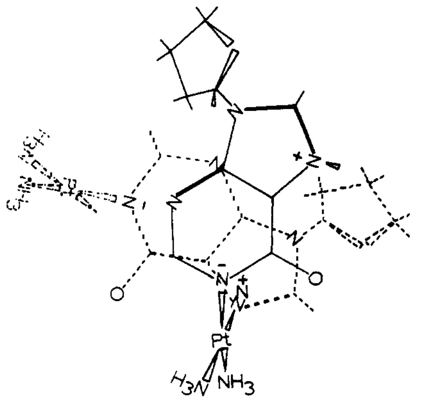

Figure 3. Proposed model for bridging of adjacent stacked bases in solutions of 1:1 *cis*-$(H_3N)_2Pt^{II}$:inosine. Only two units in the stack are illustrated.

to N(1) and N(7). Raman spectra are illustrated in Figure 1 for 25 m*M* inosine binding *cis*-$(H_3N)_2Pt^{II}$ and enPt^{II}. In D_2O at pD <5, the addition of *cis*-$(H_3N)_2Pt^{II}$ has little effect on the *intensity* of the band in the 1650-1700-cm^{-1} region, although the *frequency* increases slightly. This is illustrated in Figure 2, and the complex formed at pD 4.5 clearly has 2:1 inosine-platinum stoichiometry. The frequency shifts throughout the spectrum are very similar to those caused by CH_3Hg^{II} coordination at N(7).[22] When proton transfer from the N(1) position of inosine occurs, the band in the 1650-1700-cm^{-1} region disappears. With solutions at pH 7.6, the variation in integrated intensity of the 1675- or the 720-cm^{-1} bands indicates proton loss is complete in solutions with *equimolar* concentrations of inosine and *cis*-$(H_3N)_2Pt^{II}$. This also is illustrated in Figure 2. The scattering at other frequencies, e.g., 1580 cm^{-1}, indicates, however, that this is not a simple 1:1 reaction. The intensity passes through a minimum in a solution with 2:1 inosine: Pt(II) as can be seen in Figure 1. As more *cis*-$(H_3N)_2Pt^{II}$ is added, the 1580 cm^{-1} intensity increases up to 1:1 stoichiometry when the spectrum is very like inosine mercuriated at both N(1) and N(7).[22] The addition of more $(H_3N)_2Pt^{II}$ has little effect on the spectrum indicating that inosine interacts only weakly, if at all, at sites other than N(1) and N(7).

^{1}H NMR studies on the same solutions show that up to 12.5 m*M* $(H_3N)_2Pt^{II}$, sharp resonances due to H(2) and H(8) of free and bound inosine are present at −5.01, −5.13 and −5.04, −5.50 ppm, respectively. (An internal $N(CH_3)_4^+$ reference was used.) At higher concentrations, new signals appear at −5.28, −5.36 ppm, and at 25 m*M* $(H_3N)_2Pt^{II}$ and above a broad resonance at −5.34 ppm is observed. In addition, all of the sugar protons become complex multiplets and then broad signals. This behavior is in marked contrast to that observed for CH_3Hg^{II} binding[22] where sharp signals are present throughout. It suggests a number of slightly different environments exist for inosine in the 1:1 complex and that these are not time averaged in the ^{1}H NMR experiment as occurs in the normal nucleoside stacking.

The Raman and ^{1}H NMR data can be explained by a vertical stacking of the inosine with adjacent bases bridged by the bifunctional $(H_3N)_2Pt^{II}$. At these concentrations, stacking occurs with inosine itself.[24] Coordination of the positive platinum center at N(7) with proton loss from N(1) should result in a highly polar complex which should have a tendency to stack with the same orientation as 7-methylinosine.[25] The stacking distance, ca. 3.4 Å corresponds to the "bite" of the platinum complex, and we suggest that adjacent nucleosides are bridged as illustrated in Figure 3. The major binding site of *trans*-$PtCl_2(NH_3)_2$ to yeast tRNA^{Phe} appears to involve N(7) of each of the adjacent bases Gm34 and A35 in both the crystal and solution,[26] so the trans isomer forms bridges too.

Acknowledgments. The authors are grateful for support from the Public Health Service, Grant AM-16101, from the National Institue of Arthritis, Metabolism, and Digestive Diseases, and from the National Science Foundation, Grant MPS73-04856. We also thank Professor Dale Margerum for helpful discussions.

References and Notes

(1) B. Rosenberg, L. Van Camp, J. E. Trosko, and V. H. Mansour, *Nature (London)*, **222**, 385 (1969).
(2) B. Rosenberg, *Naturwissenschaften*, **60**, 399 (1973).
(3) M. J. Cleare and J. D. Hoeschele, *Platinum Met. Rev.*, **17**, 2 (1973).
(4) M. J. Cleare, *Coord. Chem. Rev.*, **12**, 349 (1974).
(5) T. A. Connors and J. J. Roberts, Ed., "Platinum Coordination Compounds in Cancer Chemotherapy", Springer, Berlin, 1974.
(6) S. K. Carter and M. Slavik, *Annu. Rev. Pharmacol.*, **14**, 157 (1974).
(7) H. C. Harder and B. Rosenberg, *Int. J. Cancer*, **6**, 207 (1970).
(8) J. A. Howle and G. R. Gale, *Biochem. Pharmacol.*, **19**, 2757 (1970).
(9) K. V. Shooter, R. Howse, R. U. Merrifield, and A. B. Robins, *Chem. Biol. Interact.*, **5**, 289 (1972).
(10) L. L. Munchausen, *Proc. Nat. Acad. Sci. U.S.A.*, **71**, 4519 (1974).
(11) S. Mansy, B. Rosenberg, and A. J. Thomson, *J. Am. Chem. Soc.*, **95**, 1663 (1973).
(12) P. C. Kong and T. Theophanides, *Inorg. Chem.*, **13**, 1167 (1974).
(13) P. C. Kong and T. Theophanides, *Inorg. Chem.*, **13**, 1981 (1974).
(14) I. A. G. Roos, A. J. Thomson, and J. Eagles, *Chem. Biol. Interact.*, **8**, 421 (1974).
(15) I. A. G. Roos, A. J. Thomson, and S. Mansy, *J. Am. Chem. Soc.*, **96**, 6484 (1974).
(16) P. J. Stone, A. D. Kelman, and F. M. Sinex, *Nature (London)*, **251**, 736 (1974).
(17) D. M. L. Goodgame, I. Jeeves, F. L. Phillips, and A. C. Skapski, *Biochim. Biophys. Acta*, **378**, 153 (1975).
(18) S. Mansy, T. E. Wood, J. C. Sprowles, and R. S. Tobias, *J. Am. Chem. Soc.*, **96**, 1762 (1974).
(19) S. Mansy and R. S. Tobias, *J. Am. Chem. Soc.*, **96**, 6874 (1974).
(20) S. Mansy, J. P. Frick, and R. S. Tobias, *Biochim. Biophys. Acta*, **378**, 319 (1975).
(21) S. Mansy and R. S. Tobias, *Inorg. Chem.*, **14**, 287 (1975).
(22) S. Mansy and R. S. Tobias, *Biochemistry*, **14**, 2952 (1975).
(23) See the discussion by D. M. Brown, "Basic Principles in Nucleic Acid Chemistry", Vol. 2, P. O. P. Ts'o, Ed., Academic Press, New York, N.Y., 1974, p 20.
(24) P. O. P. Ts'o in "Basic Principles of Nucleic Acid Chemistry", Vol. 1, P. O. P. Ts'o, Ed., Academic Press, New York, N.Y., 1974, p 553.
(25) P. O. P. Ts'o, N. S. Kondo, R. K. Robins, and A. D. Broom, *J. Am. Chem. Soc.*, **91**, 5625 (1969).
(26) D. Rhodes, P. W. Piper, and B. F. C. Clark, *J. Mol. Biol.*, **89**, 469 (1974), and references therein.

R. Stuart Tobias,* Grace Y. H. Chu, Henry J. Peresie

Department of Chemistry, Purdue University
West Lafayette, Indiana 47907

Received March 31, 1975

Some Deficiencies of MINDO/3 Semiempirical Theory

Sir:

In a recent series of papers,[1] Bingham, Dewar, and Lo (BDL) have documented a new semiempirical molecular orbital method (MINDO/3) which attempts to provide an inexpensive and reliable theoretical technique for investigating energetic and structural features inaccessible to experimental study. The method is applied to a wide range of molecules where experimental data are available and the results are also compared with ab initio molecular orbital treatments in some cases. The purpose of this communication is to point out that MINDO/3, although low in cost and useful in reproducing broad features of electronic structure, is nevertheless unreliable for energy prediction. In spite of direct parameterization to experimental data, it fails to reproduce certain key energetic relationships which are handled quite satisfactorily without parameterization by ab initio techniques. For brevity we shall limit our remarks to the

Table I. Energy Comparisons for Hydrocarbons

Reaction	Energy change (kcal/mol)		
	MINDO/3[a]	Hartree–Fock	Obsd[b]
1. $CH_3CH_3 + H_2 \rightarrow 2CH_4$	+7.1	−22.0[c]	−15.6 (−18.1)
2. $H_2C{=}CH_2 + 2CH_4 \rightarrow 2CH_3CH_3$	−46.2	−22.3[c]	−17.0 (−21.0)
3. $HC{\equiv}CH + 4CH_4 \rightarrow 3CH_3CH_3$	−92.0	−55.4[c]	−43.3 (−51.0)
4. $CH_3CH_2CH_3 + CH_4 \rightarrow 2CH_3CH_3$	−6.8	+1.1[d]	+2.3
5. $CH_3(CH_2)_2CH_3 + 2CH_4 \rightarrow 3CH_3CH_3$	−16.4	+1.6[d]	+5.6
6. $CH_3(CH_2)_3CH_3 + 3CH_4 \rightarrow 4CH_3CH_3$	−24.2		+8.0
7. $CH_3CH{=}CH_2 + CH_4 \rightarrow CH_3CH_3 + H_2C{=}CH_2$	−0.8	+3.9[c]	+5.2
8. $CH_3C{\equiv}CH + CH_4 \rightarrow CH_3CH_3 + HC{\equiv}CH$	+9.3	+8.1[c]	+7.7
9. $H_2C{=}C{=}CH_2 + CH_4 \rightarrow 2H_2C{=}CH_2$	+2.7	−4.4[c]	−3.2
10. $CH_3CH{=}CH_2 \rightarrow$ cyclopropane	+2.2	+7.8[c]	+7.8
11. $CH_3C{\equiv}CH \rightarrow$ cyclopropene	+24.4	+25.4[c]	+21.9
12. isobutane → *n*-butane	−5.5	+0.5[d]	+2.0
13. neopentane → *n*-pentane	−21.5		+5.2
14. isobutene → *trans*-2-butene	−8.8	+0.3[d]	+1.3
15 1,3-butadiene → 2-butyne	−19.8	+6.5[d]	+8.6
16. $C_6H_6 + 6CH_4 \rightarrow 3CH_3CH_3 + 3H_2C{=}CH_2$	+7.2	+63.6[e]	+64.2

[a] Results from ref 1. [b] Unbracketed values from heats of formation at 298 K. Bracketed values are corrected to 0 K and also corrected for zero point vibration. [c] 6-31G* results optimized STO-3G geometries. See ref 4. [d] 4-31G results using optimized or partially optimized STO-3G geometries. See ref 3 and 5. [e] As *c* except standard geometry used for benzene. See W. J. Hehre and J. A. Pople, *J. Am. Chem. Soc.*, 94, 6901 (1972).

energies of small hydrocarbons. A subsequent communication deals with equilibrium geometries.[2]

The MINDO/3 method (modified intermediate neglect of differential overlap/3) is based on a series of integral approximations which simplify a self-consistent Hartree–Fock molecular orbital treatment based on a minimal set of Slater-type atomic orbitals. These approximations lead to inexpensive computations. The remaining parameters are then adjusted to give optimum fit to experimental data. The ab initio methods, on the other hand, have proceeded by avoiding integral approximations and successively refining the Hartree–Fock theory by expansion of the basis set, admittedly at some extra cost. Even with a large basis set, as BDL point out, Hartree–Fock theory fails to take account of electron correlation. Nevertheless, considerable evidence has accumulated in recent years that Hartree–Fock theory does give a good account of the energies of certain formal reactions which compare different types of hydrocarbons and separate significant stabilizing or destabilizing features.[3-6] It is in the prediction of many of these reaction energies that MINDO/3 is inferior to good Hartree–Fock theory. This is illustrated in Table I, which gives energies for a set of 16 simple reactions as obtained by MINDO/3, the best available Hartree–Fock treatment and thermochemical measurement.

Reaction 1 is the hydrogenation of ethane to methane. It is significantly exothermic, reflecting the fact that CC single bonds are weaker than CH or HH single bonds. The best Hartree–Fock study indicates that this reaction energy is reproduced to within 4 kcal/mol if a good enough basis set is used. MINDO/3 fails to give even the correct sign.

Reactions 2 and 3 relate the energies of the simplest C=C and C≡C bonds to those of C—C bonds. Thus 2 compares one double bond to two single bonds, the number of CH bonds being retained. The reaction energy is negative, indicating that the carbon–carbon double bond is less than twice as strong as the corresponding single bond. The best ab initio Hartree–Fock study reproduces this energy well. MINDO/3 gives the correct sign but much too large a magnitude. For reaction 3, which compares a triple bond with three single bonds, the results are similar. Again, the ab initio result is good but MINDO/3 is in error by over 40 kcal/mol.

Reactions 4–9 are of the isodesmic bond-separation type. Since the number of bonds of a given formal type is retained, the heats of these reactions would be zero if bond-energy additivity truly applied. The actual values measure deviations from additivity and characterize bond-bond interactions which are important in determining thermodynamic properties of hydrocarbons. For example, 4, 5, and 6 reflect the phenomena that carbon–carbon single bonds are stabilized when connected in a linear chain. This corresponds to positive bond separation energies for the normal alkanes. The ab initio results produce an effect in the right direction, although the magnitude is too small. MINDO/3, on the other hand, predicts a large spurious effect in the wrong direction.

Reactions 7, 8, and 9 are the bond separation reactions for the unsaturated C_3 hydrocarbons. The positive energy of 7 (propene) is a measure of the stabilization given to a double bond by substitution with a methyl group. The ab initio treatment underestimates this effect somewhat, but MINDO/3 gives the incorrect sign. Reaction 8 is the corresponding effect for a methyl group attached to a triple bond. In this case MINDO/3 gives a satisfactory result. Reaction 9 is found experimentally to have a negative energy corresponding to a destabilization consequent upon cumulation of two double bonds. The ab initio study reproduces this result but MINDO/3 fails.

Reactions 10 and 11 are the energies of cyclization of propene and propyne, respectively. Both MINDO/3 and ab initio treatments give positive values for these energies as observed experimentally. The ab initio results are slightly superior, but only when a basis set including polarization functions (d functions on carbon) is used. It should be noted that BDL made a comparison between methods for these reactions but did not use the best available ab initio results.

Reactions 12 and 13 measure the well-known branching effect in alkanes, branched isomers being more stable than linear isomers. Hartree–Fock theory apparently makes some allowance for this effect, but underestimates it (possibly because of the neglect of dispersion forces). MINDO/3 predicts too large an effect in the wrong direction.

Reactions 14 and 15 refer to the prediction of the most stable isomer in the C_4H_8 and C_4H_6 systems, respectively. For C_4H_8, ab initio Hartree–Fock theory correctly predicts that isobutene is slightly more stable than *trans*-2-butene. MINDO/3 gives them in the wrong order with a substantial energy difference. For C_4H_6, the most stable isomer is 1,3-butadiene, as confirmed by the ab initio treatments. MINDO/3, on the other hand, incorrectly predicts 2-butyne to be most stable, the error in the relative energies of the two isomers approaching 30 kcal/mol.

Finally, reaction 16 is the bond separation reaction for benzene. As it reflects the deviation of additivity from single and double bond energies, the bond separation energy has been suggested as one possible measure of the resonance energy of benzene.[3] The bond separation energy is large and positive and is moderately well reproduced by Hartree-Fock theory. MINDO/3 does give a positive value but only a small fraction of the observed magnitude.

In view of the considerable parameterization[7] in MINDO/3, the extent of these deficiencies is remarkable. One possibility is that optimum parameterization has still not been achieved. BDL doubts this, remarking that "we think it likely that MINDO/3 represents the limit attainable by an INDO-based semiempirical treatment". We have had similar experience in this laboratory. Some years ago an attempt was made to develop a CNDO theory (complete neglect of differential overlap) parameterized directly on experimental energies but was abandoned because it proved impossible to obtain correct single, double, and triple bond energies with the same parameters. It seems likely that the underlying mathematical structure of CNDO/INDO theory cannot accommodate these energetic relationships whatever the parameterization. The possibility remains, as BDL point out, that a more sophisticated semiempirical theory with a structure simulating some higher level of ab initio theory, may yet achieve the objective of providing an inexpensive and reliable mathematical model for hydrocarbon chemistry. For the present, however, MINDO/3 clearly suffers many disadvantages that can be avoided if sufficiently flexible ab initio Hartree-Fock treatments are used.

Acknowledgment is made to the National Science Foundation for partial support under Grant MPS75-04776.

References and Notes

(1) R. C. Bingham, M. J. S. Dewar, and D. H. Lo, *J. Am. Chem. Soc.*, **97**, 1285, 1294, 1302, 1311 (1975).

(2) W. J. Hehre, *J. Am. Chem. Soc.*, following paper in this issue.

(3) W. J. Hehre, R. Ditchfield, L. Radom, and J. A. Pople, *J. Am. Chem. Soc.*, **92**, 4796 (1970).

(4) L. Radom, W. A. Lathan, W. J. Hehre, and J. A. Pople, *J. Am. Chem. Soc.*, **93**, 5339 (1971).

(5) P. C. Hariharan and J. A. Pople, *Chem. Phys. Lett.*, **16**, 217 (1972).

(6) W. J. Hehre and J. A. Pople, submitted for publication.

(7) For hydrocarbons there are nine adjustable parameters in MINDO/3 (ξ_s (C), ξ_p (C), ξ_s (H), B_{HH}, B_{CH}, B_{CC}, α_{HH}, α_{CH}, α_{CC}).

J. A. Pople

Department of Chemistry, Carnegie-Mellon University
Pittsburgh, Pennsylvania 15213

Received May 12, 1975

MINDO/3. An Evaluation of Its Usefulness as a Structural Theory

Sir:

In the preceding communication[1] Pople has conclusively documented that the recently introduced version of Dewar's MINDO method (MINDO/3)[2] fails to account properly for a wide variety of key energetic relationships involving polyatomic hydrocarbons. Furthermore he has pointed out that these same quantities are quite satisfactorily calculated by the ab initio Hartree-Fock model, given a sufficiently flexible basis set. Pople stresses his opinion that the underlying mathematical structure of CNDO/INDO type theories,[3] those on which Dewar's method is grounded, is intrinsically incapable of dealing adequately with such relationships, independent of exact choice of parameterization. Thus, even though MINDO/3 represents a considerable saving in computation effort over full Hartree-Fock treatments,[4] it must be considered far too unreliable for use as a general theory of chemical bonding.

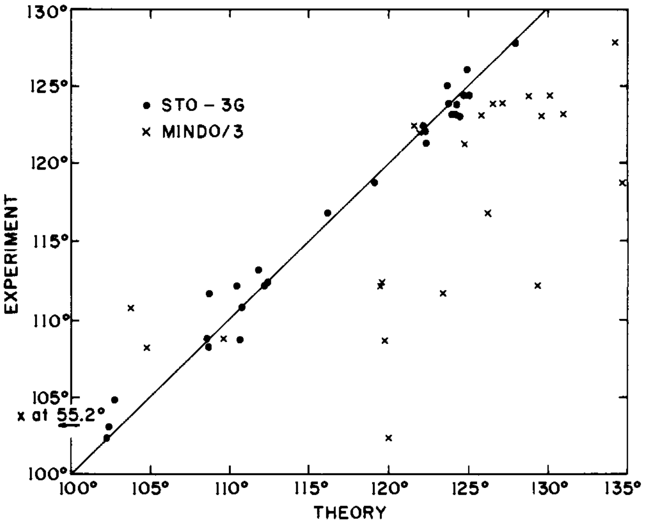

Figure 1. Calculated MINDO/3 (×) and STO-3G (●) vs. experimental skeletal bond angles.

In this manuscript we seek to point out major deficiencies in the ability of the MINDO/3 method to calculate molecular equilibrium geometries, and at the same time to indicate that such failings are not present to a comparable extent in ab initio Hartree-Fock treatments even at the minimal basis set level. Singled out for discussion are bond angles involving the heavy atom skeleton, the aspect of a molecule's equilibrium geometry which most characterizes its gross structure. Comparison of such bond angles calculated using the MINDO/3 and STO-3G[5] methods with experimental values is presented in Figure 1. The data from which it was constructed are listed in Table I. We have attempted to make comparison of the MINDO/3 and STO-3G methods as unbiased as possible. Thus, all skeletal angles of every molecule whose equilibrium geometry has been calculated by both schemes have been considered. In a few cases (formic acid, CF_2, CF_3, and carbonyl fluoride) the reported MINDO/3 geometry is incomplete with regard to specification of the skeletal bond angle (or is missing altogether) although other calculated properties are discussed in text. In these instances we have included comparison between the STO-3G data and experiment.

The following points are worthy of mention. Mean deviation of MINDO/3 calculated skeletal bond angles from experiment is 8.7° (23 comparisons). The mean error at the STO-3G level for the same set of compounds (27 comparisons) is only 0.8°,[6] an order of magnitude smaller. The largest difference between an STO-3G and experimental skeletal bond angle is 3.0°. More than a quarter of the comparisons made using MINDO/3 are in error by almost four times that amount, the greatest deviation being 47.9°. Certainly Dewar's statement about geometry comparisons[2] "Such errors are not of great chemical significance and attempts to reproduce geometries much more accurately than this are not of any real value" does not apply here.

Whereas bond angles involving one or two hydrogens in small molecules such as NH_3 and H_2O are fairly well reproduced by MINDO/3, the degree to which the skeletal geometry responds to substitution is vastly overestimated. For example, experimentally the angle about oxygen opens up approximately 7° in going from water to dimethyl ether, and diminishes only slightly (by 1.4°) as both hydrogens are replaced by fluorine atoms. The MINDO/3 calcula-