A TECHNICAL NOTE ON THE SEMI-EMPIRICAL TREATMENT OF *trans*-3,6-DIMETHOXY-1,2,4-TRIOXANE

Abraham F. Jalbout

*Department of Physics, Dillard University, 2601 Gentilly Blvd., New Orleans, LA 70112 USA;
Department of Chemistry, University of New Orleans, New Orleans, LA 70148*

Commentary and discussion

The authors of the work recently published in this journal report on a theoretical study of *trans*-3,6-dimethoxy-1,2,4-trioxane with elementary the semi-empirical AM1 and PM3 methods.[a] They state that:

"Although critics have arisen regarding the predictive properties of the PM3 and AM1 methods to reproduce the energetics of internal rotations, this does not seem to be the case for the present calculations"

How do they know this? Is there any experimental data to compare the accuracy of the calculations? From my experiences[1–4] in torsional potentials, there are much better correlations to the experimental data when more correlation is included into the study of the particular system. In fact the Fourier series fit[3] of the torsional potential data for over 90 data points (fully relaxed surface) is superiorly correlated with more advanced methods then for lower level ab initio calculations. On page 113 of their article they propose an "intermediate twist conformation", what this means however, is not known to the readers. In order for this so-called intermediate to be identified, a full torsional potential surface must be calculated, at moderate dihedral angle rotations (i.e. intervals of 10-20 degrees for the angles involved in the axial-axial to equatorial-equatorial conversions).

Despite the fact that the authors report good correlations with experimental data for the geometrical parameters, it is well known that with some of these cyclic systems the geometries between the AM1/PM3 methods and more advanced treatments (i.e. Density functional theory) are similar, however the energies are not. Thus, this does not prove too much about the reliability of the calculated results.[5] Also, the reference for the presented experimental coordinates is not provided, how shall we be able to validate their results then?

On page 117, the heats of formation are reported. How were these values computed? Was an isodesmic approach used?[6] Or was the result simply the reading of the computer output file?

They report in the conclusions of an n $\rightarrow \sigma^*$ stereoelectronic effects, but no discussion of the bond strength were reported.[7] The force constant (or vibrational frequency) should be addressed in order for this effect to be better studied, or at the least the bond dissociation energy can be calculated. From figure 1 we have plotted the lowest unoccupied molecular orbital and the highest occupied molecular orbital for the lowest energy isomers calculated by the AM1,[13] PM3,[14] MNDO,[15] and MNDO/3[16] methods. In table 1 we have shown the relative band gaps, thus quantitatively showing the aromatic stabilization in the molecular species.
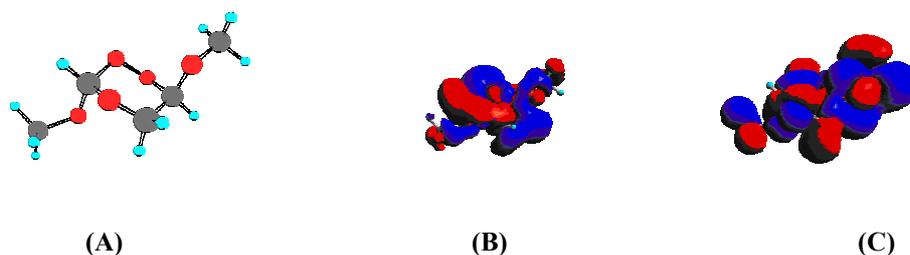

| (A) | (B) | (C) |

Figure 1A-C. AM1 Plot of the optimized geometry (A), LUMO (B) and HOMO (C) of the lowest energy isomer of trans-3,6 Dimethoxy-1,2,4-Trioxane using a grid of 30X30X30 and an isocontour surface of 0.01 a.u.

Method	HOMO (E_h)	LUMO (E_h)	Band Gap (eV)
MNDO	-0.411722	0.082731	13.45
MNDO/3	-0.368415	0.004937	10.16
AM1	-0.400118	0.072328	12.86
PM3	-0.406301	0.003189	11.15

Table 1. The energy of the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) in hartrees (E_h) and their relative differences.

Overall a few points need to be clarified. While the parameterization of much semi-empirical method have been evaluated for carbon clusters,[8] we have shown[3] that when high level *ab initio* methods are compared to these types of modifications to a MNDO-d (more advanced then MNDO) type of method (i.e. ClOOCl decomposition pathways: ClOOCl → 2ClO, ClOOCl, ClOO + Cl, ClOOCl → 2Cl + O_2)[9] our results show a 20-30% improvement in most cases when compared to the experimental data. The same authors as in reference 8, have also later reported very accurate CCSD (T) *ab initio* data[10,11] for carbon clusters of similar length (C_2-C_{10}) that are in excellent agreement with experimental data, which otherwise could not be calculated by neither the AM1 or PM3 methods.[5] We feel that it is possible nowadays with modern computational resources to compare semi-empirical and DFT data quite easily. For example, Basuschlicher[12] reported the AM1 and ONIOM (a combined universal force field, UFF, calculation for the low-level treatment, and DFT for the high level description) calculated results for carbon nano-tubes up to $C_{200}H_{120}$.

In conclusion, we can safely say that there are many advantages and disadvantages when using semi-empirical methods. From table 2 we can see the spectrum of atoms covered by the AM1, PM3, and MNDO methods. Although, it is extensive, from table 3[16] we see that the choice of basis sets (that can be coupled to either a high level *ab initio* method or to a density functional theory method) is much more broad that can allow for much more user flexibility. If the specialist would like EPR constants there is a basis set designed for this purpose, if a quick optimization and Vibrational analysis is needed then gaussian basis sets are often the solution, where in cases where accuracy is the key a cc-pvQZ method can be applied.[17]

Atom #	Atom	PM3	AM1	MNDO	MNDO/3
1	H	X	X	X	X
3	Li	X	---	X	---
4	Be	X	X	X	---
5	B	X	X	X	X
6	C	X	X	X	X
7	N	X	X	X	X
8	O	X	X	X	X
9	F	X	X	X	X
11	Na	X	---	---	---
12	Mg	X	---	---	---
13	Al	X	X	X	---
14	Si	X	X	X	X
15	P	X	X	X	X
16	S	X	X	X	X
17	Cl	X	X	X	X
19	K	X	---	---	---
20	Ca	X	---	---	---
30	Zn	X	X	X	---
31	Ga	X	---	---	---
32	Ge	X	X	X	---
33	As	X	---	---	---
34	Se	X	---	---	---
35	Br	X	X	X	---
37	Rb	X	---	---	---
38	Sr	X	---	---	---
48	Cd	X	---	---	---
49	In	X	---	---	---
50	Sn	X	X	X	---
51	Sb	X	---	---	---
52	Te	X	---	---	---
53	I	X	X	X	---

Table 2. Available atoms for the semi-empirical methods described in this work.

On the other hand semi-empirical MO methods are indispensable when thermal averaging is required,[18] or when a quantum dynamical study of an enzymatic reaction is studied,[19] in ligand-receptor interactions[20] and even in the modeling of homo, and heteropolymeric systems (i.e. DNA)[21] is the object of a particular investigation.

All in all, the AM1, PM3 and MNDO method can be a route to allow for studies not attainable by traditional, more computationally demanding methods, these methods should be used for further validation of theoretical results to increase there usefulness in practical applications or for pre-experimental modeling.[22,23]

Basis sets	Atoms	Polarization Functions	Diffuse Functions
STO–3G	H-Xe	*	
3-21G	H-Xe	* or * *	+
6-21G	H-Cl	(d)	
4-31G	H-Ne	(d) or (d,p)	
6-31G	H-Kr	(3df,3pd)	++
6-311G	H-Kr	(3df,3pd)	++
D95	H-Cl except Na, Mg	(3df,3pd)	++
D95V	H-Ne	(d) or (d,p)	++
SHC	H-Cl	*	
CEP-4G	H-Rn	*	
CEP-31G	H-Rn	*	
CEP-121G	H-Rn		
LanL2MB	H-Ba, La-Bi		
LanL2DZ	H, Li-Ba, La-Bi		
SDD	all but Fr and Ra		
cc-pVDZ	H, B-Ne, Al-Ar		aug
cc-pVTZ	H, B-Ne ,Al-Ar		aug
cc-pVQZ	H, B-Ne, Al-Ar		aug
cc-pV6Z	H, B-Ne		aug
SV	H-Kr		
SVP	H-Kr		
TZV	H-Kr		(3df,3pd)
MidiX	H, C, N, O, F, P, S, Cl		
EPR-II,III	H, B, C, N, O, F		

Table 3. Available atoms for the basis sets described in this work.

Acknowledgements

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