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TETRAHEDRON

Some Difficulties Encountered with AM1 and PM3 Calculations

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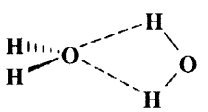
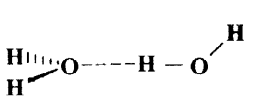
Abstract: AM1 and PM3 underestimate frontier interactions with respect to steric repulsions. Therefore, if two structures differ by ~1 kcal/mol, their calculated ordering is unreliable. Activation energies tend to increase with substitution, regardless of electronic effects. Atomic charges are sometimes unrealistic (in enolates, the negative charge is larger on C than on O). At van der Waals distances, acid-base and coulombic interactions can prevail over steric repulsions. At all distances, basicities are overestimated and nucleophilicities underestimated. This may lead to anomalous ion-molecule and transition structures in gas phase reactions. Transition structures are tighter than in *ab initio* calculations. Optimisations may give chemically unreasonable structures. Minimum energy paths are then difficult to obtain. Usually, but not systematically, PM3 gives more reliable structures and AM1 more realistic energies.

Rapid, inexpensive, user-friendly, AM1 and PM3 are probably the two most popular semi-empirical methods. It is therefore important to assess their strengths and limitations. Their reliability in reproducing heats of formation, bond lengths and bond angles, dipole moments... has been extensively discussed[2]. Comparison with *ab initio* and other semi-empirical methods (MINDO/3, MNDO) has also been made[3]. These papers usually stress the capabilities of AM1 and PM3, although some shortcomings have been mentioned. For example, AM1 gives the "bifurcated" structure **1** for the water dimer, whereas *ab initio* and PM3 calculations give the "linear" structure **2**[4]. We would like to report here some difficulties we have encountered. The point of view is that of *organic users*, mostly interested in mechanistic and stereochemical problems, rather than that of computational chemists.



1 AM1



2 PM3 and *ab initio*

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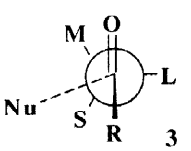
METHODS

The study is restricted to HF-level calculations on isolated molecules or gas phase reactions. AM1 and PM3 calculations were carried out with the MOPAC programs (version 6.00)[5], using the PRECISE option. The conformational minima were fully optimised and the maxima partially optimised, with the torsional angle frozen. Calculations were performed "normally", *i.e.* we did not take advantage of all available options in order to get the best results possible. Whenever the optimisation procedure gave a chemically reasonable structure, we did not try to refine further. Transition structures were obtained using the SADDLE and TS (or NLLSQ) routines. Except for the conformational maxima, all transition structures were characterised by a harmonic frequency calculation.

Ab initio calculations were carried out with the GAUSSIAN 94 program[6]. Many of them are rather low-level (no polarisation functions for Br, Cl; no diffuse functions for anions; inadequate basis set and absence of correlation in transition states calculations...). Their results therefore are not always reliable and cannot be sytematically taken as references. They are however useful checks: large discrepancies with semi-empirical results are usually tell-tale signs of AM1 or PM3 artefacts.

CONFORMATIONAL ANALYSES

In mechanistic studies, we often need to compare transition structures which are conformers of the supermolecule formed by the interacting reagents (*e.g.* **3-5** in 1,2 asymmetric induction, **6-8** in aldol addition). Conformational analysis is thus a crucial test. Semi-empirical methods being parameterised on "normal" molecules, it seems interesting to examine whether they can reproduce unusual conformations, such as those observed in the anomeric effect, in the gauche effect, or in R-CH=X compounds (*e.g.* vinyl ethers, alkenes, alkanals, imines and oximes).



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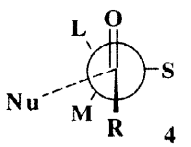

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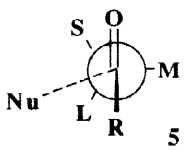

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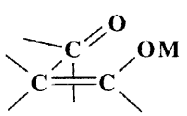

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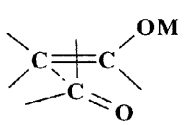

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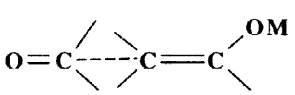

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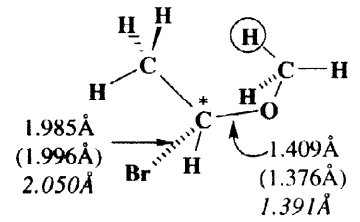
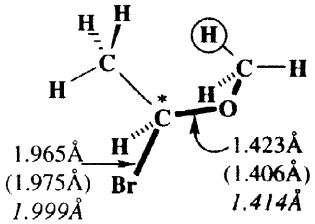
The anomeric effect[7]

α–bromo-oxane is modelled by CH_3-O-CHBr-CH_3, in which CC*OC and the circled hydrogen represent 5 atoms of the oxane ring. According to AM1, PM3 and 3-21G calculations, **9** ("axial" Br) is a stable conformation. However, conformation **10** ("equatorial" Br, with BrC*OC ~180°) is not stable. In order to compare **9** and **10**, the BrC*OC dihedral angle in **10** (bold line) was frozen at 180° in the calculations. As expected, **9** is found to be more stable. It is interesting to note that frontier orbital analysis[8] suggests that in **9**, the OC* bond is shortened and the BrC* bond lengthened. These predictions agree well with X-ray diffraction of anomeric compounds[9] and are nicely reproduced by all three methods.



BrC*OC = 72° (AM1
69° (PM3)
67° (3-21G)

9 AM1 0 kcal/mol
(PM3 0 kcal/mol)
3-21G 0 kcal/mol



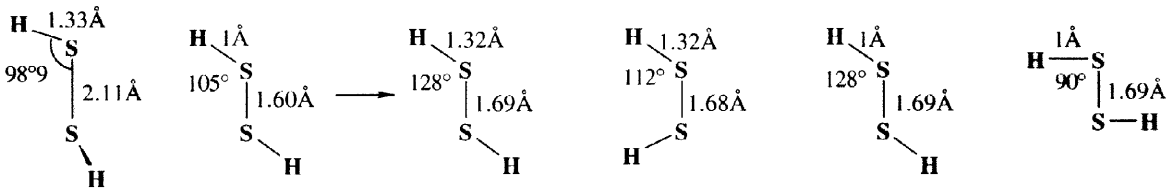
BrC*OC = 180°

10 AM1 2.99 kcal/mol
(PM3 3.68 kcal/mol)
3-21G 4.44 kcal/mol

The gauche effect[10,11]

According to both methods, H_2S_2 is stable in the gauche conformation **11** (calculated dihedral angle: 98°5 (AM1), 93°7 (PM3); experimental value: 90°5[12]). AM1 gives the same prediction for H_2O_2. The calculated dihedral angle is 127°, not far from the *ab initio* value of 123° found by Veillard[13], but appreciably different from the experimental value (111°[14]). However, the potential surface is rather flat, the energy raising by only 0.05 kcal/mol when the dihedral angle is increased to 150°. Interestingly, PM3 calculations indicate that H_2O_2 is stable in the trans but *not* in the gauche conformation.

$ClCH_2$-CH_2Cl is a more stringent test. In the gas phase, the gauche is more stable than the trans conformation by 1.2 kcal/mol, but in the liquid, they have the same energy[15]. Experimental data[16] and 4-31G calculations[11a] give FCH_2-CH_2CH_3 slightly more stable in the gauche than in the trans conformation. For both compounds, the trans conformer is found by AM1 and PM3 to be more stable, although the energy differences are small. Thus, the gauche conformer of 1,2-dichloroethane is less stable by 0.75 kcal/mol (AM1) and 0.6 kcal/mol (PM3) respectively. Again, the semi-empirical Cl-C-C-Cl dihedral angles are larger (AM1: 71°6; PM3: 67°5; 4-31G: 61°5; exper.: 63°). This is probably due to a surestimation of repulsive interactions (*vide infra*).



11 0 kcal/mol **12** **13** 26.3 kcal/mol **14** 46.3 kcal/mol **15** 84.3 kcal/mol **16** 119.4 kcal/mol

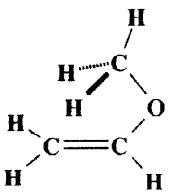
The "over-accommodating" optimisation routines

The AM1 and PM3 optimisation routines are *too* obliging: convergence can be obtained with absurd trial geometries, even when all parameters are set for optimisation. Take the H_2S_2 molecule. Starting with a reasonable guess (SS = 2.15 Å, HSS = 95°), AM1 optimisation gives conformation **11**, whose geometry is close to that reported by Wolfe[10a], Schleyer[12] and Oae[17]. Let us now start with the unreasonable guess **12**. The optimised structure is then **13** (26.5 kcal/mol higher than **11**!), whose rigid rotator conformational curve has two minima, corresponding to the trans and cis conformers. The optimised cis conformer **14** lies 20 kcal/mol higher than **13**. A gauche conformer of **13** will optimise into **11**, if its dihedral angle lies in the 30°-160° range. Otherwise, it will give **13** or **14**. These spurious potential wells are surprisingly deep. Thus, optimisation of **15** or **16** (respectively 58 and 93 kcal/mol higher than **13**!) gives back **13**[18].

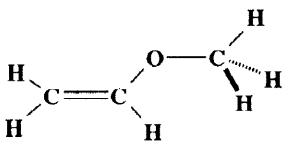
Admittedly, any chemist in his sound mind would check first in the literature the usual bond lengths and bond angles for his compound and thus easily avoids crude mistakes like **12**. However, in mechanistic studies, the fact that AM1 and PM3 readily give chemically unreasonable structures may cause trouble in the search for minimum energy paths (*vide infra*: **Transition structures and reaction paths**).

Methyl vinyl ether

According to both AM1 and PM3, there are two stable conformers, the cis (**17**) lying at lower energy than the trans (**18**), in agreement with experimental data[19].



17 AM1 0 kcal/mol
PM3 0 kcal/mol
3-21G 0 kcal/mol

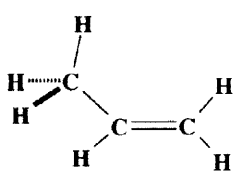


18 AM1 2.06 kcal/mol
PM3 1.66 kcal/mol
3-21G 3.41 kcal/mol

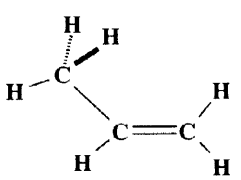
Propene and 1-butene

Both AM1 and PM3 give correctly **19** as the stable conformation of propene, and **20** as a maximum on the conformational curve. The calculated barrier (~0.5 kcal/mol) is lower than the experimental value (2 kcal/mol)[20].

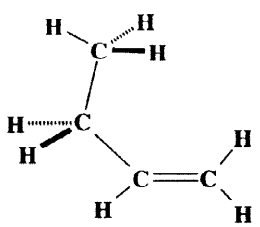
However, if the methyl substituent is replaced by an ethyl group, AM1 and PM3 systematically favour the gauche (anticlinal) conformation. Thus, the conformational curve of 1-butene has two minima (**21**, **23**) and two maxima (**22**, **24**). AM1 and PM3 put the trans conformer **24** ~0.5 kcal/mol below the cis conformer **21**, when it should lie 1.5-2 kcal/mol higher[20]. This suggests that *steric interactions are overestimated with respect to frontier interactions*. In line with this idea, it is observed that, compared to 3-21G calculations, AM1 and PM3 yield similar or smaller CCCC dihedral angles in the unstable synclinal conformer **22** (PM3: 40°; 3-21G: 48°; AM1: 48°5) and larger dihedral angles in the stable anticlinal conformer **23** (3-21G: 119°, PM3: 131°; AM1: 135°).



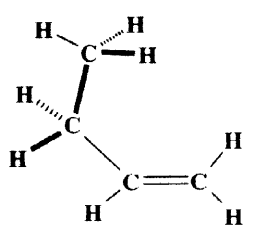
19 AM1 0 kcal/mol
PM3 0 kcal/mol



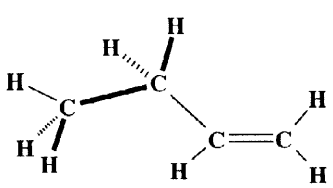
20 AM1 0.55 kcal/mol
PM3 0.67 kcal/mol



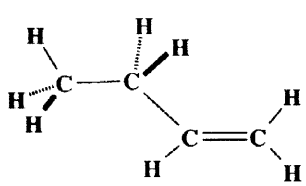
21 AM1 0.68 kcal/mol
PM3 0.88 kcal/mol
CCCC = 0°



22 AM1 1.09 kcal/mol
PM3 1.17 kcal/mol
CCCC = 45° ± 5°



23 AM1 0 kcal/mol
PM3 0 kcal/mol
CCCC = 130° ± 10°

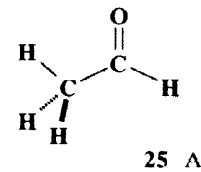


24 AM1 0.24 kcal/mol
PM3 0.35 kcal/mol
CCCC = 180°

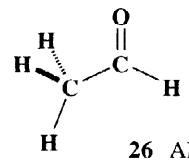
Ethanal and propanal

According to AM1 and PM3, **25** is a minimum and **26** a maximum on the ethanal conformational curve. Their calculated energy difference (~0.5 kcal/mol) is smaller than the experimental value (1.1 kcal/mol)[21].

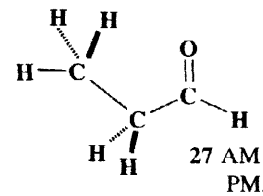
In propanal, the anticlinal conformer is again favoured. There are two minima (**27**, **29**) and two maxima (**28**, **30**) on the conformational curve. However, the cis conformer **27** is found to be less stable (0.7 kcal/mol) than the anticlinal (CCCO ~140°) conformer **29**, in contradiction with experimental data (- 1 kcal/mol)[20,22]. AM1 and PM3 even put **27** 0.6 kcal/mol higher than the trans conformer **30**, instead of 1.5-1.9 kcal/mol lower. Compared with 3-21G calculations, they give a CCCO dihedral angle ~15° smaller for the unstable synclinal conformer **28** (PM3: 54°; AM1: 57°5; 3-21G: 71°) and 15°-20° larger for the stable anticlinal conformer **29** (3-21G: 127°; PM3: 139°5; AM1: 150°5). These results, as well as the 1-butene results, suggest that *in the conformational analysis of a C-C-C=X system, AM1 and PM3 overestimate steric interactions with respect to frontier interactions, whereas the reverse is true for 3-21G calculations*[20]. For a methyl group eclipsing a double bond, the absolute error is 1-2 kcal/mol for AM1 or PM3 calculations and ~1 kcal/mol for 3-21G calculations. It follows that *when two conformers differ by ~1 kcal/mol, their calculated ordering is uncertain*. This interpretation can be checked by examining the conformations of imines and oximes.



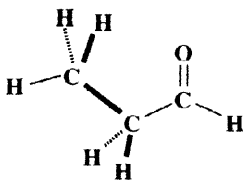
25 AM1 0 kcal/mol
PM3 0 kcal/mol



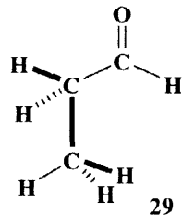
26 AM1 0.4 kcal/mol
PM3 0.6 kcal/mol



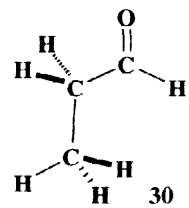
27 AM1 0.66 kcal/mol
PM3 0.73 kcal/mol
CCCO = 0°



28 AM1 1.03 kcal/mol
PM3 1.23 kcal/mol
CCCO = 60° ± 10°



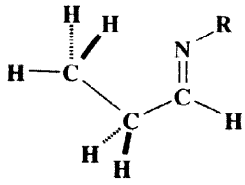
29 AM1 0 kcal/mol
PM3 0 kcal/mol
CCCO = 140° ± 10°



30 AM1 0.04 kcal/mol
PM3 0.16 kcal/mol
CCCO = 180°

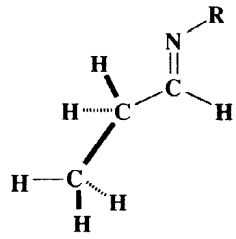
Imines and oximes

On the basis of the Hehre-Salem theory[23], we expect that in unsaturated compounds, the lower the π^* orbital, the higher the stability of the eclipsed conformation. Therefore, in the aldehydes-imines-oximes-alkenes series, in which the π^* energy increases steadily, this conformation should become less and less favourable. Indeed, it is found experimentally that the eclipsed conformation **31a** of N-methylpropanalimine is more stable than the anticlinal **32a** by 0.2 kcal/mol. The order is reversed in propanaloxime: **31b** is less stable than **32b** by 0.5 kcal/mol[22]. As these values are smaller than 1 kcal/mol, AM1 and PM3 calculations, which overestimate steric interactions, should give the incorrect result for N-methylpropanalimine and the correct result for propanaloxime; while the reverse is anticipated for 3-21G calculations. This prediction is borne out by the calculations. The angles indicated in **32** are the optimised values of CCCN. In agreement with our interpretation, they are larger in AM1 and PM3 than in 3-21G calculations.



31a R = Me
AM1 0.43 kcal/mol
PM3 1.28 kcal/mol
3-21G 0 kcal/mol

31b R = OH
AM1 0.42 kcal/mol
PM3 1.32 kcal/mol
3-21G 0 kcal/mol

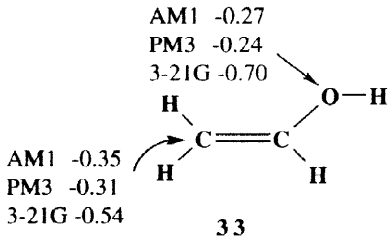


32a R = Me
AM1 0 kcal/mol (135°5)
PM3 0 kcal/mol (133°)
3-21G 0.84 kcal/mol (120°)

32b R = OH
AM1 0 kcal/mol (134°5)
PM3 0 kcal/mol (132°)
3-21G 0.29 kcal/mol (118°)

CHARGE DISTRIBUTION

Rather unusual atomic charges are obtained with AM1 and PM3. For example, in CH_2=CHOH (**33**) and CH_2=CHO^- (**34**), the negative charge is larger on the carbon than on the oxygen atom. Solvating the enolate with two molecules of water equalizes the two charges (**35**).



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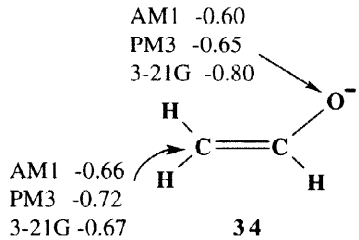

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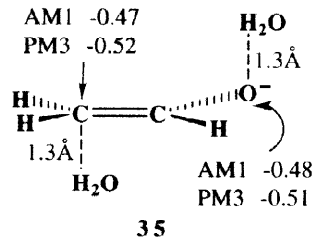
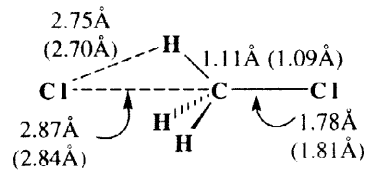


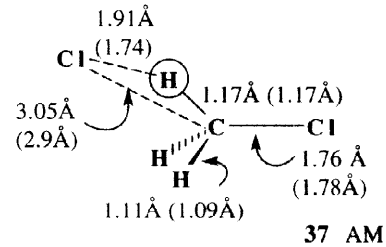
35

BASICITIES AND NUCLEOPHILICITIES. GAS PHASE CLUSTERS

We reported earlier[24] that basicities are overestimated by AM1, while nucleophilicities are underestimated. Thus, in the (Cl^- + MeCl) gas phase reaction, two initial clusters **36** and **37** were obtained, the first one, leading to S_N2 reaction, being *less* stable by 1.94 kcal/mol. The second cluster **37** is the cluster for proton abstraction, as can be seen from the much longer CH bond (1.17Å *vs* 1.11Å). There is a small interaction between the nucleophile and the carbon atom, as shown by the CCl bond lengthening (1.76Å in **37** *vs* 1.74Å in MeCl), which explains why Cl^-, the circled H and C are not on a straight line. PM3 exaggerates the basicity even more (bracketed values in **36** and **37**). In contrast, 3-21G[24a], 6-31G* or MP2/6-31G* calculations[25] give only the S_N2 cluster **36**. The *ab initio* C-Cl^- distances are noticeably longer: respectively 2.99Å (3-21G), 3.25Å (6-31G*) and 3.16Å (MP2/6-31G*).

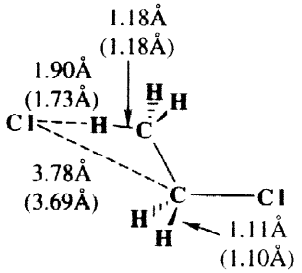


36 AM1 1.94 kcal/mol
(PM3 3.60 kcal/mol)

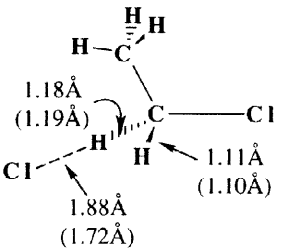


37 AM1 0 kcal/mol
(PM3 0 kcal/mol)

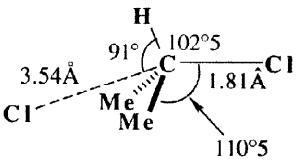
We were unable to obtain, either with AM1 or PM3, a S_N2 cluster for the reaction of Cl^- with EtCl: **38** and **39** correspond to proton abstraction on the methyl and methylene groups respectively. We also found[24a] that in the AM1 *i*-PrCl cluster, Cl^- is *attracted* by the alkyl substituents (**40**)[26]. The *ab initio* cluster on the contrary shows that Cl^- is repelled by these groups (**41**). These results suggest that in AM1 and PM3 calculations, *acid-base interactions prevail over steric repulsions at van der Waals distances.*



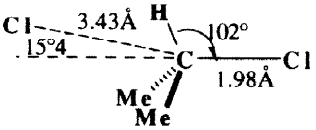
38 AM1 0 kcal/mol
(PM3 0 kcal/mol)



39 AM1 0.39 kcal/mol
(PM3 0.09 kcal/mol)



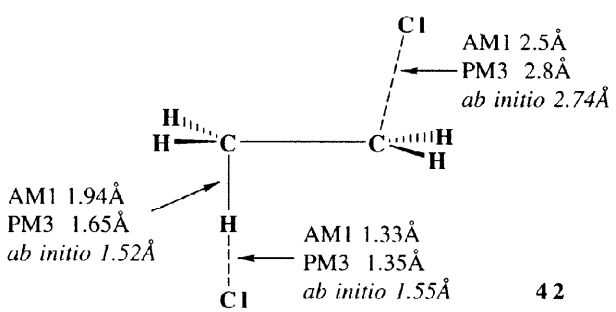
40 AM1



41 3-21G

TRANSITION STRUCTURES AND REACTION PATHS

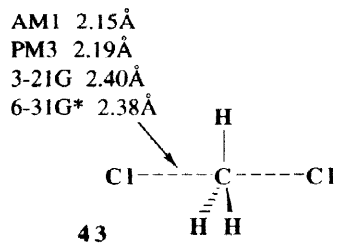
If nucleophilicity is grossly underestimated at van der Waals distances, it is better accounted for at bonding distances. Thus, for the (Cl^- + EtCl) reaction, despite the fact that no S_N2 cluster could be found, the S_N2 transition state lies 6.4 kcal/mol (AM1) or 3.33 kcal/mol (PM3) lower than the E2 transition state. According to 3-21G(+p) calculations[27], the difference is 28 kcal/mol. Compared with *ab initio* calculations, the Cl^- basicity is still exaggerated, as can be seen on the E2 transition structure **42**. Clearly, the *ab initio* transition structure is E2, whereas the AM1 structure is E1cB-like. PM3 calculations give intermediate results.



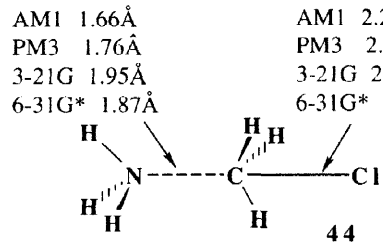
42

AM1 and PM3 give tighter transition structures than *ab initio* methods. Thus, in the (MeCl + Cl^-) reaction, the Cl^-...C bond is ~0.2Å longer in *ab initio* calculations (**43**)[24a]. The difference is less marked in pericyclic reactions, but remains sizable. For example, in the (butadiene + ethylene) cycloaddition, the length of the incipient CC bond is 2.12Å (AM1), 2.14Å (PM3) and 2.21Å (3-21G) respectively[3i]. This tightness may probably be traced back to the overcorrection of the core repulsion functions when going from MNDO to AM1 or PM3[28] and, in the case of ionic reactions, also to the overestimation of coulombic interactions.

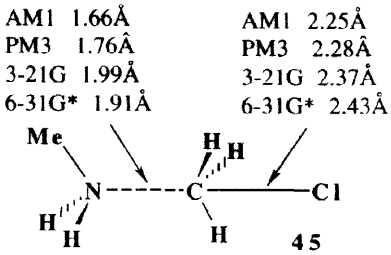
In cycloadditions[3i,j,m], AM1 and PM3 methods tend to favour asynchronous transition structures, even biradicaloid ones. Houk suggested several years ago[29] that this may be a consequence of the neglect of overlap. Interestingly, in the cyclodimerisation of cyclopentadiene (CP) and in the reactions (acrylonitrile + butadiene or CP), (maleonitrile + butadiene or CP)[3i], (cyclopropene + butadiene)[30], *exo* transition states are favoured with respect to their *endo* counterparts. This confirms that frontier interactions are underestimated with respect to steric interactions[31]. In line with this interpretation, in the reactions of butadiene with ethylene, acrylonitrile and maleonitrile, the calculated activation barriers increase steadily, in contradiction with experimental results[3i].



43



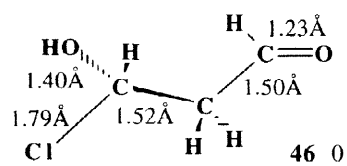
44



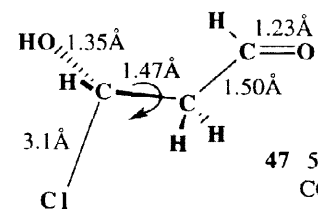
45

Another illustration is given by transition structures **44** and **45**. Methylamine being more nucleophilic than ammonia, **45** is expected to be earlier than **44**[32], with a lower activation barrier, and indeed this is what was found with *ab initio* calculations. However, nucleophilicity being underestimated by AM1 and PM3, the geometry remains practically the same in **44** and **45**. As steric repulsion increases with substitution, the activation barrier is *raised* when going from **44** to **45**[24b].

As seen in the S_2H_2 case, AM1 and PM3 calculations readily converge on almost any structures and this may cause trouble in mechanistic studies, as this defect is enhanced in UHF calculations. Consider for example the unimolecular decomposition of Cl-CHOH-CH_2-CHO. Starting with the stable conformer **46**, the Cl-C bond was stretched by steps, up to a value of 3.1Å. With AM1/UHF calculations[33], the heat of formation increased steadily from -99.98 to -41.14 kcal/mol but, although all the other variables were set for optimisation, only the geometry at C_3 was slightly modified and the CH_2CHO fragment remained practically unchanged. At the following step (Cl-C = 3.4Å), a failure occurred and SCF was not achieved.

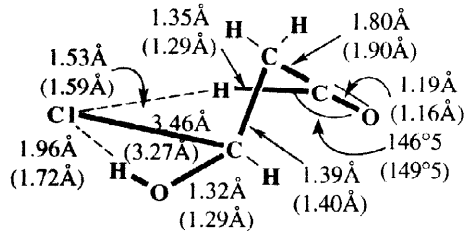


46 0 kcal/mol
CCCO = 160°

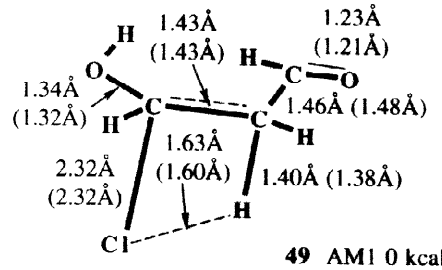


47 58.84 kcal/mol
CCCO = 151°

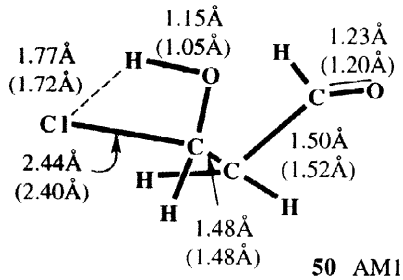
Clearly, a realistic reaction path cannot be obtained in this manner. A more detailed (and time-consuming!) exploration of the potential surface was then made. For each Cl-C value, two conformational curves, corresponding to rotations around C_1C_2 and C_2C_3, were calculated and the most stable conformer was taken as a point on the reaction path. Rotation around C_2C_3 (**47**, arrow) occurred along this path, allowing Cl to approach and finally abstract the aldehydic hydrogen[34], triggering a fragmentation of **46** into (ClH + CO + CH_2=CH-OH).



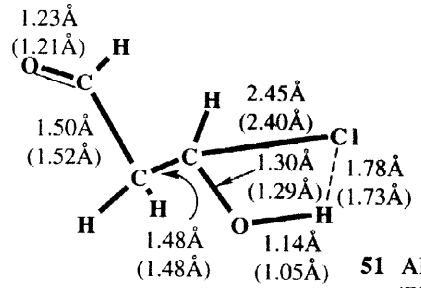
48 AM1 5.9 kcal/mol
(PM3 0 kcal/mol)



49 AM1 0 kcal/mol
(PM3 3.33 kcal/mol)

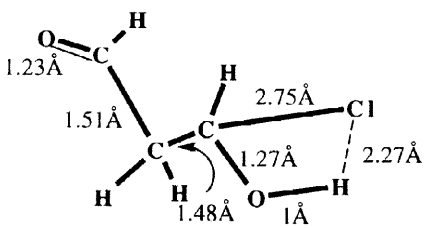


50 AM1 5.07 kcal/mol
(PM3 8.18 kcal/mol)
HO-CCC = 5° (AM1)
= 17° (PM3)



51 AM1 5.06 kcal/mol
(PM3 7.89 kcal/mol)
HO-CCC = 164° (AM1)
= 155° (PM3)

The transition structure corresponding to this cheletropic-like reaction is shown in **48**. Three other transition structures were also found: **49** for the reaction (Cl-CHOH-CH_2-CHO → ClH + HO-CH=CH-CHO) and the two last ones (**50**, **51**) for the reaction (Cl-CHOH-CH_2-CHO → ClH + CHO-CH_2-CHO). Based on the Cl...H bond length, **50** and **51** are earlier than **49**, which is earlier than **48**. Both methods indicate that **49** is lower in energy than **50** and **51**. A major difference is observed with **48**, which is highest in energy according to AM1 and lowest in energy according to PM3. This is probably due to the hydrogen bonding between Cl and the hydroxylic hydrogen, which is treated differently by AM1 and PM3 (compare **1** and **2**).



51bis 3-21G

Full comparison with *ab initio* calculations has not been made. Preliminary studies indicate that the results may be quite different. For instance, the 3-21G transition structure **51bis** strongly suggests a decomposition into an ion pair (Cl^- + CHO-CH_2-C=OH^+). This is disfavoured by AM1 and PM3 which exaggerate coulombic interactions and therefore prefer the (Cl-CHOH-CH_2-CHO → ClH + CHO-CH_2-CHO) neutral pathway. Other discrepancies between *ab initio* and semi-empirical results in unimolecular reactions have been reported. Thus in the decomposition of azides, two pathways are found with AM1 and only one with 4-31G calculations[35]. Another example is the gas phase decomposition of 2-chloropropionic acid, which occurs in two steps. Elimination of ClH and cyclisation yield first an α-lactone, which expels CO to give Me-CHO. According to

AM1 and *ab initio* (MP2/6-31G**, MP2/6-31++G, CISD/6-31G**, BLYP/6-31G**) calculations, the α-lactone cyclisation involves the carbonylic oxygen. According to PM3, this step involves the hydroxylic oxygen[36].

CONCLUSION

Let us recapitulate the principal limitations of AM1 and PM3 and the practical consequences resulting from them. It must be pointed out however that, due to the limitations of our study, the following remarks may require some amendments when correlation and/or solvent effects are taken into account.

AM1 and PM3 calculations underestimate frontier interactions with respect to steric repulsions. Therefore, in R-CH_2-CH=X systems (R ≠ H), they will systematically favour the anticlinal conformation (RCCX ~120°) and disfavour the cis conformation (RCCX ~ 0°). Usually, they even put the cis conformer - a local minimum - above the trans (RCCX ~ 180°), a local maximum. In cycloadditions, the *endo* isomer is disfavoured for the same reason. In fact, the effect may be more pronounced here, as semi-empirical transition structures are tighter than *ab initio* TS. As a general rule, when two structures (conformers or isomers) differ by ~1 kcal/mol, their calculated ordering is unreliable. Another rule of thumb is that, within a homologous series of reactions (*e.g.* reactions of NH_3, $MeNH_2$, Me_2NH and Me_3N with RX), AM1 and PM3 tend to give activation energies which increase with substitution. The Alder rule is not reproduced: when the diene is substituted by a donor and/or the dienophile by an attractor, the activation energy is raised, according to these calculations.

Steric repulsions in turn are dominated by acid-base and coulombic interactions, especially at van der Waals distances. Basicities are always overestimated and nucleophilicities underestimated, even if the bias is less pronounced in the transition states. It follows that AM1 and PM3 are more suitable for pericyclic than for ionic reactions. In particular, unimolecular decompositions into ion pairs are not favoured by these methods. In the study of gas phase bimolecular ionic reactions, anomalous initial ion-molecule clusters may be observed and in these cases, activation barriers are not reliable. Atomic charges may be unrealistic and should not be used as reactivity indices. They may also lead to structural anomalies, due to exaggerated coulombic interactions.

AM1 and PM3 converge readily on chemically unreasonable structures, even when all parameters are set for optimisation. The potential surface then contains spurious minima and, consequently, spurious saddle-points. These artefacts can usually be discarded without much difficulty. Modelisation of reaction paths cause more trouble, especially in unimolecular reactions.

Despite all these shortcomings, we believe that AM1 and PM3 remain quite useful for exploratory work. The results may be incorrect for isolated cases, but the trends within a series of homologous reactions are often significant. Generally, but not systematically, PM3 structures are closer to *ab initio* results. On the other hand, AM1 energies appear to be more realistic than PM3 energies. In a certain sense, the very defects of AM1 and PM3 may be a benediction in disguise by compelling us to interpret carefully and cautiously the calculations. The reliability of the output being uncertain, we have to justify *chemically* why the programs must give these results.

Even the most sophisticated method is not without defect and an imperfect method can be used fruitfully if its limitations are known. After all, some of the most important theoretical results (the aromaticity rules, the conservation of orbital symmetry) have been obtained with simple Hückel or Extended Hückel calculations.

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