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A Theoretical Study of the Minimum Energy Structures of Diethylstilbestrol and Its Analogues by Molecular Mechanics (MM2p), MNDO, and ab Initio Calculations

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Abstract: Molecular mechanics (MM2p), modified neglect of diatomic overlap (MNDO), and ab initio (STO-3G) calculations are performed on a class of similar molecules which bind to the estrogen receptor. The molecules studied are diethylstilbestrol (DES), (*Z*)-pseudodiethylstilbestrol (ZPD) and (*E*)-pseudodiethylstilbestrol (EPD). The MM2p method finds two local minima in the region of the X-ray conformation, but only one is found for the MNDO and STO-3G calculations. MM2p agrees most closely with X-ray for all three cases, although for DES, the STO-3G calculations are similar to those of MM2p. The STO-3G and MM2p potential energy surfaces in the X-ray region are substantially flatter than the MNDO surface. MM2p and MNDO calculations were also performed with the constraints used in the ab initio calculation to determine the sensitivity of the minima to constraints. Discrepancies are found between the X-ray and calculation geometries as well as among the calculation geometries themselves. Possible explanations include undetermined contributions from crystal lattice forces (for DES, however, we find the hydrogen bond component to be small) and the quality of the various calculation programs used.

Diethylstilbestrol (DES, see structure in Figure 1a) is a nonsteroidal estrogen first synthesized and described by Dodds.[1] It has significant oral activity as an estrogenic substance and invokes a strong hormonal response equivalent to an injected dose of steroidal estradiol-17β. For a number of years DES was used as a therapeutic agent during gestation. While the full extent of its use is not known, it is estimated that 2 to 3 million pregnant women may have been exposed to the drug. The association between gestational treatment with DES and the subsequent appearance of a rare vaginal cancer in some of the daughters[2] and, more recently, genital tract abnormalties in sons[3] has raised concern over the safety of exposure to estrogenic substances in utereo.

A DES analogue, called pseudo-DES, in which the double bond is between C_7 and $C_{7'}$, can exist in isomeric forms designated as *Z* and *E* (see Figure 1b,c). Biological testing revealed that while both isomers retained appreciable affinity for the estrogen receptor, the *Z* isomer (ZPD) has twice the uterotropic activity of the *E* (EPD) isomer.[4] Careful investigations of the molecular features of the numerous natural and synthetic products that have estrogenic or antiestrogenic properties have been attempted in order to possibly identify those structural features that are responsible for receptor binding and hormonal function. One of the most definitive approaches to this problem is X-ray crystallographic measurements, and the crystallographically observed molecular structures of a number of natural and synthetic estrogens and antiestrogens have been compared.[5] Such studies are consistent with a model incorporating estradiol A-ring control of receptor binding and D-ring control of subsequent nuclear events that lead to hormonal response. A significant conformational difference between ZPD and EPD, therefore, might account for the observed difference in biological activity.

In conformationally flexible structures such as these, a minor conformer may sometimes be responsible[6] for activity. Thus, one desires to determine low-energy conformations which are most similar to the active form of estradiol. With a theoretical and quantum chemical approach to this problem, one has the ability to reach conformations, i.e., search the potential energy surface, inaccessible to experiments. Since theoretical calculations vary from empirical to the ab initio level with associated increases in time and costs, we examined as models the low-energy regions of the potential energy surfaces of these structurally and biologically well-defined molecules in the X-ray region with three different theoretical techniques.

Duax et al.[8] have recently compared the X-ray and energy minimized molecular mechanics (MM2p level)[9-12] geometries of DES and its isomers ZPD and EPD. In this study,[13,14] we extend the theoretical comparison by performing semiempirical level MNDO and ab initio level STO-3G[15,16] calculations on low-energy regions of the potential energy surfaces of these molecules. The effect of intermolecular hydrogen bonding on the minimum energy conformation of DES is also studied. We are thus able to assess the quality of information that can be obtained for intermediate-sized molecules of geniune biological interest from theoretical techniques of substantially different origin and intent.

Methods

The molecular mechanics calculations were performed with the MM2p program kindly supplied by D. Rohrer.[10a] This version for a VAX-11/780 was motivated by N. Allinger's MMp2 molecular mechanics program[10b] and incorporates the variable electronegativity self-consistent-field procedure of the program MMp1[11] into the program MM2.[12] These empirical molecular mechanics methods are discussed in detail by others.[12] The semiempirical MNDO[13] calculations were per-

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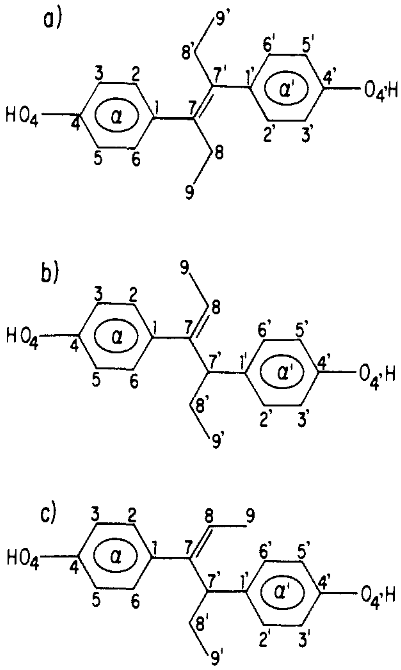

Figure 1. Structures of (a) DES and pseudo isomers (b) ZPD and (c) EPD.

Table I. Torsion Angles Used in Defining DES Geometries (Figure 1a). The Third Column Gives the Constraints of the Rigid Symmetrical Geometry

	torsion angle	constraints
ϕ_1	C_1–C_7–$C_{7'}$–$C_{1'}$	(180.0)
ϕ_2	C_2–C_1–C_7–$C_{7'}$	
ϕ_3	C_7–$C_{7'}$–$C_{1'}$–$C_{2'}$	$(-\phi_2)$
ϕ_4	$C_{7'}$–C_7–C_8–C_9	
ϕ_5	C_7–$C_{7'}$–$C_{8'}$–$C_{9'}$	$(-\phi_4)$
ϕ_6	C_1–C_7–C_8–C_9	$180.0 + \phi_4$
ϕ_7	$C_{7'}$–C_7–C_8–H8A	$\phi_4 + 120.0$
ϕ_8	$C_{7'}$–C_7–C_8-H8B	$\phi_4 - 120.0$
ϕ_9	C_7–$C_{7'}$–$C_{8'}$–H8′A	$\phi_5 + 120.0$
ϕ_{10}	C_7–$C_{7'}$–$C_{8'}$–H8′B	$\phi_5 - 120.0$

formed with a VAX-11/780 version[14] of the program. Although both MM2p and MNDO are parameterized with experimental data, the MNDO method is generally applicable to a broader class of chemical situations[17] than MM2p; however, MNDO is more than an order of magnitude slower than MM2p. Both methods use sophisticated geometry optimization techniques; MM2 utilizes a second derivative Newton-Raphson method[18] and MNDO employs a Davidson–Fletcher–Powell algorithm.[19]

The STO-3G calculations were carried out with an IBM version[15] of GAUSSIAN 80.[16] Because of program restrictions and the expense of doing ab initio calculations on molecules the size of DES and its *E* and *Z* isomers, we were restricted to search only interesting regions of the potential surface and to drop the OH groups. A statistical quadratic fitting function[20] was used to estimate the local minima in terms of two variables for desoxy-DES and four variables for the analogous *E* and *Z* isomers. Generally, simple ab initio methods are two orders of magnitude slower than MNDO but have been shown[21] to be somewhat more accurate.

Table II. Torsion Angles Used in Defining pseudo-DES Geometries (Figure 1, b and c). The Third Column Gives the Constraints of the Rigid Geometry

	torsion	constraints
ϕ_1	C_2–C_1–C_7–C_8	
ϕ_2	C_1–C_7–$C_{7'}$–$C_{1'}$	
ϕ_3	C_7–$C_{7'}$–$C_{1'}$–$C_{6'}$	
ϕ_4	C_7–$C_{7'}$–$C_{8'}$–$C_{9'}$	
ϕ_5	C_2–C_1–C_7–$C_{7'}$	$(\phi_1 + 180.0)$
ϕ_6	C_1–C_7–$C_{7'}$–$C_{8'}$	$(\phi_2 - 120.0)$
ϕ_7	C_1–C_7–$C_{7'}$–H7′	$(\phi_2 + 120.0)$
ϕ_8	C_7–$C_{7'}$–$C_{8'}$–H8′A	$(\phi_4 + 120.0)$
ϕ_9	C_7–$C_{7'}$–$C_{8'}$–H8′B	$(\phi_4 - 120.0)$
ϕ_{10}	C_1–C_7–C_8–C_9	0.0 for ZPD, 180.0 for EPD
ϕ_{11}	C_1–C_7–C_8–H8	180.0 for ZPD, 0.0 for EPD

Because of the relative times to do a single-point calculation (STO-3G ≫ MNDO > MM2p) it becomes prudent to initially explore the potential surfaces for local minima for the molecules using MM2p before employing the more time consuming approaches.

The geometry labels are given in Figure 1 and the definition of important torsional angles are given in Tables I and II.

Results and Discussion

A complete energy minimization with MM2p and MNDO was performed for all three molecules starting with an initial conformation which we label as (i). The (i) conformations are near those of the X-ray coordinates and are available upon request. The minimum energy conformations (mec) for complete minimization are defined as (all) conformations. For DES, five torsion angles are used to describe the mec (ϕ_1–ϕ_5 in Table I). For EPD and ZPD, four torsion angles are used to define the mec (ϕ_1–ϕ_4 in Table II). A much more constrained ab initio energy minimization was performed for DES; only the torsion angles ϕ_2 and ϕ_4 were varied; ϕ_1 was fixed at 180.0°, ϕ_3 was fixed at $-\phi_2$, and ϕ_5 was fixed at $-\phi_4$. The remaining important conformation-defining angles were then fixed as shown in Table I. For EPD and ZPD, the ab initio minimization was carried out for the four angles ϕ_1–ϕ_4 with the remaining angles fixed as shown in Table II. All other bond distances and angles were chosen to match those of the (i) conformations.

For discussion purposes, we define the following energies: E(i) = energy of the initial (near X-ray) conformation. E(all) = energy of the final conformation for which all geometric variables are minimized. $E(\phi_2,\phi_4)$ = energy for DES for which a single point calculation is done with ϕ_2 and ϕ_4 fixed (with appropriate locking of the related angles) and with all other parameters taken from the (i) set; $E(2) = E(\phi_2,\phi_4)$ with ϕ_2 and ϕ_4 taken from the all set. $E(\phi_1,...,\phi_4)$ = energy for EPD or ZPD for which a single-point calculation is done with ϕ_1–ϕ_4 fixed (with appropriate locking of the related angles) and with all other parameters taken from the (i) set; $E(4) = E(\phi_1,...,\phi_4)$ with $\phi_1,...,\phi_4$ taken from the all set. $\Delta E_{\text{all}} = E(\text{i}) - E(\text{all})$; this quantity gives an estimate of the drop in energy to reach the (mec) from the initial conformation. $\Delta E_2 = E(\text{i}) - E(2)$; this quantity gives an estimate of the relaxation in changing only the two critical angles ϕ_2 and ϕ_4 for DES from the (i) to the $E(2)$ conformation. $\Delta E_4 = E(\text{i}) - E(4)$; similar to $\Delta E(2)$ but for EPD and ZPD.

DES. Table III contains a summary of the DES calculations. Calculations were done for both DES and desoxy DES for MM2p and MNDO and for only desoxy DES (dDES) for the ab initio case. Geometry results were very similar with and without OH (this conclusion is also true for the EPD and ZPD molecules); for the remainder of the paper we will focus on the desoxy forms. In order to quantitate the comparison we define the average absolute error (AAE) to be the average of the absolute differences

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(20) A grid of conformations for desoxy-DES and the *Z* and *E* isomers was generated by systematically varying ϕ_2 and ϕ_4 (see Table I) in the case of desoxy-DES and ϕ_1, ϕ_2, ϕ_3, ϕ_4 in the case of the *Z* and *E* isomers (see Table II) and constraining the remaining internal coordinates as described above (see Results and Discussion). The values of these dihedrals given by the minimal energy conformations obtained by MNDO (see Tables III–V) were used as starting points. The STO-3G energy was calculated at each of these conformations, and a quadratic function was fit to the energy with standard multivariate regression with the SAS statistical package (J. Service, A User's Guide to the Statistical Analysis System, Aug. 1972). In all cases, the fit was highly statistically significant and the quadratic function was convex and therefore minimizable. The STO-3G energy was calculated at the predicted minimum, and this new information was used to update the regression data. The procedure was iterated until covergence occurred to approximately ± 1 degree in the dihedrals.

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Table III. DES Geometry and Energy Data. The X-Ray Geometry Is Summarized in Ref 8

geometry[a]	ϕ_1	ϕ_2	ϕ_3	ϕ_4	ϕ_5	AAE[c]	ΔE_{all}[b]	ΔE_2
X-ray	180	63	-63	-123	123			
MM2p X-ray[d] w/o[g]	180	62	-62	-146	146			
$\lvert\Delta\rvert$	0	1	1	23	23	12	-8.5	-1.2
MM2p X-ray w	180	61	-61	-145	145			
$\lvert\Delta\rvert$	0	2	2	22	22	12	-9.3	-1.2
MM2p MNDO[e] w/o	180	73	-73	-82	82			
$\lvert\Delta\rvert$	0	10	10	41	41	25	-8.6	-2.4
MM2p MNDO[e] w	180	72	-73	-81	81			
$\lvert\Delta\rvert$	0	9	10	42	42	26	-9.4	-2.4
MNDO w/o	179	84	-84	-95	95			
$\lvert\Delta\rvert$	1	21	21	28	28	25	-23.1	-7.8
MNDO w	179	84	-84	-95	95			
$\lvert\Delta\rvert$	1	21	21	28	28	25	-30.4	-7.9
STO-3G w/o[f]	180	76	-76	-109	109			
$\lvert\Delta\rvert$	0	13	13	14	14	14		-1.8

[a] Torsion angle definitions for ϕ_1–ϕ_5, respectively: $C_1–C_7–C_{7'}–C_{1'}$, $C_2–C_1–C_7–C_{7'}$, $C_7–C_{7'}–C_{1'}–C_{2'}$, $C_{7'}–C_7–C_8–C_9$, $C_7–C_{7'}–C_{8'}–C_{9'}$, the atomic numbering as in Figure 1a. [b] Energy drop below the energy at the initial (almost X-ray) geometry in kcal/mol. ΔE_{all} for full variation. ΔE_2 represents a single point calculation in which ϕ_2 and ϕ_4 are defined at their all-variation value; all other parameters are fixed at the chemically reasonable values used to define the initial coordinates. [c] Average absolute error is defined for ϕ_2–ϕ_5, the comparison is to the X-ray structure. [d] Minimization started at the X-ray geometry. [e] Minimization started at the MNDO minimum geometry. [f] ϕ_1 fixed at 180°, ϕ_2 fixed to be $-\phi_3$, ϕ_4 fixed to be $-\phi_5$. [g] w = with OH groups, w/o = without OH groups

Table IV. EPD Geometry and Energy Data. The X-ray Geometry Is Summarized in Ref 8

geometry[a]	ϕ_1	ϕ_2	ϕ_3	ϕ_4	AAE[c]	ΔE_{all}[b]	ΔE_4
X-ray	-48	77	55	-58			
MM2p w/o	-47	81	59	-59			
$\lvert\Delta\rvert$	2	4	4	1	3	-17.8	+0.3
MM2p w	-46	81	59	-59			
$\lvert\Delta\rvert$	2	4	4	1	3	-20.6	+0.5
MNDO w/o[d]	-92	61	92	-69			
$\lvert\Delta\rvert$	44	16	37	11	27	-37.8	-10.6
MNDO w	-91	63	92	-70			
$\lvert\Delta\rvert$	43	14	37	12	27	-52.7	-10.7
STO-3G w/o	-87	53	88	-72			
$\lvert\Delta\rvert$	39	24	33	14	27		-3.2

[a] Torsion angle definitions ϕ_1–ϕ_4, respectively: $C_2–C_1–C_7–C_8$, $C_1–C_7–C_{7'}–C_{1'}$, $C_7–C_{7'}–C_{1'}–C_{6'}$, $C_7–C_{7'}–C_{8'}–C_{9'}$. [b] Energy drop below the energy at the initial (near X-ray) geometry in kcal/mol. ΔE_{all} is for full variation. ΔE_4 has ϕ_1 through ϕ_4 fixed at their all-variation values; all other parameters are chosen at the chemically reasonable values used to define the initial coordinates. [c] Average absolute error is defined with comparison to the X-ray structure. [d] w = with OH groups, w/o = without OH groups.

of the angles between the (all) or $E(2)$ conformation and the (i) conformation. Angles 2–5 were included in the sum. We find that AAE is smallest for the MM2p conformation (that is, most similar to X-ray) although the AAE for the STO-3G conformation is quite similar. Two local minima are found for MM2p (but not for MNDO or STO-3G): one using the (i) conformation as starting geometry and one using the (all) (mec) for MNDO as the starting geometry for MM2p, the latter is 0.13 kcal/mol lower than the former and is thus the global minimum. Duax et al.[8] found the (mec) starting from (i) minimum in a similar MM2p calculation but did not report the other. The (mec) starting from (i) is not similar to the MNDO or STO-3G (mec). Only one minimum was found for MNDO and STO-3G. The (mec) found for MM2p (starting at (i)), the MNDO (mec), and the STO-3G (mec) are all more or less in the region of the (i) conformation. The ΔE_2 values for the MNDO calculation are considerably steeper than those for the other two methods; this indicates that the STO-3G and MM2p are relatively flat in the (i) region.

EPD. Table IV gives a summary of the EPD calculations. In this case the AAE for the MM2p calculation is the smallest of the three calculation techniques indicating that the (all) (mec) for MM2p is geometrically nearest the (i) conformation. The AAE's for MNDO and STO-3G are quite similar. As was true for DES, all three calculations appear to give (mec) in the general region of (i); however, the MNDO and STO-3G calculations show the largest differences from X-ray in the ϕ_1 and ϕ_3 angles. The STO-3G and MM2p surface appear to be relatively flat; the MNDO surface appears to be the steepest.

ZPD. Table V gives a summary of the ZPD calculations. The only structural difference between EPD and ZPD is the 180° flip of the ethylenic bond. Overall most results are similar to those found for EPD. The MM2p (mec) is nearest the X-ray (i) form based on AAEs. The AAEs for the STO-3G and MNDO calculations are similar. Most of the variations from X-ray for STO-3G and MNDO are in ϕ_1 and ϕ_3; most of the MM2p variation from X-ray is in ϕ_3. The MNDO surface is steepest in the (i) region; the STO-3G and MM2p surfaces are flattest (based on ΔE_2 values). The ZPD form is found more stable than the EPD form by 5–6 kcal/mol for the STO-3G, MNDO, and MM2P calculations based on $E(4)$; however, for MM2p, EPD and ZPD are of approximately equal stability based on E(all). DES is at least 6 kcal/mol more stable than ZPD for the STO-3G and MNDO $E(4)$ but of equal stability to ZPD for MM2p. However, DES is 1.1 kcal/mol less stable than EPD/ZPD for MM2p while more stable by 7 kcal/mol for MNDO based on E(all) calculations.

Comparison of Surfaces. So that we can have a feeling for the relative energy values on the potential surfaces calculated by different methods, we computed $E(i) - E(\phi_2,\phi_4)$ for DES and $E(i) - E(\phi_1,...,\phi_4)$ for ZPD and EPD from single-point calculations at the (mec) and other defined geometries for each of the three methods for the desoxy molecules. The results are summarized in Tables VII–VIII for the DES, EPD, and ZPD, respectively. For DES, the MM2p (mec) used is the (i) derived one; it is clear that this is a relatively low energy point for the MNDO and STO-3G surfaces. It is apparent from these tables that the MNDO surface is the steepest of the three. The actual shapes of a selected region of the $E(\phi_2,\phi_4)$ surfaces for the three calculational methods for DES as functions of ϕ_2 and ϕ_4 are shown in Figure 2. The relative flatnesses of the STO-3G and MM2p surfaces are apparent.

Since the STO-3G calculations were by necessity highly constrained, it is of interest to determine the effect of imposing the same constraints used in the ab initio calculation for MNDO and MM2p. The minima found for MNDO are close to the mecs for all three molecules (Tables VI–VIII, footnote *c*); however, for MM2p, these constrained minima (Tables VI–VIII, footnote *b*) show significant deviations (up to 37°) from the mecs for ZPD and EPD. The constrained DES minimum is quite close to X-ray; we speculate that the large constraint ZPD/EPD deviation is due to the locking of the bond angles about $C_{7'}$ to tetrahedral (the X-ray angles are significantly nontetrahedral). The other parameters from the all set (not shown) for MM2p and MNDO have similar values, thus no clear reason emerges for the differences in the response of the methods to the constraints.

Conclusions

Overall we find that in all three cases the MM2p minimum geometries agree more closely with X-ray; for EPD and ZPD, the STO-3G and MNDO calculations are in agreement with one another. For DES, the STO-3G deviations are similar to those for MM2p. The (mec) with and without OH's on the rings are quite similar.

Part of the discrepancy between X-ray and calculation geometries might be due to the fact that the calculations on single molecules do not take into consideration near-neighbor interactions which are present in the crystal lattice.[22] In the case of DES and its analogues the opportunity for some degree of hydrogen bonding is present. This possibility is discussed by Weeks et al.[9] for the X-ray structure of DES with the conclusion that there probably is significant intermolecular hydrogen bonding in pure solid DES. Since hydrogen bonding of the –O- - -H–O– variety can stabilize two interacting molecules by perhaps as much as 5 kcal/mol, it is possible that some difference between the X-ray (mec) and the calculational (mec) could be related to hydrogen bonding in the phenyl para positions. If so, the largest deviations would be expected for ϕ_1 and ϕ_3, the torsional angles defining the orientation of the phenyl rings; these are the angles that should depend most strongly on the intermolecular hydrogen bonding.

In order to assess the influence of intermolecular forces present in the DES crystal packing, STO-3G calculations were repeated with the presence of the hydroxyl groups on DES in addition to including two interacting water molecules. The water molecules were positioned in such a manner as to model the hydrogen bonding between interacting hydroxyl groups of adjacent DES units as suggested by Weeks et al.[9] Weeks[9] reported a $O_{DES(A)}$–$O_{DES(B)}$ distance of 3.026 Å and a $H_{DES(A)}$–$O_{DES(B)}$ distance of 2.1 Å. The H_2O orientations were obtained by superimposing the H_2O atomic positions with those of the H–O–C hydrogen-bonding fragments of the adjacent DES units derived from the crystallographic coordinates. The O–H water distances were fixed at 0.921 Å with a H–O–H angle of 107.25° to simulate the C–O–H arrangement. Furthermore, the waters were fixed spacially relative to the central carbons C_7, $C_{7'}$, C_1 ($C_{1'}$) so that their positions were invariant to rotations about the angles of interest (ϕ_2 and ϕ_4) and so as to preserve C_i symmetry.

With the presence of the hydrogen bonding waters, a series of single point ab initio calculations were made at the STO-3G level for a range of dihedral angles ϕ_2 and ϕ_4. We find a slight shift

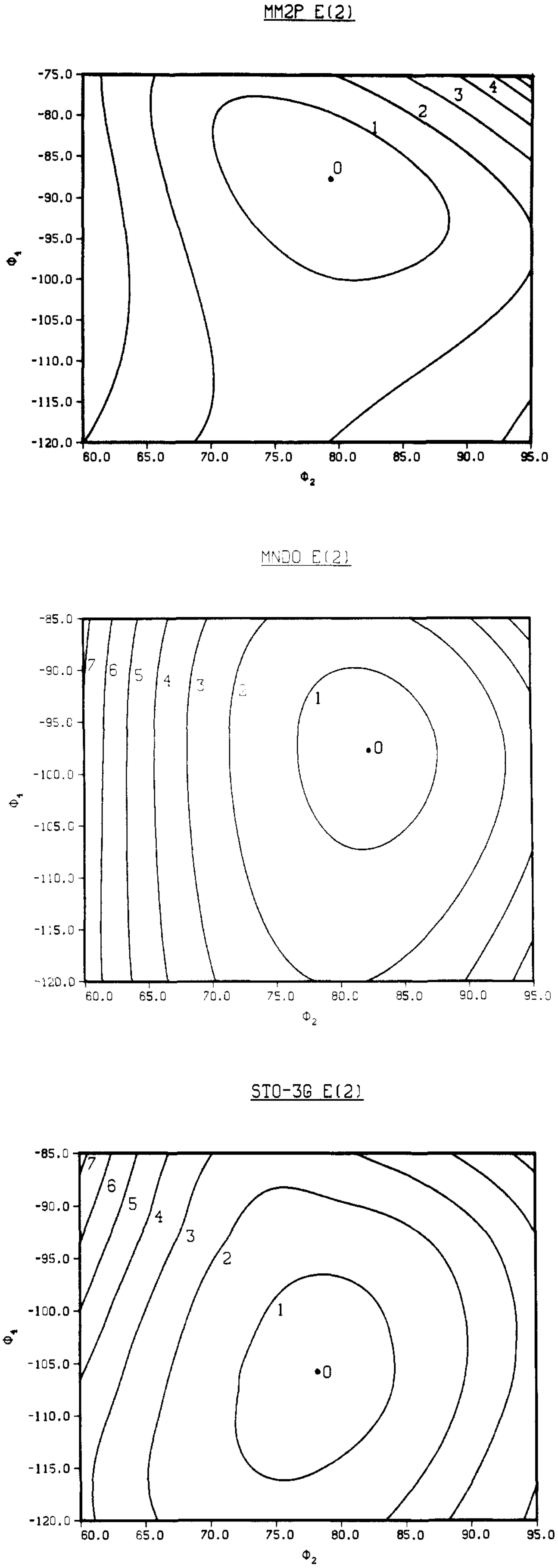

Figure 2. $E(2)$ surfaces for three calculational methods for DES as a function of ϕ_2 and ϕ_4: (a) MM2p surface; (b) MNDO surface; (c) STO-3G surface. Curve k is at energy $E(i) - \delta(k)\Delta E_2$ where $\delta(k)$ = 1.00, 0.95, 0.85, 0.7, 0.5, 0.3, 0.15, and 0.005 for k = 0, 1, 2, ..., 7, respectively.

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Table V. ZPD Geometry and Energy Data. The X-ray Geometry Is Summarized in Ref 8

geometry[a]	ϕ_1	ϕ_2	ϕ_3	ϕ_4	AAE[c]	ΔE_{all}[b]	ΔE_4
X-ray	−63	76	50	−58			
MM2p w/o[d]	−59	78	65	−63			
|Δ|	4	2	15	5	7	−13.8	−0.6
MM2p w	−62	79	70	−64			
|Δ|	1	3	20	6	8	−16.4	−0.9
MNDO w/o	−91	57	91	−69			
|Δ|	27	19	41	11	25	−34.0	−10.7
MNDO w	−90	57	91	−69			
|Δ|	27	19	41	11	25	−47.6	−10.9
STO-3G w/o	−87	55	89	−69			
|Δ|	24	21	39	11	24	–	−5.2

[a] Torsion angle definitions same as Table II. [b] Energy drop below the energy at the initial (almost X-ray) geometry in kcal/mol. See footnote *b* to Table II. [c] Average absolute error is defined with comparison with the X-ray structure. [d] w = with OH groups, w/o = without OH groups.

Table VI. Comparison of DES Potential Surfaces by the Different Techniques. The Tabulated Value Is $E(i) - E(\phi_2,\phi_4)$. All Values in kcal/mol. All Calculations Are for the Desoxy Molecule

geometry ϕ_2, ϕ_4	MM2p (mec) 62, −146[a]	MNDO (mec) 84, −95[a]	STO-3G min 76, −109
method			
MM2p (−2.7)[b]	−1.2	−2.5	−1.7
MNDO (−8.0)[c]	+2.0	−7.9	−6.9
STO-3G	+0.6	−1.2	−1.8

[a] Angles in mec; not the minimum for the two variable surface. [b] Minimum value of $E(i) - E(\phi_2,\phi_4)$ attained at ϕ_2,ϕ_4 = 79,−87, respectively. [c] Minimum value of $E(i) - E(\phi_2,\phi_4)$ attained at ϕ_2,ϕ_4 = 82,−98, respectively.

Table VII. Comparison of the EPD Potential Surfaces by the Various Techniques. The Tabulated Value Is $E(i) - E(\phi_1,...,\phi_4)$. All Values in kcal/mol. All Calculations Are for the Desoxy Molecule

geometry	MM2p (mec)	MNDO (mec)	STO-3G minimum	X-ray/MNDO midpoint
ϕ_1–ϕ_4	−47, 81, 59, −59[a]	−92, 61, 92, −69[a]	−87, 53, 88, −72	−70, 69, 73, −63
method				
MM2p (−2.3)[b]	+0.3	−1.1	−2.2	−0.1
MNDO (−11.3)[c]	+1.7	−10.1	−11.2	−6.1
STO-3G	+0.7	−2.9	−3.2	

[a] Angles in mec; not the minimum for the four variable surface. [b] Minimum value of $E(i) - E(\phi_1,...\phi_4)$ attained at $\phi_1,\phi_2,\phi_3,\phi_4$ = −77,81,90,−77, respectively. [c] Minimum value of $E(i) - E(\phi_1,...,\phi_4)$ attained at $\phi_1,\phi_2,\phi_3,\phi_4$ = −87,56,87,−74, respectively.

in the minimum geometry: ϕ_2, 76° → 71°, ϕ_4, 109° → 113° (the first conformation is our STO-3G minimum found in the absence of water, the second with waters added). The lowering in energy is approximately 0.4 kcal/mol. Our conclusion is, in agreement with Duax et al.,[8] that the intramolecular forces, in this case hydrogen bonding, do not have a dominant effect on the minimum energy conformation.

Alternative explanations for these results must address the quality of the calculation approaches used to generate the calculation geometries. For MM2p the most significant differences occur in the torsion angles defining the orientation of the ethyl side chains. The MM2p algorithm does not have explicit parameters for dihedrals about sp^2–sp^3 bonds; some small improvement might be effected by the addition of this kind of interaction.

Table VIII. Comparison of ZPD Potential Energy Surfaces by the Various Techniques. The Tabulated Value Is $E(i) - E(\phi_1,...,\phi_4)$. All Values in kcal/mol. All Calculations Are for the Desoxy Molecule

geometry	MM2p (mec)	MNDO (mec)	STO-3G minimum	X-ray/ MNDO
ϕ_1–ϕ_4	−59, −78, 65, −63[a]	−91, 57, 91, −69[a]	−87, 55, 89, −69	−76, 66, 70, −63
method				
MM2p (−5.4)[b]	−0.6	−3.4	−4.0	−2.1
MNDO (−11.6)[c]	−0.3	−10.3	−11.0	−6.5
STO-3G	+0.3	−4.9	−5.2	−2.8

[a] See footnotes to Table VII. [b] Minimum value of $E(i) - E(\phi_1,...,\phi_4)$ attained at $\phi_1,\phi_2,\phi_3,\phi_4$ = −86,41,98,−73, respectively. [c] Minimum value of $E(i) - E(\phi_1,...,\phi_4)$ attained at $\phi_1,\phi_2,\phi_3,\phi_4$ = −88,56,89,−76, respectively.

There is one major caveat that should be mentioned with respect to the ab initio calculations. The STO-3G basis set was the simplest—and also most economical—one that we had available. It is well-known that molecular properties are somewhat more reliably given by extended split valence sets of the 4-21G variety.[21] A possible reason that the discrepancy between X-ray and STO-3G geometries for unsymmetrical systems such as ZPD and EPD is greater than for the symmetrical DES is that the use of the small STO-3G basis set leads to uneven "improvement" of the orbitals on one side of the molecules by nonvanishing orbitals from the other side of the molecule—essentially an uneven superposition error inherent in small basis sets. It will ultimately be worthwhile to repeat these calculations with a modern gradient minimization technique[21] to determine sensitivity to basis set for (mec) results for large molecules such as those studied here. In the meantime, we plan to examine the torsional relationship involving an sp^2–sp^3 formal single bond in a smaller model system using both STO-3G and 4-21G for comparison.

We feel that studies of this type are important for developing improved calculation programs that will be able to accurately predict the energies and shapes of metastable conformers of drugs and toxic chemicals. Such minor conformers may be responsible for both desired and undesired biological activity but may not be crystallizable.

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