Especially demonstrative in this respect is the series of cycloalkanes where the MP2/6-31+G* and observed E_{RS} differ by less than 0.4 kcal/mol. Inclusion of electron correlation generally yields ring strain energies in better agreement with experiment than the HF/6-31+G* strain energies, for example, cyclopropene, cycloheptene, ethylene oxide (three-membered cyclic ether), and pyrrolidine (five-membered cyclic amine). Thus, inclusion of electron correlation appears to be quite important in determining E_{RS} for rings containing multiple bonds (cycloalkenes) or heteroatoms with lone pairs (cyclic ethers and amines). However, it has a smaller effect in the case of saturated mono- and bicyclic hydrocarbons. The MP2/6-31+G* calculations predict that the strain energies of seven-membered cyclic ether and cyclic amine are comparable to their five-membered ring counterparts, in analogy to cycloheptane and cycloheptene.

The ring strain energy of the six-membered ring in each series was also evaluated relative to its open-chain *all-trans*-counterpart using eq 5. This value was then added to the E_{RS} (relative to a reference cyclic molecule) for the other rings in the series. The results in Table 2 show that six-membered rings, often thought of as strain-free, possess about 3 kcal/mol of strain energy. For example, cyclohexane, with an experimental E_{RS} equal to 0 kcal/mol,[7] was calculated to have a ring strain energy of 2.5 kcal/mol (MP2/6-31+G* level). This reflects the fact that the six-membered ring is forced to adopt an energetically unfavorable *gauche* conformation, whereas *n*-hexane can exist in a strain-free trans−trans−trans conformation.

To provide qualitative information about the contribution of different molecular parameters, such as bond lengths, bond angles, and dihedral angles, to the ring strain, ring strain parameters were evaluated for some representatives of the cycloalkane family (Table 3). Cyclohexane was taken as a reference molecule. The smallest ring in the series—cyclopropane—is characterized by an abnormally small ring bond angle of 60°. This is considered to be the main source of ring strain in the molecule, which is expected to be reflected in the respective ring strain parameter. Indeed, RSP(α_{CCC}) is negative and has the highest magnitude in the series. In cyclobutane, cyclopentane, and cycloheptane the ring bond angles increase (to 88°, 102−105°, and 114−117°, respectively), leading to a decrease in both the computed strain energy and the magnitude of RSP(α_{CCC}). Ring strain parameters with respect to C−C bond stretching and HCCC dihedral angle for cyclopropane and cyclobutane are at least an order of magnitude smaller than RSP(α_{CCC}), thus they do not contribute significantly to the strain energy. However, the magnitude of RSP(τ_{HCCC}) increases with increasing ring size such that for cycloheptane it dominates the other ring strain parameters, indicating that the ring strain is mainly due to nonbonded interactions between hydrogen atoms which are implicitly reflected in RSP(τ_{HCCC}).

Cyclic Hydrogen Fluoride Clusters and Magnesium Dialdehyde Chelates. Ring strain energies have also been evaluated for cyclic systems containing *noncovalent* bonds, specifically, hydrogen fluoride clusters $(HF)_n$ ($n = 3, 4, 5, 6$), and 1:1 Mg^{2+} complexes of α, β, γ, and δ dialdehydes (Table 4). For both series the respective six-membered rings are taken as a reference. At first glance, it may seem surprising that the

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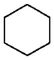
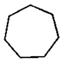
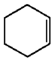
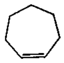
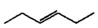
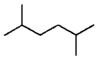
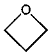
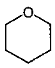
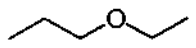
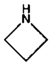
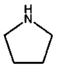
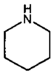
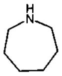
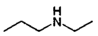
Table 2. Strain Energies (in kcal/mol) for Covalently Bonded Mono- and Bicyclic Molecules

						
Reference molecule: cyclohexane						
Experiment[a]	27.5	26.5	6.2	0	6.3	
HF/6-31+G*	27.6	25.8	5.9	0	7.8	
MP2/6-31+G*	27.7	26.5	6.4	0	6.7	
Reference molecule: all-trans-hexane						
HF/6-31+G*	31.8	30.0	10.1	4.2	12.0	0
MP2/6-31+G*	30.2	29.0	8.9	2.5	9.2	0

						
Reference molecule: cyclohexene						
Experiment[a]	55.5	28.7	4.4	0	3.9	
HF/6-31+G*	58.0	31.8	4.7	0	5.2	
MP2/6-31+G*	55.9	31.4	4.7	0	3.7	
Reference molecule: all-trans-3-hexene						
HF/6-31+G*	62.3	36.1	9.0	4.3	9.5	0
MP2/6-31+G*	59.0	34.5	7.8	3.1	6.8	0

						
Reference molecule: bicyclo[2.2.2]octane						
Experiment[a]	60.6	29.6	7.0	0		
HF/6-31+G*	58.3	27.6	4.7	0		
MP2/6-31+G*	58.4	27.4	4.5	0		
Reference molecule: 2,5-dimethyl-hexane						
HF/6-31+G*	73.7	43.0	20.1	15.4		0
MP2/6-31+G*	72.3	41.3	18.4	13.9		0

						
Reference molecule: tetrahydropyran						
Experiment[b]	26.3	24.7	5.4	0	–	
HF/6-31+G*	28.9	24.3	4.1	0	6.0	
MP2/6-31+G*	26.6	25.3	4.7	0	5.3	
Reference molecule: all-trans-ethylpropyl ether						
HF/6-31+G*	34.4	29.8	9.6	5.5	11.5	0
MP2/6-31+G*	30.0	28.7	8.1	3.4	8.7	0

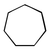
						
Reference molecule: piperidine						
Experiment[c]	26.7	25.2	5.8	0	–	
HF/6-31+G*	28.0	24.5	4.3	0	6.9	
MP2/6-31+G*	27.7	25.4	5.4	0	6.1	
Reference molecule: all-trans-ethylpropyl amine						
HF/6-31+G*	33.1	29.6	9.4	5.1	12.0	0
MP2/6-31+G*	31.1	28.8	8.8	3.4	9.5	0

[a]From Ref. [7]; [b]From Ref. [6]; [c]From Ref. [5].

six-membered ring in the HF cluster series is the most strained structure. The bigger cycles $(HF)_n$ ($n = 4, 5, 6$) possess less strain by 13.6, 19.3, and 21.1 kcal/mol, respectively (MP2/6-31+G* calculations). However, upon closer inspection of the optimized geometrical parameters the ring strain in the series was found to correlate with the magnitude of the HFH and FHF angles (see Table 4). Since the geometry of the cycles is dictated by the heavy (fluorine) atoms, the HF clusters can be considered as pseudo three-, four-, five-, and six-membered rings, respectively. Thus, the pseudo six-membered ring has the least strain in the series.

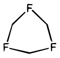
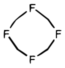
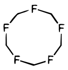
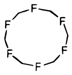
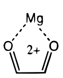
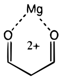
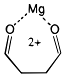
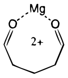
A similar trend in the ring strain energy changes was observed for the series of Mg^{2+} dialdehyde chelates, where the ring strain was relieved upon increasing the ring size. These results can be associated mainly with changes in the OMgO bond angle, which is 79°, 91°, 100°, and 108° in the five-, six-, seven-, and eight-membered ring, respectively. The magnesium complex of the five-membered ring has the most strain not only due to the small OMgO bond angle, but also due to the energetically unfavorable s-cis position adopted by the two carbonyl groups, which have been reported to be in a s-trans position in free glyoxal molecule in the gas phase.[27]

Table 3. Ring Strain Parameters with Respect to Stretching, Bending, and Dihedral Internal Coordinates from HF/6-31+G* ab Initio Calculations[a]

Molecule	Strain energy (kcal mol^{-1})	RSP(r_{CC}) (kcal mol^{-1} Å^{-1})	RSP(α_{CCC}) (kcal mol^{-1} rad^{-1})	RSP(τ_{HCCC}) (kcal mol^{-1} rad^{-1})
	27.6	−0.20	−18.33	0.29
	25.8	0.36	−6.42	0.29
	5.9	0.85	−2.12	0.63
	7.8	0.22	0.86	−1.09

[a] The reference molecule is cyclohexane.

Table 4. Ring Bond Angles (in deg)[a] and Strain Energies (in kcal/mol) for Noncovalently Bonded Cyclic Hydrogen Fluoride Clusters and 1:1 Magnesium Dialdehyde Chelates

∠HFH	89.3	103.6	112.7	119.1
∠FHF	150.7	166.4	175.3	179.1
				
Reference molecule: hydrogen fluoride cyclic trimer				
HF/6-31+G*	0	−11.5	−14.4	−13.1
MP2/6-31+G*	0	−13.6	−19.3	−21.1
∠OMgO	78.9	90.7	100.4	107.6
∠MgOC	115.1	129.6	138.2	144.4
				
Reference molecule: Mg^{2+} malondialdehyde chelate				
HF/6-31+G*	41.6	0	−14.5	−27.0
MP2/6-31+G*	36.3	0	−13.0	−25.8

[a] From MP2/6-31+G* *ab initio* calculations.

Cyclic Phosphoesters. The ring strain energies for a series of cyclic phosphates and phosphonates are summarized in Table 5. The experimental strain energies were obtained from the differential in heat released upon alkaline hydrolysis of the cyclic and acyclic species.[13] Note that these have been measured in solution. Furthermore, the ring strain energy of five-membered ring methyl ethylene phosphate (5-MEP) and methyl propylene phosphonate have been determined relative to dimethyl hydroxyethyl phosphate and dimethyl (hydroxyethyl)phosphonate, respectively, instead of their acyclic counterparts with the same number of heavy atoms; i.e., trimethyl phosphate (a-TMP) and dimethyl ethylphosphonate.[13] Since experimental ring strain data are available only for five-membered rings vs their acyclic analogues, the respective acyclic counterparts, (a-TMP) and dimethyl ethylphosphonate, are taken as reference in Table 5. The computed ring strain energies of the five-membered ring phosphate and phosphonate relative to their acyclic analogues are in fortuitous close agreement with the experimental values. In particular, the computed ring strain energy difference between the five-membered ring phosphate and phosphonate (1.7−1.9 kcal/mol) is in accord with the measured difference of 2.2 kcal/mol.

For the series of cyclic phosphates, the MP2/6-31+G* strain energies decrease with increasing ring size. The changes in ring strain energies correlate with the deviations of the OPO and COP ring bond angles from the corresponding acyclic values. The MP2/6-31+G* calculations predict that the three-membered ring phosphate has a very high ring strain energy (86 kcal/mol), whereas the six- and seven-membered rings have comparable strain energies. As observed for the monocyclic molecules in Table 2, the six-membered ring phosphate has about 3 kcal/mol of strain energy, thus the ring strain energies relative to six-membered ring methyl propylene phosphate (6-MPP) are correspondingly lower than those relative to a-TMP. In sharp contrast, the six-membered ring phosphonate, unlike its phosphate counterpart, is practically strain-free, possessing only 0.1 kcal/mol (MP2/6-31+G* calculations) strain energy relative to the acyclic reference molecule despite significant deviations of the OPC, COP, and CCP ring bond angles from the corresponding acyclic values. On the other hand, the seven-membered ring phosphonate has 2.4 kcal/mol of strain energy, even though its OPC, COP, and CCP ring bond angles show the least deviations from the respective acyclic values in the phosphonate series. In analogy to the cyclic phosphates, the three-membered ring phosphonate exhibits markedly higher ring strain than the other members in the series; however, it is less strained than the corresponding three-membered cyclic phosphate.

The ring strain energy formulas (eqs 4 and 5) presented in Methods can be applied not only to covalently and noncovalently bonded ring systems but also to transient species such as transition states and intermediates of a chemical reaction. In previous work,[28] the rate-limiting transition states for the alkaline hydrolysis of five-membered ring 5-MEP, its acyclic analogue a-TMP and its six-membered ring counterpart, 6-MPP, have been determined. The optimized geometries of the rate-limiting transition states in the gas phase and in solution were employed in the calculation of ring strain energy of the rate-limiting transition state for 5-MEP alkaline hydrolysis relative to its six-membered ring counterpart and acyclic analogue using eqs 4 and 5, respectively. The results are summarized in Table 6. The HF and MP2 ring strain energies show similar trends and differ by less than 2 kcal/mol. The ring strain energies of the rate-limiting transition state of 5-MEP alkaline hydrolysis (Table 6) indicate that the five-membered ring transition state is strained relative to its acyclic analogue or to its six-membered ring counterpart, and it is significantly more strained relative to the former than the latter, as in the case of 5-MEP. With respect to its acyclic analogue, the five-membered ring transition state is more strained than the ground state (by about 3−4 kcal/mol), whereas relative to its six-membered ring counterpart, the five-membered ring transition state is slightly less strained than 5-MEP (by about 1−3 kcal/mol). In analogy to the five-membered ring transition state, the six-membered cyclic transition state is strained relative to the acyclic molecule and is more strained than 6-MPP (by about 5−6 kcal/mol). In sharp contrast to the five-membered ring transition state, the five-membered cyclic intermediate (Table 6) has less strain than its acyclic analogue or its six-membered ring counterpart. However, the six-membered ring phosphate intermediate still possesses about 2−3 kcal/mol of strain energy relative to the acyclic intermediate.

To disclose the source of strain in 5-MEP and the corresponding transition state, ring strain parameters were evaluated. The results in Table 7 reveal that distortion of the ring OPO

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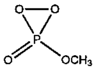
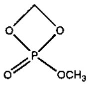
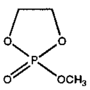
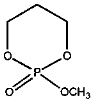
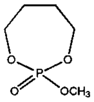
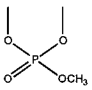
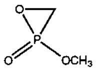
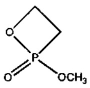
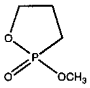
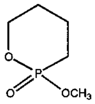
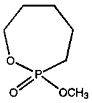
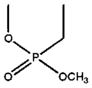
(27) Barton, D., Ollis, W. D., Eds. *Comprehensive Organic Chemistry*; Pergamon Press: Oxford, **1979**; Vol. 1.

(28) Chang, N.-Y.; Lim, C. *J. Am. Chem. Soc.* **1998**, *120*, 2156.

Table 5. Ring Bond Angles (in deg)[a] and Strain Energies (in kcal/mol) for Covalently Bonded Ground-state Cyclic Phosphoesters

∠OPO	61.1	83.0	96.7	102.4	104.2	102.7[b]
∠COP[b]	–	89.5	109.6	113.8	118.4	118.4
						
Reference molecule: trimethyl phosphate						
Experiment[c]	–	–	5.9	–	–	–
HF/6-31+G*	103.6	20.5	7.1	3.1	4.7	0
MP2/6-31+G*	86.1	18.5	6.7	2.6	2.3	0
Reference molecule: methyl propylene phosphate						
HF/6-31+G*	100.5	17.4	4.0	0	1.6	
MP2/6-31+G*	83.5	15.9	4.1	0	–0.3	
∠OPC	55.2	82.4	95.9	101.7	105.1	103.6[b]
∠COP	66.4	92.9	112.7	114.0	118.4	118.8[b]
∠CCP	-	84.9	102.2	108.3	112.3	111.7
						
Reference molecule: dimethyl (ethyl) phosphonate						
Experiment[c]	–	–	3.7	–	–	–
HF/6-31+G*	50.8	21.0	5.2	0.8	5.1	0
MP2/6-31+G*	45.9	19.7	5.0	0.1	2.4	0
Reference molecule: methyl butylphosphonate						
HF/6-31+G*	50.0	20.2	4.4	0	4.3	
MP2/6-31+G*	45.8	19.6	4.9	0	2.3	

[a] From MP2/6-31+G* *ab initio* calculations.

[b] Averaged value.

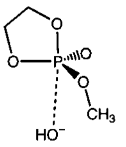
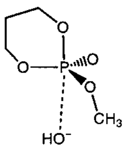
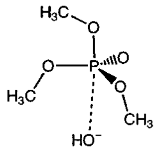
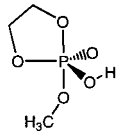
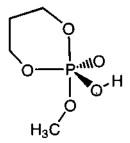
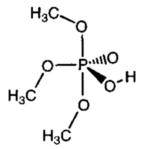
[c] From Ref. [13]; see text about the experimental conditions.

and COP bond angles from their equilibrium values governs the magnitude of the strain energy in the ground state; the dihedral angle ring strain parameters are an order of magnitude smaller and do not contribute as much to the strain energy of the five-membered cyclic phosphate. Distortions of the ring OPO angle dominate over the ring COP angle distortions in determining the ring strain of 5-MEP relative to a-TMP [RSP(α_{OPO}) = -8.5 vs RSP(α_{OPO}) = -4.0 kcal mol^{-1} rad^{-1}] and to its six-membered counterpart [RSP(α_{OPO}) = -6.0 vs RSP(α_{OPO}) = -3.6 kcal mol^{-1} rad^{-1}]. The larger 5-MEP ring strain energy relative to a-TMP (7.1 kcal mol^{-1}) compared to that relative to 6-MPP (4.0 kcal mol^{-1}) correlates with the greater magnitude of the bond angle ring strain parameters for 5-MEP relative to a-TMP compared to those relative to 6-MPP. This trend, in turn, correlates with the greater deviations of ring bond angles from the corresponding values in the reference molecule (see Table 5). Furthermore, the ring strain parameters with respect to the ring COPO and HCOP dihedral angles for 5-MEP relative to 6-MPP are positive, implying that distortion of the ring COPO or HCOP dihedral angle from its equilibrium value leads to a greater increase in the energy of 6-MPP compared to 5-MEP. In other words, the six-membered ring is more sensitive than the five-membered ring to strain in the ring COPO and HCOP dihedral angles.

For a given reference state, comparison of the respective ring strain parameters in the transition state and the ground state provides clues to the observed changes in the ring strain energy of the five-membered ring transition state relative to the ground state. With respect to the acyclic species, only RSP(α_{OPO}) becomes more negative in the five-membered cyclic transition state (-9.5) compared to 5-MEP (-8.5) as distortion of the ring OPO angle results in a smaller energy increase in the acyclic transition state compared to a-TMP. In contrast, the other ring strain parameters in Table 7 are smaller in magnitude in the five-membered ring transition state compared to 5-MEP due mainly to the smaller energy increase in the former compared to 5-MEP upon distortion of the COP, COPO, and HCOP angles. Thus, with respect to the acyclic species, the increase in strain energy of the five-membered ring transition state (10 kcal/mol) relative to 5-MEP ($\sim$7 kcal/mol) correlates with the better ability of the acyclic transition state to accommodate OPO angle strain compared to a-TMP.

Relative to the six-membered ring species, the ring strain parameters, RSP(α_{OPO}) and RSP(α_{COP}), become less negative in the five-membered cyclic transition state compared to 5-MEP due mainly to the larger energy increase in the six-membered ring transition state compared to 6-MPP upon distortion of the OPO and COP angles. In contrast, the corresponding RSP(τ_{COPO}) and RSP(τ_{HCOP}) become more positive in the five-membered cyclic transition state compared to 5-MEP as distortion of the COPO and/or HCOP dihedral angles leads to a smaller energy increase in the five-membered ring transition

Table 6. Bond Angles (in deg)^{a} and Strain Energies (in kcal/mol) in the Rate-Limiting Transition States and Intermediates Formed during Alkaline Hydrolysis of 5-MEP, 6-MPP, and a-TMP

∠OPO (ring)	93.2	97.2	–
∠COP	113.1^{b}	116.5^{b}	124.1^{b}
∠O$_a$PO$_e$	89.8^{b}	89.8^{b}	89.8^{b}
∠O$_e$PO$_e$	116.3^{b}	116.7^{b}	117.5^{b}
Transition state			
Reference molecule: a-TMP...OH$^-$ transition state			
HF/6-31+G*	10.3^{c}	9.2^{c}	0
MP2/6-31+G*	10.7^{d}	7.5^{d}	0
MP2/6-31+G*	10.0^{e}	8.5^{e}	0
Reference molecule: 6-MPP...OH$^-$ transition state			
HF/6-31+G*	1.1^{c}	0	
MP2/6-31+G*	3.2^{d}	0	
MP2/6-31+G*	1.5^{e}	0	
∠OPO (ring)	84.2	87.5	–
∠COP	114.5^{b}	119.4^{b}	121.2^{b}
∠O$_a$PO$_e$	89.9^{b}	89.9^{b}	89.9^{b}
∠O$_e$PO$_e$	119.9^{b}	119.8^{b}	119.9^{b}
Intermediate			
Reference molecule: a-TMP–OH$^-$ intermediate			
HF/6-31+G*	–1.0	2.8	0
MP2/6-31+G*// HF/6-31+G*	–1.0	1.6	0
Reference molecule: 6-MPP–OH$^-$ intermediate			
HF/6-31+G*	–3.8	0	
MP2/6-31+G*// HF/6-31+G*	–2.6	0	

[a] From HF/6-31+G* *ab initio* calculations.

[b] Averaged value.

[c] Calculations based on gas-phase TS.

[d] Calculations based on TS in solution relocated using CDM solvation free energies.[28]

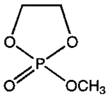
[e] Calculations based on TS in solution relocated using PSGVB solvation free energies.[28]

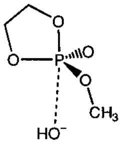
state compared to 5-MEP but a larger energy increase in the six-membered ring transition state compared to 6-MPP. Thus, with respect to the six-membered ring species, the decrease in strain energy of the five-membered ring transition state (1 kcal/mol) relative to 5-MEP (4 kcal/mol) seems to be due mainly to the poorer ability of the six-membered cyclic transition state to accommodate strain in the ring angles and dihedrals compared to the six-membered ring ground state.

Discussion

As evidenced from the data presented in the previous section, the procedure employing ab initio molecular energies (see Methods) gives satisfactory estimates of the ring strain energies of different classes of cyclic molecules. The approach is *straightforward.* It uses only a few parameters, namely, the energy balancing terms, which can be widely used to calculate the ring strain energies for a large number of cyclic systems. As the energy balancing terms can be determined from ab initio calculations and do not need to be parametrized against experimental data, the method is *general.* It is not restricted to covalently bonded ring molecules, but can be applied to noncovalent cyclic systems as well as to transient species such as transition states and intermediates. Furthermore, both cyclic and acyclic species can serve as reference structures. The results

Table 7. Ring Strain Energies and Ring Strain Parameters [RSP (= $\Delta E_{\mathrm{MEP}}/\Delta I - \Delta E_{\mathrm{ref}}/\Delta I$) with Respect to Ring Bond Angles (α) and Dihedral Angles (τ) (in kcal mol^{-1} rad^{-1}) in the Ground State and Rate-Limiting Transition State of 5-MEP Alkaline Hydrolysis from HF/6-31+G* ab Initio Calculations

 **5-MEP GS**	Reference molecule: **a-TMP** E_{RS} = 7.1 kcal mol^{-1}			Reference molecule: **6-MPP** E_{RS} = 4.0 kcal mol^{-1}		
I	$\Delta E_{MEP}/\Delta I$	$\Delta E_{ref}/\Delta I$	RSP	$\Delta E_{MEP}/\Delta I$	$\Delta E_{ref}/\Delta I$	RSP
α_{OPO}	−14.99	−6.47[a]	−8.52	−14.99	−8.99	−6.00
α_{COP}	−6.78[b]	−2.82[c]	−3.96	−6.78[b]	−3.18[b]	−3.60
τ_{COPO}	−0.42[d]	−0.21[e]	−0.21	−0.42[d]	−0.92[d]	0.50
τ_{HCOP}	−0.38	−0.09	−0.29	−0.38	−0.68	0.30

 **5-MEP...OH$^-$ TS**	Reference molecule: **a-TMP** E_{RS} = 10.3 kcal mol^{-1}			Reference molecule: **6-MPP** E_{RS} = 1.1 kcal mol^{-1}		
I	$\Delta E_{MEP}/\Delta I$	$\Delta E_{ref}/\Delta I$	RSP	$\Delta E_{MEP}/\Delta I$	$\Delta E_{ref}/\Delta I$	RSP
$\alpha_{OPO'}$	−15.32	−5.84	−9.48	−15.32	−11.72	−3.60
α_{COP}	−5.19	−2.82	−2.37	−5.19	−3.89	−1.30
τ_{COPO}	−0.17	−0.31	0.14	−0.17	−0.85	0.68
τ_{HCOP}	−0.19	−0.05	−0.14	−0.19	−0.97	0.78

[a] Averaged over the three O–P–O bond angles.
[b] Averaged over the two ring C–O–P bond angles.
[c] Averaged over the three C–O–P bond angles.
[d] Averaged over the two ring C–O–P–O torsional angles.
[e] Averaged over the six C–O–P–O torsional angles.

presented in the previous section also show that the ring strain parameters (eqs 9 and 10) can be employed to disclose the importance of the different strain-inducing sources to the ring strain energy.

Compared to previous ab initio estimates of ring strain employing the group equivalent scheme or eqs 2 and 3, our approach is less expensive. Ring strain estimates using eq 2 require the ab initio energy evaluation of two cyclic and two acyclic molecules, whereas our method based on eq 4 requires half the computational work; i.e., the ab initio energies of the cyclic compound of interest and its cyclic counterpart, given the balancing term.

Our approach also has several advantages relative to calculations of ring strain energies employing molecular mechanics methods; e.g., eq 1. Molecular mechanics calculations based on an empirical force field are inexpensive and give explicitly the contributions of various intramolecular parameters to the molecular energy. However, the parameters in the empirical force field, which have been adjusted to reproduce molecular properties of a particular group of compounds, may not always be transferable. This is the case for small (three- and four-membered) rings, where the C−C−C bending force constants differ from that of bigger rings.[7,16] In addition to assuming the transferability of parameters, only diagonal force constants are employed in evaluating the ring energy. While this may be a good approximation for treating open-chain molecules or large cyclic systems, neglecting off-diagonal force constants is not justifiable in the case of smaller ring molecules whose internal coordinates are strongly coupled since the off-diagonal force constants, reflecting various intramolecular interactions, contribute to the molecular energy. This is illustrated in Table 8, which compares ab initio force constants for open-chain *all-trans-n*-alkanes (propane, butane, pentane, and hexane) with those for cyclopropane, cyclobutane, cyclopentane, and cyclohexane. The off-diagonal force constants for *n*-alkanes are 1−2 orders of magnitude smaller than the diagonal terms, whereas those for cycloalkanes are comparable in magnitude to the diagonal terms. Furthermore, both diagonal and off-diagonal force constants are hardly transferable from open-chain alkanes to the cyclic paraffins. The diagonal force constants for the cycloalkanes, especially the bending terms, are significantly smaller than those for *n*-alkanes. In contrast, the off-diagonal force constants of cycloparaffins are often larger in magnitude than the respective constants for the open-chain hydrocarbons.

Table 8. Stretching and Bending Force Constants Evaluated from HF/6-31+G* ab Initio Calculations for *n*-Alkanes[a] and Cycloalkanes (in au)

	n-alkanes	cyclo-propane	cyclo-butane	cyclo-pentane	cyclo-hexane
		Diagonal Terms[b]			
k_r	0.318	0.193	0.224	0.257	0.276
k_θ	0.149	0.034	0.064	0.074	0.063
		Cross Terms[b]			
$k_{rr'}$	0.008	0.058	0.008	0.004	0.000
$k_{rr''}$	0.000	−	0.063	0.035	0.007
$k_{r\theta}$	0.012	−0.027	−0.027	−0.017	−0.022
$k_{\theta\theta'}$	0.024	−	−0.045	−0.048	−0.034
$k_{\theta\theta''}$	0.005	−	−	0.012	0.012

[a] The series includes propane, *trans*-butane, *trans*,*trans*-pentane, and *all-trans*-hexane. [b] r = C−C stretch and θ = CCC bending; ′ denotes neighboring internal coordinate, and ″, the second farthest neighboring coordinate.

In particular, the stretch−stretch force constants for cyclopropane and cyclobutane are nearly 1 order of magnitude higher than those for *n*-paraffins.

The accuracy of ring strain calculations based on our approach depends on the computational method, basis set employed, and treatment of electron correlation. As shown in Table 2, inclusion of electron correlation significantly improves the accuracy of the results obtained. Medium basis sets, such as the 6-31+G* basis used in the present study, perform well yielding MP2/6-31+G* strain energies in good agreement with experiment. Thus, MP2/6-31+G* calculations represent a reasonable compromise between the computational expense and the accuracy of the quantities evaluated.

Applications. The usefulness of our approach is exemplified in the ring strain energy and ring strain parameter calculations of the ground state and rate-limiting transition state of 5-MEP alkaline hydrolysis. These calculations have helped to elucidate the role of ring strain in the observed enhanced rates of alkaline hydrolysis of 5-MEP relative to its acyclic analogue or six-membered ring counterpart. Ring strain was originally and commonly assumed to be the chief driving force for the enhanced rates of ring cleavage,[3,18] on the basis of the assumption that the transition states for reaction of both the cyclic and acyclic species were free of strain and therefore the strain energy in the five-membered ring ground state would be relieved upon formation of the transition state. The ring strain energies presented in Table 6 show this assumption to be invalid. The rate-limiting transition state for alkaline hydrolysis of 5-MEP is not strain-free. In fact, relative to the acyclic species, the five-membered cyclic transition state (E_{RS} = 10−11 kcal/mol) has more strain than the ground state (E_{RS} = ∼7 kcal/mol). Thus, the 5-MEP strain energy, which is dominated by OPO and COP angle strain in the five-membered ring, is not relieved upon formation of the transition state, but is relieved instead upon forming the pseudorotated TBP intermediate (E_{RS} = −1 kcal/mol, Table 6). Thus, ring strain does not account for the observed millionfold rate acceleration of 5-MEP alkaline hydrolysis relative to a-TMP base hydrolysis. On the other hand, relative to the six-membered ring species, the five-membered ring transition state (E_{RS} = 1−3 kcal/mol) has less strain than the ground state (E_{RS} = ∼4 kcal/mol). The decrease in strain energy is not due inasmuch to the relief of angle strain in 5-MEP upon forming the five-membered ring transition state but is due primarily to the poorer ability of the six-membered cyclic transition state to accommodate strain in the ring angles and dihedrals compared to the six-membered ring ground state. This is supported by the finding that the six-membered cyclic TBP intermediate has more strain than the corresponding five-membered cyclic intermediate (by about 3 kcal/mol, Table 6).

Conclusions

A new approach using ab initio calculations to compute ring strain energies (eqs 4 and 5) and the relative contributions of individual intramolecular parameters to the ring strain energy (eqs 9 and 10) has been presented. Ring strain is calculated as an energy difference between the molecule of interest and a reference species, plus/minus an additional strain-free energy term balancing the difference in the number of atoms and bonds in the two molecules.

The method yields strain energies in good agreement with experiment (Table 2). Hence, it is especially useful in cases where experimental strain energies are not available; e.g., for compounds that can only be obtained in small quantities or can only be observed under unusual conditions such as matrix isolation and molecular beams.

The application of the method is not limited to covalently bonded cyclic systems but can be employed to estimate ring strain energies of noncovalently bonded cyclic clusters (Table 4) or short-lived transition states and intermediates of cyclic molecules (Table 6).

The method has been used to compute ring strain energies and ring strain parameters of the ground state and rate-limiting transition state of 5-MEP alkaline hydrolysis (Tables 5−7). The calculations reveal that ring strain does *not* play a role in the millionfold increase in the rate of alkaline hydrolysis of 5-MEP compared to its acyclic analogue, a-TMP, but it does provide part of the contribution to the observed rate enhancement of 5-MEP relative to its six-membered ring counterpart, 6-MPP.

JA973895X