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A New Approach to Empirical Intermolecular and Conformational Potential Energy Functions. III. Application of EPEN to the Conformational Analysis of 1,2-Disubstituted Ethanes[1]

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Abstract: An empirical potential using electrons and nuclei (EPEN) is described briefly and used to study the conformational properties of a set of 1,2-disubstituted ethanes, $X{\cdot}CH_2{\cdot}CH_2{\cdot}Y$ where X,Y = CH_3, NH_2, or OH. Minimum-energy conformations and dipole moments predicted by the EPEN calculations are in reasonable agreement with available experimental data. The EPEN method provides a computationally rapid yet reliable tool for obtaining dihedral angles, relative energies, and dipole moments of local minimum-energy conformations, as well as the dihedral angles and heights of internal rotational barriers between local energy minima, for alkanes, amines, and alcohols.

One important aspect of chemistry and biochemistry is the elucidation and understanding of the conformational properties of small and large molecules. Considerable progress has been made in the development and implementation of conformational analysis of organic molecules using a wide range of experimental and theoretical techniques. The present report is concerned with a new approach to empirical conformational energy calculations,[3] developed from the concept that molecules should exhibit conformational properties expected from the interactive properties of their constituent electrons and nuclei. This approach makes use of an empirical potential using electrons and nuclei (EPEN).[4,5]

A brief description of EPEN has appeared earlier,[4] and initial tests[5] showed that this approach could reproduce the conformational characteristics of several alkanes, alcohols, amines, and carbohydrates without the need to resort to special add-on energy terms such as intrinsic torsional potentials[6] to treat interactions between atoms across a bond (1–4 interactions), or to special energy functions to treat interactions between atoms participating in a hydrogen bond.[6] It was also possible to compute the lattice constants and lattice binding energies of crystals with EPEN, using the same parameters;[4,5] by considering the lone-pair electrons explicitly, EPEN was found to account for both directionality and hydrogen-bond strength in the crystals studied to date.[4,5] In the present study, EPEN is used to calculate the dipole moments and all zero-gradient points on the conformational energy surfaces of several 1,2-disubstituted ethanes. Where possible, the results are compared to experimental data and to the results of recent ab initio molecular orbital calculations[7] on the same molecules.

Rigid geometry (fixed bond lengths and bond angles) has been used; the only degrees of freedom allowed are the dihedral angles for rotations about bonds. This approximation makes it possible to treat large molecules in a reasonable amount of computer time without significant losses of accuracy; there is experimental and theoretical evidence that bond lengths and bond angles in noncyclic molecules remain remarkably constant in different intermolecular environments and in different minimum-energy conformations.[6,8-16]

In the earlier papers,[4,5] we derived the EPEN parameters for C, N, and O fragments with approximately tetrahedral geometry about the heavy atom, and used these fragments and parameters to study the properties of some saturated molecules. We apply them here to some 1,2-disubstituted ethanes. Work is presently in progress to derive EPEN parameters for other molecular fragments that will be useful for the study of unsaturated molecules such as acids, esters, ketones, aldehydes, polypeptides, and proteins.

Empirical Potential Using Electrons and Nuclei (EPEN)

The derivation and parameterization of EPEN, based on the transferability of molecular fragments from one molecule to another, has been reported previously,[4] and only a brief description will be presented here. In the present formulation, each molecule is constructed from molecular fragments consisting of a single heavy atom (nonhydrogen) nucleus, any hydrogen atom nuclei bonded to this nucleus, and point charges representing the bonding and lone-pair electrons associated with this heavy-atom fragment.

The operational procedure for assembling a molecule

Table I. Standard Experimental Bond Lengths and Bond Angles[a]

Bond lengths		Bond angles	
Type	Length. Å	Type	Angle, deg
C–C	1.530[b]	CCC	112[c]
C–N	1.469[d]	CCN	112[e]
C–O	1.425[f]	CCO	112[g]
C–H	1.09[b]	CCH	111[b]
N–H	1.014[d]	CNH	112[d]
O–H	0.96[f]	COH	108.3[f]

[a] The methyl hydrogen atoms were placed with C_3 symmetry about their C–C bonds with τ(CCH) = 111°. The amino hydrogens were placed with τ(CNH) = 112° and τ(HNH) = 106.7°. Methylene hydrogen atoms were placed so as to reflect into each other through the bisector of the XCC bond angle, with τ(HCH) = 107.9°. [b] Reference 18. [c] Reference 19a. [d] Reference 20. [e] Reference 21. [f] Reference 22. [g] Reference 23.

from molecular fragments requires a knowledge of the molecular geometry and a set of "rules" for positioning the bonding and lone-pair electrons of the fragments within the molecule. The experimental geometries of the *molecules* (bond lengths and bond angles) are used when available (i.e., the positions of both the heavy atoms and hydrogen atoms are made to conform to experimental data when the molecule is assembled from fragments); if sufficient experimental data are not available, "standard" geometries are adopted (Table I). Once the molecular geometry has been fixed, the bonding and lone-pair electrons are placed; in all cases, the intrafragment distances of the electrons from the heavy atoms of the fragment are maintained at the corresponding distances determined in the studies in which the fragments were derived,[4] while the angles between the electron point charges are allowed to adapt to the geometry of the molecule under study. In particular, the bonding electrons are constrained to lie along the bonds they represent, the oxygen lone pairs in the R_1–O–R_2 group are found to be 60° above and 60° below the plane containing the R_1–O and R_2–O bonds so as to reflect into each other through the bisector of the R_1–O–R_2 bond angle (i.e., equidistant from the two bonds to O), and the nitrogen lone pair in the R_1–NR_2–R_3 group is placed along the vector that is the sum of unit vectors along the R_1–N, R_2–N, and R_3–N bonds (i.e., as far away as possible from the three bonds to N). If the adaptation of the fragment (from the geometry used in the derivation of the fragment to the geometry of the molecule under study) corresponds to a change of bond angle of more than several degrees, then the transferability of the fragment to the molecule under study is of questionable validity; this is because large changes in geometry are accompanied by significant changes in electron distribution.[15] Since we are dealing with relatively unstrained molecules in this study, the adopted geometry of the fragments would not be expected to vary much from molecule to molecule; hence, the adoption of "standard" geometry should not introduce any large artifacts. The EPEN representation of 2-aminoethanol in its calculated lowest-energy conformation is shown in Figure 1, as an example. The charges on each heavy-atom nucleus are taken to be the nuclear charge (atomic number) plus the charge on the 1s electrons (−2e). It was assumed that the 1s electrons do not contribute any overlap repulsion when measuring either rotational barriers or intermolecular interactions. This concept is supported by a quantum mechanical study which demonstrated that these electrons may be rigorously subtracted from the wave function without altering its molecular characteristics.[17]

The conformational energy and intermolecular orientational characteristics are calculated using a pairwise summation over *only* those interactions that vary with the degrees of freedom under investigation. One of the consequences of this procedure is that the two −1e electron point charges in the heavy atom–heavy atom bonds act *effectively* as an electron pair; this occurs because the distance between the two electron point charges (typically ≈ 0.1 Å) is much less than the distance between either of these point charges and the nearest point charge whose interaction with the bonding pair is computed. There are three types of interactions to be evaluated when using EPEN:[4] (i) overlap repulsion between electrons of the form, $A\ \exp(-Br)$, (ii) coulombic interactions between all charge centers (electrons and nuclei) of the form q_iq_j/r, where q_i and q_j are the charges at two points separated by a distance r, and (iii) dispersion and other attraction terms resulting from the interaction of fragments (this is taken to be effective between heavy atom nuclei only, and is of the form C/r^6). The parameters for EPEN have been given in Table 2 of ref 4.

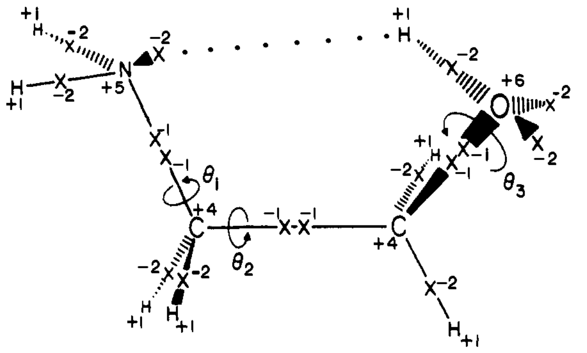

Figure 1. EPEN representation of the most stable conformer of 2-aminoethanol. The O–H···N interaction is shown by the dotted line. The hydroxyl proton is directed toward the lone-pair electrons of the amine fragment. The positions of the electron point charges are indicated by the X's, and the nuclei are represented by their appropriate atomic symbols. The charges are in atomic units. θ_1, θ_2, and θ_3 represent the dihedral angles varied in the search for zero-gradient points of the 1,2-disubstituted ethanes.

Approximations Made in the Derivation and Application of EPEN

For all empirical potential energy functions, it is necessary to make a number of assumptions and approximations in their derivation and application in order to achieve the computational speed that makes them (as opposed to ab initio potentials, for example) so attractive. In this section, we discuss the principal approximations for EPEN.

(i) The total interaction energy can be partitioned effectively into coulombic, overlap repulsion and R^{-6} attraction components. Although this partitioning is not strictly valid (i.e., this partitioning scheme, or any other partitioning scheme with rapidly calculable components, has not been derived from a rigorous argument starting with the Schrödinger equation), nevertheless, experience has shown that conformational and intermolecular potential energy surfaces may be well-represented with a partitioning scheme of this sort. Because of the inexact nature of any partitioning scheme, physical significance may be attached only to the *total* interaction potential; detailed assignment of the physical origins of each individual component is questionable, and should be limited to no more than an approximate estimate of the nature of the various components.

(ii) The coulombic, overlap repulsion and R^{-6} attraction components are effectively pairwise additive. This approximation is a computational necessity for large systems because the explicit evaluation of three-body and higher-order interactions would greatly increase the amount of computer time required to calculate the potential energy of interaction for a large system. Because of this approximation, EPEN is best classed as an effective pairwise additive potential in which the higher-order interactions are accounted for in the parameterization.

(iii) The dielectric constant equals unity. This approximation was made because of the considerable uncertainty in the behavior of the dielectric constant over the short distances in which particular intra- and intermolecular interactions occur.

(iv) The localized electron orbitals (bonding, lone pair, and inner shell) from molecular orbital theory may be represented as point charges for the calculation of the coulombic component. The localized orbitals are treated as point charges so that the coulombic component may be evaluated rapidly; the treatment of the orbitals as charge "clouds" would require much more computer time. It should be noted that the electrons are not treated entirely as point charges in EPEN, since the overlap repulsion and the R^{-6} attractive components help to simulate the interactions of the electron "clouds".

(v) The molecules have a rigid nuclear geometry (i.e., fixed bond lengths and bond angles). This approximation has been made to reduce the number of degrees of freedom ($3N - 6$) total, where N is the number of atoms in the interacting system) to a set of manageable size.

(vi) The crystal lattice constants and compressibilities at 0 K are determined entirely by the potential energy. In reality, the zeropoint vibrational energy affects (usually expands) the crystal lattice. However, to compute the contribution of the zeropoint vibrational energy to the observed lattice constants properly, the vibrational frequencies would have to be calculated as a function of the lattice constants, and this calculation would require a great amount of computer time.

(vii) The potential energy function for large molecules can be constructed directly from transferable molecular fragments. The transferability of molecular fragments is based upon the notion that the same chemical moiety in different molecules has approximately the same charge distribution. The approximation of transferability greatly reduces the number of independent parameters to be evaluated for the empirical potential, and allows the construction of the potential energy functions for many molecules from a few molecular fragments.

In spite of all these approximations, we have shown[4,5] that EPEN adequately approximates both intramolecular (conformational) and intermolecular potential energy surfaces as well as permanent electric dipole moments. In order to place these approximations in the proper context, it should be kept in mind that approximations of this sort are made in the derivation and application of *all* empirical potentials, especially those used for large molecules.

Geometry and Notation

The geometries of the 1,2-disubstituted ethanes studied here were generated using a "standard" set[4,5] of bond lengths and bond angles derived from experiments.[18-23] The values for the "standard" bond lengths and bond angles are given in Table I (see footnote *a* of Table I for the method for placement of hydrogen atoms).

Although the actual values of the dihedral angles were calculated for each rotational isomer (local energy minimum) and conformational transition state (at the top of the barrier), the usual qualitative description (gauche, trans, cis, staggered, and eclipsed) of each conformation has also been used. The dihedral angles θ_1, θ_2, and θ_3 refer to dihedral angles for rotation around the X–C$_1$, C$_1$–C$_2$, and C$_2$–Y bonds, respectively (see Figure 1). The symbols T (trans, $\theta_2 \approx 180°$) and G (gauche, $\theta_2 \approx 60°$) are used to describe the conformation around the central C–C bond relative to the cis position ($\theta_2 \approx 0°$). The conformations of the hydroxyl and amine fragments (determined by θ_1 and θ_3) are described by the symbols t (θ_1 or θ_3 = 180°), g (θ_1 or θ_3 = 60°) and g′ (θ_1 or $\theta_3 = -60°$). The position, θ_1 or θ_3 = 0°, is defined as that dihedral angle in which the hydroxyl proton or amine long-pair electrons lie cis to C$_1$ in the C_1C_2O and C_1C_2N plane, respectively. The positions of the methyl protons are described differently, i.e., as eclipsed (θ_1 or $\theta_3 \approx 0°$) or staggered (θ_1 or $\theta_3 \approx 60°$). Rotation about a bond is positive when, looking along the bond in the direction X, C$_1$, C$_2$, Y, the distal group rotates clockwise relative to the near group.

Methods

The conformational space (θ_1, θ_2, θ_3) for the 1,2-disubstituted ethanes studied here was investigated using EPEN.[4,5] A search was made for all the zero-gradient points ($\partial U/\partial\theta_1 = \partial U/\partial\theta_2 = \partial U/\partial\theta_3 = 0$) by starting from all of the different combinations of 0°, ±60°, ±120°, and 180° for each dihedral angle. The alterations in dihedral angles were then directed, using a multidimensional Newton–Raphson procedure,[24,25] until the zero-gradient point nearest to the starting point was located. Second derivatives, $\partial^2U/\partial\theta_i\partial\theta_j$, were evaluated numerically, using double precision arithmetic. Saddle points, minima, and maxima were identified from the signs of the diagonal elements of the diagonalized second derivative matrix evaluated at each zero-gradient point. The entire set of zero-gradient points for all six 1,2-disubstituted ethanes studied here (well over 500 points) was located in less than 4 min of central processor time on an IBM 370/168 computer.

Results and Discussion

Before we compare our calculated conformational energy results with the corresponding experimental results,[19,26-38] it is important to consider what energy quantity is calculated using EPEN, and the relationship between this quantity and the experimental quantity. The enthalpy difference between conformations a and b, $\Delta H_{a\text{-}b}$, is usually evaluated experimentally from the variation with temperature of an experimentally observable and conformationally dependent property (e.g., the intensity of an infrared-active vibrational transition). From the temperature dependence of the property, an approximate value of $\Delta H_{a\text{-}b}$ is computed. The quantity that we have calculated using EPEN is the relative conformational *potential* energy, $\Delta U_{a\text{-}b}$(rigid), between conformations a and b under the assumption of rigid geometry (fixed bond lengths and bond angles). In order to calculate $\Delta H_{a\text{-}b}$ for an isolated molecule (when treating *experimental* data) from $\Delta U_{a\text{-}b}$(rigid), the following correction terms must be added to $\Delta U_{a\text{-}b}$(rigid) (neglecting the very small PV term): (i) the change in potential energy associated with the relaxation of the bond lengths and bond angles from the "standard" values to the values at the local potential energy minimum b for all $3N - 6$ internal degrees of freedom minus the corresponding quantity for the local potential energy minimum a, (ii) the sum of the zeropoint vibrational energies for all $3N - 6$ vibrational modes of conformation b minus the corresponding quantity for conformation a, and (iii) the difference in thermal excitation energy for the $3N - 6$ vibrational modes of conformation b minus the corresponding quantity for conformation a. It must be kept in mind for the following discussion that the relative conformational energies in Table II are ΔU's, not ΔH's; however, in practice $\Delta U_{a\text{-}b}$(rigid) should be a reasonable approximation to $\Delta H_{a\text{-}b}$. In order to calculate $\Delta H_{a\text{-}b}$ properly, we would need to consider a potential energy function with many more degrees of freedom and, hence,

Table II. Calculated and Experimental Conformational Energies and Dipole Moments for Disubstituted Ethanes ($X{\cdot}CH_2{\cdot}CH_2{\cdot}Y$)

	Dihedral angles, deg												
	Calcd			Exptl			Conformation[a] and barrier	Relative conformational energy, kcal/mol		X···Y distance, Å		Dipole moment, D	
Molecule	θ_1	θ_2	θ_3	θ_1	θ_2	θ_3		Calcd	Exptl	Calcd	Exptl	Calcd	Exptl
n-Butane[b]	60	180	60				T	0.00	0.00[e]	3.90		0.00	
$CH_3CH_2CH_2CH_3$	52	65	52		67.5,[c] 66[d]		G	0.68	0.96[e]	3.08		0.05	
	60	121	60				T → G	3.94	3.6–4.2[f]	3.64		0.03	
	60	0	60				G → G	13.74	6.1[g], 7.4[f]	2.68		0.06	
Ethylene glycol	−176	53	−54		G[h,i]		tGg'	0.00		2.85	2.97[j]	2.6	2.3[k]
$HOCH_2CH_2OH$	−45	54	75				g'Gg	1.12		2.86		2.6	
	179	51	179				tGt	1.64		2.84		2.7	
	−180	180	180				tTt	3.33		3.71		0.0	
	−52	−4	179				G → G	2.75		2.60		3.3	
	−177	122	−177				G → T	6.86		3.48		1.3	
1-Propylamine	62	62	−56				Gg'	0.00		3.01		1.5	1.2[l]
$CH_3CH_2CH_2NH_2$	53	61	47				Gg	0.42		3.01		1.4	
	61	−178	56				Tg	1.01		3.84		1.4	
	52	60	171				Gt	1.18		2.99		1.4	
	60	180	180				Tt	1.60		3.84		1.4	
	60	122	180				G → T	5.50		3.60		1.4	
	57	−1	−45				G → G	7.37		2.65		1.5	
1-Propanol	62	62	178		64[m]		Gt	0.00	0.00[m]	3.00		1.8	1.56–1.67[m,n]
$CH_3CH_2CH_2OH$	62	62	63				Gg	0.58		2.99		1.8	
	52	61	−72				Gg'	0.72		2.98		1.8	
	60	180	180				Tt	0.87	0.29[m]	3.80		1.8	
	59	177	61				Tg	1.28		3.80		1.8	
	1	60	176				Methyl-G[o]	3.46.	2.9[m]	2.98		1.8	
	0	180	180				Methyl-T[o]	4.41	3.1[m]	3.80		1.8	
	60	120	67				G → T	4.97		3.55		1.8	
	60	0	180				G → G	5.44		2.64		1.8	
2-Aminoethanol	−50	58	−46	−41[p]	55[p]	−28[p]	g'Gg'	0.00	0.00[p]	2.92	2.81[p]	2.9	3.05[p]
$NH_2CH_2CH_2OH$	43	52	−72				gGg'	0.55		2.86		1.7	
	60	60	−178				gGt	0.55		2.94		1.4	
	53	−179	178				gTt	2.80		3.75		1.4	
	−54	0	55				G → G	3.52		2.61		2.2	
	−53	125	−69				G → T	6.45		3.53		2.0	
Ethylenediamine	48	55	48		64[q,r]		gGg	0.00		2.92		0.3	1.94[k]
$NH_2CH_2CH_2NH_2$	179	54	−55				tGg'	0.42		2.91		2.3	
	−51	60	63				g'Gg	0.44		2.97		2.2	
	54	−177	54				gTg	2.80		3.79		2.3	
	57	0	57				G → G	3.85		2.63		1.3	
	53	124	180				G → T	7.50		3.56		2.5	

[a] The conformation of methyl groups is always near staggered ($|\theta_1|$ or $|\theta_3| \approx 60°$), except when the methyl rotational barrier is being calculated, and is not listed explicitly in this table. The symbol a → b designates the barrier to rotation in going from conformer a to conformer b; the dihedral angles reported are for the conformational transition state with the lowest value of U between a and b. [b] The results reported here for *n*-butane differ slightly from those in ref 4, since experimental geometry was used in ref 4, but standard geometry (Table I) was used here. [c] Reference 19a. [d] Reference 19b. [e] Reference 26. [f] Reference 27. [g] Reference 28. [h] The experimental conformation is reported to be gauche ($\theta \approx 60°$) without a specific value of θ_2 being given. [i] References 29–31. [j] Reference 29. [k] Reference 32. [l] Reference 33. [m] Reference 34. [n] Reference 35. [o] Barrier for methyl rotation. [p] Reference 36. [q] Reference 37. [r] Reference 38.

many more parameters than appear in EPEN; for the example of *n*-butane, we have considered only three degrees of freedom (the three torsional degrees of freedom, θ_1, θ_2, and θ_3) while there are actually $3(14) - 6 = 36$ internal degrees of freedom. Correction terms (i) to (iii) apply to isolated molecules; in a liquid or solid environment, the enthalpy differences between local conformational energy minima and heights of barriers between minima can be affected significantly depending upon the strength of the interaction between the molecule and its environment. It is important to note that, in using empirical potentials, the inclusion of all degrees of freedom for a large molecule would make it impossible to search for all of the possible minimum-energy conformations, and it is unlikely that enough experimental information exists to develop accurate parameters for a potential function that includes all degrees of freedom.

The results of the EPEN calculations of the 1,2-disubstituted ethanes are presented in Table II. The positions of some of the zero-gradient points (specified by θ_1, θ_2, and θ_3) which are relevant to experimental measurements, the distance between the heavy-atom nuclei of fragments X and Y, the relative potential energy of the conformation (normalized to zero for the lowest energy conformer for each molecule), and the calculated dipole moment of each molecule are reported. Although there are many zero-gradient points for each molecule, only the minima and a selection of others (saddle points) which correspond to the lowest rotational barriers between minima have been reported in Table II. The others are not reported here but can be computed easily by those readers interested in (multiple) transition states. It is a general result of these calculations that the conformations of the X and Y fragments in local energy minima deviate from the $\theta_1 = \theta_3 = \pm 60°$ conformations whenever θ_2 is removed from 180°. It should be emphasized that small variations of θ_2 away from the gauche and trans positions can lower the energy of a particular conformation significantly; therefore, it is *not* a good procedure to study the conformational energy surface using a 60° grid.[7,10] When hydrogen-bonding interactions occur between X and Y, the calculated values of both θ_1 and θ_3 deviate by up to 14° from the ±60° conformations, while the calculated value of θ_2 is lower than 60° (as low as 53° for ethylene glycol). Agreement between the experimental and the calculated dipole moments is very good considering that the calculated dipole moment depends on geometry, conformation (i.e., θ_1, θ_2, and θ_3), relative populations of conformational states (statistical weights), and electron distribution. The sensitivity of the dipole moment to the positions of the point charges may be appreciated by noting that the calculated dipole moment changes by as much as 0.1 D if an electron pair is translated by only 0.01 Å. A discussion of the results for the individual molecules is given below. The calculated conformational properties are compared to experimental values and to the results of other calculations on the same molecule, where available.

***n*-Butane.** EPEN is a reasonably reliable tool for the calculation of the conformational properties of acyclic hydrocarbons.[4,5] The most stable conformation of *n*-butane[4] was calculated with EPEN to be at $\theta_2 = 180°$ (trans) with staggered end methyl groups. The calculated value of θ_2 for the *n*-butane conformation near the gauche minimum is 65°, which is close to the experimental values (67.5 ± 1.1° [19a] and 66 ± 1° [19b]). The calculated trans-gauche energy difference (0.68 kcal/mol) is also in approximate agreement with the latest experimental estimate of 0.96 kcal/mol.[26] While the calculated trans-gauche barrier (3.94 kcal/mol) is in the experimental range[27] of 3.6-4.2 kcal/mol, the calculated value of the $G \rightarrow G$ barrier (Table II) is 13.7 kcal/mol, which is much higher than the range measured experimentally, viz., 6.1[28] to 7.4[27] kcal/mol. The results of Radom et al.,[7] using ab initio molecular orbital theory, indicate that flexible geometry must be used before satisfactory agreement between experiment and theory can be obtained for the height of the cis barrier. Although the empirical calculations of Engler et al.[8] (using flexible geometry) give a reasonable gauche-gauche barrier (5.8 kcal/mol), the results of Allinger et al.[10] indicate that their own approach (also using flexible geometry) gives too small a barrier for the $G \rightarrow G$ transition (4.55 kcal/mol). A comparison of the EPEN results[4,5] for acyclic hydrocarbons with those of other empirical methods[8,10,39] shows that EPEN (which was derived for many types of molecules) performs overall just as well as the potentials designed specifically for use with hydrocarbons.

Ethylene Glycol (Ethane-1,2-diol). The most stable form of ethylene glycol located using EPEN has a gauche (G) conformation around the C-C bond. This is in agreement with experimental studies by electron diffraction,[29] infrared,[30] and Raman[31] spectroscopy, where the gauche form is reported to be the most stable. The electron diffraction study of Bastiansen[29] indicated that the O···O distance is 2.97 Å; however, calculations using EPEN resulted in a minimum at an O···O distance of 2.85 Å. Considering the more recent experimental studies on 2-aminoethanol[36] and ethylenediamine,[37] where the N···O and N···N distances are 2.81 and 2.88 Å, respectively, it might be expected (by extrapolation) that the true O···O distance at the minimum of the potential energy surface would be less than the value reported by Bastiansen.[29] However, the intramolecular O···O separation measured by Bastiansen for ethylene glycol[29] is very similar to the intermolecular O···O distance reported for the water dimer (2.98 Å),[40] where the interactions which control the orientation of the water molecules are quite similar to those in ethylene glycol. In both cases, the experimentally determined structures may represent averages, with contributions from excited librational states which lie considerably above the bottom of the potential well because of librational zeropoint energy; thus, the O···O distance would be slightly larger than in the conformation at the minimum of the potential well.[41] Other theoretical studies have also indicated that the gauche conformer should be the most stable.[7,42] Recent studies by Raman spectroscopy[31] and NMR[43] have indicated the presence of both gauche and trans conformers in the *liquid* phase, with the gauche conformer having the greater population. The experimentally reported enthalpy difference between the trans and gauche conformers in the pure liquid is ≈0.7 kcal/mol,[31,43] whereas the energy difference between the trans (T) and gauche (G) conformers calculated by EPEN for an *isolated* molecule is 3.33 kcal/mol [cf. ref 7, where $\Delta U_{\text{T-G}} = 2.01$ kcal/mol, and ref 42, where $\Delta U_{\text{T-G}} = 1.23$ kcal/mol]. Intermolecular interactions (e.g., competing hydrogen-bonded networks in the liquid) would be expected to favor the trans conformer considerably.[42] While EPEN and the ab initio molecular orbital[7] calculations on ethylene glycol indicate that the hydroxyl protons in the most stable trans (T) conformer are trans (t) to the C-C bond (as in the analogous case, ethanol, where the trans (t) conformation is observed[23]), the other empirical calculation[42] predicts that the gauche (g) conformation would be preferred for these protons. The dipole moment calculated using EPEN (2.6 D) is in good agreement with the observed value (~2.3 D,[32] for the liquid).

1-Propylamine. The most stable conformation of 1-propylamine was calculated to have a gauche (G) conformation around the central C-C bond. Experimentally gauche (G) and trans (T) conformers are observed in both the liquid[44] and vapor[45] states, although there are no quantitative data that indicate which conformer is more stable. The five most stable conformers predicted by EPEN are those suggested by Scott[45] to be present, from a vibrational analysis of 1-propylamine. The three most stable conformations, Gg′, Gg, and Tg (where the amine lone-pair electrons are gauche to the central C-C bond), are consistent with the preferred gauche (g) conformation of ethylamine.[21,45] The ab initio calculations[7] on this molecule indicated that Tg was more stable than Gg′ by 0.11 kcal/mol, although the large grids used for selecting values of θ_1, θ_2, and θ_3 in the calculation quite likely introduced error into this value. The experimental dipole moment has been reported[33] as 1.2 D (which is presumed to apply to a mixture of the G and T conformers), and the calculated value (with G and T having almost identical dipole moments of 1.5 and 1.4 D, respectively) is in good agreement with this.

1-Propanol. The Gt conformer of 1-propanol was calculated to be 0.87 kcal/mol more stable than the Tt conformer. This small energy difference suggests that both should be found experimentally, and indeed microwave spectroscopic evidence[34] indicates that both conformers are present. The results obtained by EPEN are very similar to those from the ab initio calculations by Radom et al.,[7] although the energy difference between the T and G conformers predicted by the ab initio method is only 0.18 kcal/mol. Experimentally,[34] the enthalpy difference was reported to be 0.29 ± 0.15 kcal/mol. The barriers to rotation of the methyl group in the T and G conformers were reported[34] as 3.1 and 2.9 kcal/mol, respectively. The calculated values for these barriers using EPEN were 4.4 kcal/mol for the trans (T) conformer and 3.5 kcal/mol for the gauche (G) conformer. The experimental value for θ_2 in the G conformer was reported[34] to be 64° while the calculated value for this dihedral angle is 62°. The dipole moment of 1-propanol has been reported to be in the range 1.56-1.67 D,[34,35] and the value calculated by EPEN (1.8 D) is in good agreement (see Table II).

2-Aminoethanol. The most stable EPEN conformer of 2-aminoethanol was g′Gg′; however, two other gauche conformers within 0.55 kcal/mol of the global minimum were also found, viz., gGg′ and gGt. The most stable conformation of 2-aminoethanol has an O-H···N hydrogen bond (Figure 1), and the most stable conformations with N-H···O hydrogen bonds (gGg′ and gGt) are approximately 0.6

kcal/mol less stable. This result is in agreement with the microwave[36] studies on this molecule. The microwave results indicate that $\theta_1 = -41°$, $\theta_2 = 55°$, and $\theta_3 = -28°$, and this conformation is analogous to the lowest energy conformation found by EPEN ($\theta_1 = -50°$, $\theta_2 = 58°$, $\theta_3 = -46°$). The experimental[36] O···N distance (2.81 Å) and dipole moment (3.05 D) reported for the most stable conformer of 2-aminoethanol agree well with the corresponding values from the EPEN calculation (2.92 Å and 2.9 D, respectively). Penn and Curl[36] developed a point charge model specifically for the calculation of the low-energy conformers and dipole moments of 2-aminoethanol. The results of their calculations are also in reasonable agreement with the microwave results. Infrared investigations have reported that both the gauche (G) and trans (T) conformers of 2-aminoethanol exist in dilute solutions (0.11-1.0%) in tetrachloroethylene.[46] The conclusion about the existence of both G and T conformers was made on the basis of the detection of infrared absorption bands for "free" and "hydrogen-bonded" NH_2 and OH groups. From the relative intensities of the "free" and "hydrogen-bonded" bands, Krueger and Metee[46] have suggested that the trans (T) conformer is more stable than the gauche (G), in contrast to the microwave results.[36] However, at least three gauche conformers appear to be stable, both by the EPEN calculations and by the ab initio calculations of Radom et al.[7] and, while the OH group is the hydrogen-bond donor in one of these, the NH_2 group is the donor in the other two (G) conformations. Thus, one would expect to find a mixture of both "free" and "hydrogen-bonded" modes in the vibrational spectra for both the NH_2 and OH groups in the gauche (G) conformation;[46] this would greatly complicate the interpretation of the ir spectrum in terms of a conformational equilibrium between gauche (G) and trans (T) conformers. The results of the EPEN calculations, and of the ab initio calculations of Radom et al.,[7] indicate that only gauche (G) conformers are likely to be detected in the vapor state and in dilute solution in nonpolar solvents.

Ethylenediamine. The most stable EPEN conformation of ethylenediamine was (hydrogen bonded) gauche (G) with respect to the central C-C bond. This is in agreement with the results of an electron-diffraction study[37,38] where θ_2 was found to be 64°. Three low-energy gauche (G) conformations were located using EPEN, viz., gGg, tGg′, and g′Gg; the average N···N distance for these conformers is 2.92 Å, which is close to the N···N distance observed experimentally[37] for ethylenediamine. Since the experiment gives the N···N distance, and θ_2 is a derived value which depends on several interatomic distances, the comparison of the N···N distances is a more valid one. The calculated dipole moment is sensitive to the orientation of the amine fragments. The gGg conformer has a small dipole moment (0.3 D) but the dipole moments of the other two low-energy conformers tGg′ and g′Gg (2.3 and 2.2 D, respectively) are close to the experimentally observed dipole moment for ethylenediamine (1.94 D).[32]

Conclusions

Conformational analysis of acyclic saturated hydrocarbons, alcohols, and amines using EPEN generally leads to reliable predictions of the lowest energy structure and barrier positions. However, there is a tendency to overestimate the height of cis barriers in systems where there is crowding in the cis position; in reality, the crowding would be relieved by opening up bond angles, but these are frozen in EPEN. The dipole moments of these molecules also appear to be well-represented by EPEN. When interpreting the results, no attempt has been made to analyze the stabilizing or destabilizing interactions within any given conformation in terms of the components of EPEN. These types of interpretations would reflect only the artificial partitioning of the total energy into the components of EPEN (coulombic, overlap repulsion, and R^{-6} attraction). At best a qualitative estimate could be obtained, but the significance of any quantitative importance attributed to individual terms of an empirical potential is dubious. It should be possible to use EPEN for calculations on the low-energy conformers of much larger molecules and to expect reliable results. In all cases where intramolecular hydrogen bonds (conformations in which two heavy-atom nuclei are bridged by a hydrogen atom) were likely to occur, they were located using EPEN, and these always resulted in a stabilization of the gauche (G) relative to the trans (T) conformations. The EPEN potential predicts the approximate gas-phase properties of these molecules at 0°K. The results should be corrected for contributions from conformational equilibria before detailed comparisons are made to experimental results obtained at higher temperature. However, the correlation between the calculated and experimental conformations suggests that useful information can be obtained even before a full quantum statistical mechanics treatment is invoked.

It should be emphasized that we have found the positions of the minima and rotational barriers in θ_1, θ_2, θ_3 space (within ±1°) for the EPEN potential of these disubstituted ethanes. Our procedure differs significantly from the usual procedures for calculations of this type using molecular orbital (MO) theory or empirical potentials. In particular, the standard way to carry out the calculations using MO theory is to estimate the positions of the minima and then vary at most one degree of freedom to refine the position of the minimum, and the barrier positions are located in the same way; with empirical potentials, the minima are usually located by varying *all* degrees of freedom (as we have done) but typically the barrier positions are either estimated or refined by varying at most one degree of freedom. The procedure adopted for MO calculations is dictated by the computational expense; because the computational expense is much less for empirical potential calculations, we recommend that the procedure that we have adopted here or a similar procedure be used to locate positions for the rotational barriers (within ±1°). In general, the barriers for a molecule with two or more coupled rotors can be quite complex, depending on the extent of the coupling.

It is important to point out why we have not calculated the statistical weights of the various conformations for each molecule. Strictly speaking, without considering *every* internal mode, the statistical weights could not be calculated rigorously using either classical or quantum statistical mechanics. It is not proper to consider only a small set of internal degrees of freedom (such as θ_1, θ_2, and θ_3) in the calculation of the statistical weight because, in reality, these modes are coupled (sometimes strongly) by both kinetic and potential energy to the arbitrarily frozen modes. Faced with the practical fact that, for a large system of many atoms, the computations required to consider *all* internal modes require a prohibitively large amount of computer time, the approximation is usually made that the coupling of the torsional modes to the rest of the internal modes (bond angle bends and bond stretches) is usually small because torsions are much easier (energetically) for the molecule to undergo than are bond angle bends and bond stretches. Once the approximation is made to treat torsional modes only, another practical fact, viz., that the **G** matrix[47] for torsional modes is very difficult to construct for an arbitrary large molecule, leads to use of classical statistical mechanics rather than quantum statistical mechanics to avoid the use of the **G** matrix by the separation of the kinetic and potential energy (this separation is not possible in quantum statistical mechanics). For the small molecules studied here, especially those with hydrogen-bonded conformations, the modes involving torsions of terminal hydrogens in hydrogen-bonded arrangements would be expected to have torsional vibrational energy level separations that are not small compared to kT at room temperature. It follows that the use of classical statistical mechanics is not valid for these conformations and could result in poor approximations to the statistical weights.

With the extension of EPEN to unsaturated molecules (now in progress), it is anticipated that it will then be applicable to large molecules such as proteins, within reasonable amounts of computing time. The technique has already been applied successfully to intermolecular interactions in crystals, and is now being used to treat systems of molecules (such as those involved in determining the effect of solvation on conformation). EPEN has also been applied successfully to a study of the structures, energetics, and dynamics of water clusters.[48]

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References and Notes

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(3) Empirical conformational energy calculations have also been called "molecular mechanics" and "consistent force field" calculations.

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