Proline Catalyzed Asymmetric Aldol Cyclization II. Hajos Parrish Reaction named by Claude Agami. Brief History of the Discovery and Interpretation of the Reaction Mechanism.

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Abstract

Reaction of the starting material 2-methyl-2-(3-oxobutyl)-1,3-cyclopentanedione at its aliphatic butyl side chain carbonyl group with the secondary amino group of the (S)-(-)-proline catalyst proceeds by an enamine mechanism. Alternatively, the reaction may occur at the more reactive cyclic dione site by the carbinolamine or by the tautomeric iminium hydroxide mechanism. The enamine mechanism has been our primary choice without computer assisted modeling. MOPAC minimizations described in this paper show a preference for the iminium hydroxide and for the tautomeric carbinolamine. The iminium hydroxide showed the lowest heat of formation, and the difference between the S and the R was the largest with the iminium hydroxide in the MOPAC. This large energy difference explains the excellent stereoselectivity of the (S)-(-)-proline catalyzed intramolecular cyclization reactions. The tautomeric carbinolamine was second best in the MOPAC. The iminium intermediate formed from the iminium hydroxide by the loss of water was third best by the MOPAC minimization method. The MOPAC studies have been reinforced by the MM2 minimizations.

Keywords

Proline, Hajos-Parrish, MOPAC and MM2 minimizations, organocatalysis, enamine, carbinolamine, iminium hydroxide, iminium intermediates, intramolecular, asymmetric, cyclization, organocatalysis, reaction mechanism, stereoselective.

Introduction

In 1974 we published the results on the "Asymmetric Synthesis of Bicyclic Intermediates of Natural Product Chemistry" [1]. In this day and age to some it seems commonplace to have discovered the proline catalyzed asymmetric ring closure. In those days, however, one of the referees wanted the last few lines of the 1974 paper deleted. They are as follows: "We believe our results may be considered an example of a simplified model of a biological system in which (S)-(-)-proline plays the role of an enzyme." It seems time was not ripe to understand the essence of the results described in the 1974 paper. This similarity to enzyme action has later been referenced in a publication by Mohammad Movassaghi and Eric N. Jacobsen of the Department of Chemistry and Chemical Biology, Harvard University, The Simplest "Enzyme" *Science*, 6 December 2002, Vol. 298, 1904-1905 [2].

During a trip to Basel on August 11, 1969 upon the invitation of Andor Furst of Hoffmann-La Roche, Basel [3] the findings had to be presented to the audience of the mother company. During the question and answer period a person unidentified asked the following question: "Sir, you mentioned the execution of the asymmetric synthesis using 3 mol % of proline. Do you think, it

would be possible to completely omit the use of the proline in future experiments?" Momentarily perplexed I then answered: "I believe this already happened on Earth at the beginning of time. So as soon as I become God, I'll be able to execute the reaction without the use of proline." Big laughter and applause followed the answer. This again shows that in those days some considered the discovery with a dash of irony and skepticism.

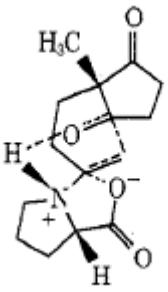
The presentation in Basel was followed in July of 1970 by a major talk on the "Stereo Controlled Total Synthesis of Steroids" at the Gordon Research Conference on Natural Product Chemistry upon the invitation of Professor Hans Muxfeldt. The company allowed the presentation provided the asymmetric synthesis data will not be presented. Later during the year, in November, 1970 the present author resigned, therefore the work did not continue. The results described in the 1974 paper have been described earlier in the 1971 patent [4]. Although the project stopped following the resignation, a slow, albeit steady build up of references shows the impact of the 1974 paper. In 1985 Professor Agami coined the name "Hajos Parrish Reaction." [5].

In a Chemical and Engineering News interview paper published in 2002 Professor Carlos F, Barbas III. gave credit to the 1974 publication in the following fashion: "Work in the 1970s on proline-catalyzed intramolecular aldol addition reactions by synthetic organic chemists Zoltan G. Hajos and David R. Parrish of the chemical research department at Hoffmann-La Roche, Nutley, N.J., inspired us to look more closely at parallels between small-molecule catalysts and enzymes" [6]. In a highly important review article in 2011 by K.N. Houk *et al.* [7] the following was stated: "The Hajos-Parrish reaction is sometimes considered to be the first organocatalytic enantioselective transformation to be reported (1971)." The expression "sometimes" confers uncertainty to the reader.

To the author of the 1974 paper it seemed compulsory to speculate on the reaction mechanism in the original paper. In those days this was done without the use of computers postulating the reaction mechanism upon the knowledge of the principles of organic chemistry. The speculations were not only theoretic, but they have been supported by well designed experiments. The first lines of the Discussion of the 1974 paper refer to the primarily suggested enamine intermediate of the reaction mechanism and are followed by the image thereof (Figure 1).

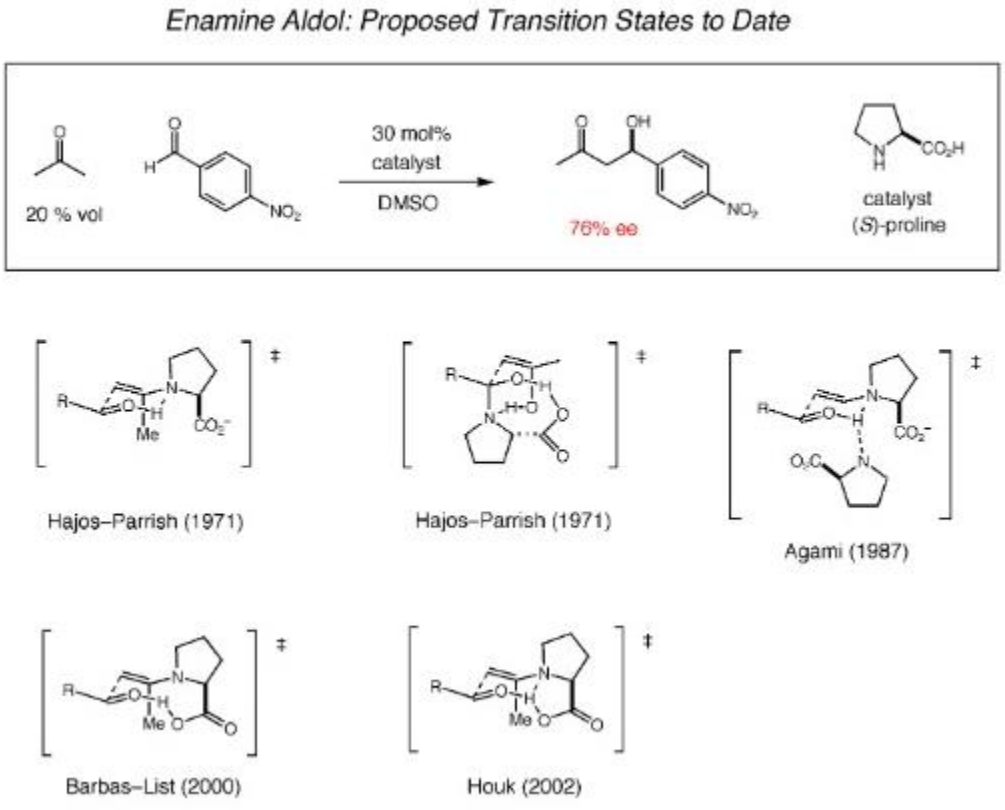
"Based on the evidence accumulated so far we consider two possible mechanisms for the asymmetric synthesis with (S)-(-)-proline. The first would involve the formation of a protonated enamine and of an oxazolidone ring." [8].

Figure 1.



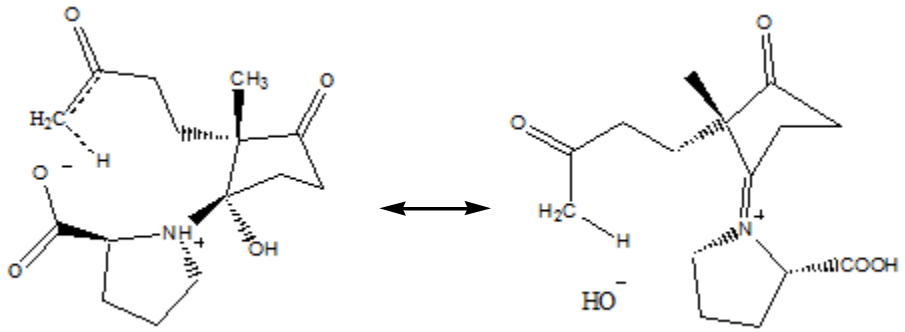
Of the experimental support to the reaction mechanism the experiment using O^{18} labeled water should be emphasized. In agreement with the rigorous disciplines of organic chemistry a stoichiometric amount of the labeled water was used, and a control experiment with the reaction product and the labeled water has been executed. This experiment contradicted the enamine mechanism, therefore the carbinolamine mechanism became the secondary choice [8].

Carbinolamines and iminium hydroxides are tautomers. For intermolecular aldol reactions an iminium mechanism has been suggested by Professor David MacMillan [9]. The slide of Professor MacMillan at Princeton University summarizes the historical events concerning the reaction mechanism: http://www.princeton.edu/chemistry/macmillan/research/MacMillan%20Lecture%202.pdf



Of these the Hajos-Parrish carbinolamine (1971) and the iminium hydroxide are tautomers (Figure 2).

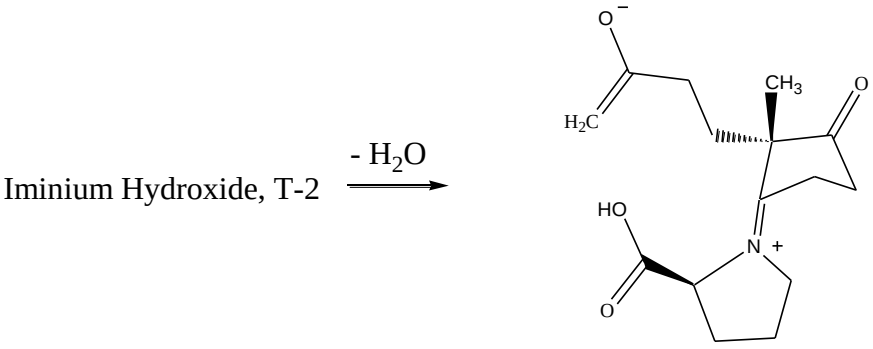
Figure 2.



Carbinolamine, T-1 Iminium Hydroxide, T-2

Nucleophilic attack of the hydroxide anion causes enolization of the side chain ketone with the loss of water to give T-3 the intermediate iminium-enol-carboxylic-acid (Figure 3), which was investigated by the MOPAC and by the MM2 minimization methods.

Figure 3.



T-3

An essay by Zoltan Hajos entitled “Proline Catalyzed Asymmetric Cyclization.Theory of the Reaction mechanism” has been published in 2002 on the ChemWeb Preprint server at http://www.sciencedirect.com/preprintarchive/article/B7J22-4DNMR08-22/2/7e47d5d0bd80be28df693b74ec631b3e Chemistry Preprint Archive, Volume 2002, Issue 9, September 2002, Pages 84-100. In that essay the Carbinolamine intermediate has been postulated. However, it did not include investigations of the Iminium Hydroxide tautomer and the MOPAC minimizations.

In the present communication the iminium intermediate T-3 as well as the Iminium Hydroxide tautomer have been investigated by the MOPAC method. To corroborate the results the Allinger MM2 method has also been applied . There were two recent scientific publications which initiated the author to rethink the reaction mechanism of the Proline catalyzed intramolecular ring closure, and to present the results in this paper. Firstly the already cited Houk Review [7], secondly the recent review paper by Henry S. Rzepa *et al.* [10], which presents an excellent insight into the field of organocatalysis.

Methods

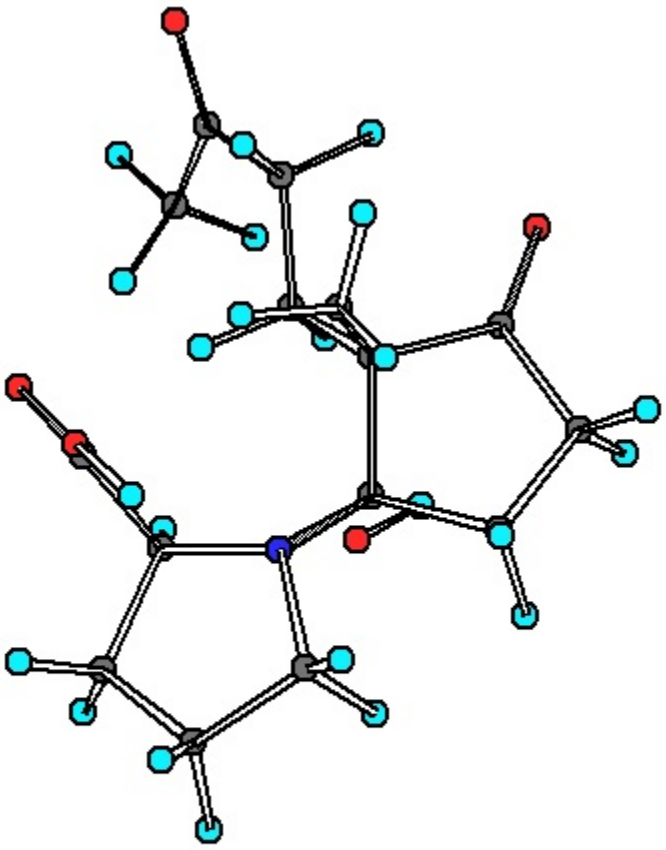
All through the paper the CambridgeSoft ChemOffice Ultra 01 program has been used. The applications ChemDraw Ultra and Chem3D Ultra of the main program have been applied; Chem3D Ultra allowed the use of the CSMopac menu. Using the MOPAC the heat of formation of the molecule has been determined. MOPAC is a widely used computer program in computational chemistry. It was designed to implement semi-empirical quantum chemistry

algorithms; it was largely written by Michael Dewar's research group at the University of Texas at Austin [11-14].The name MOPAC is an abbreviation derived from the expression: *Molecular Orbital PACkage*. Occasionally the results obtained in ChemOffice Ultra 01 have been pictured in the CambridgeSoft ChemOffice14 program. In addition the assumed reaction intermediates have been investigated using CambridgeSoft Corporation's Chem3D MM2 energy minimization menu based on Allinger's Molecular Mechanics force field version [15]

Results

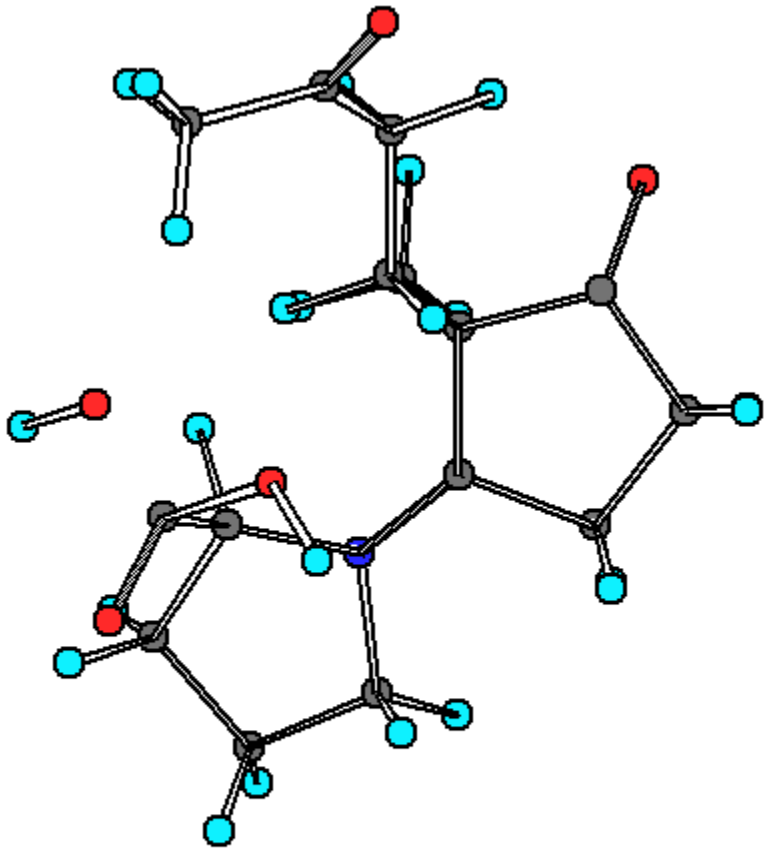
Due to the centro-symmetric structure of the triketone starting material [2-Methyl-2-(3-oxobutyl)-1,3-cyclopentanedione, Figure 22] the ChemDraw program could not differentiate the stereochemistry of the angular methyl group attached to the "meso" carbon atom of the Hajos-Parrish type S and R enamine intermediates. However, the ChemDraw program readily assigned the stereochemistry of the same carbon atom to the Iminium or Carbinolamine intermediates. Of course, this does not mean that this feature of the ChemDraw program taught us the basics of stereochemistry. Figures 6 and 8 show the S and the R intermediates of type T-3; the insert shows the stereochemical assignment of the C(1) carbon atom. The assignment was fortified by the ChemDraw modeling system. Figures 4 – 13 show the MOPAC minimization studies of four different intermediate structures. Figures 14 – 21 show the MM2 minimization results of the same four. This has been executed in addition to the MOPAC studies.

Figure 4. S-iminium-hydroxide-MOPAC-minimized



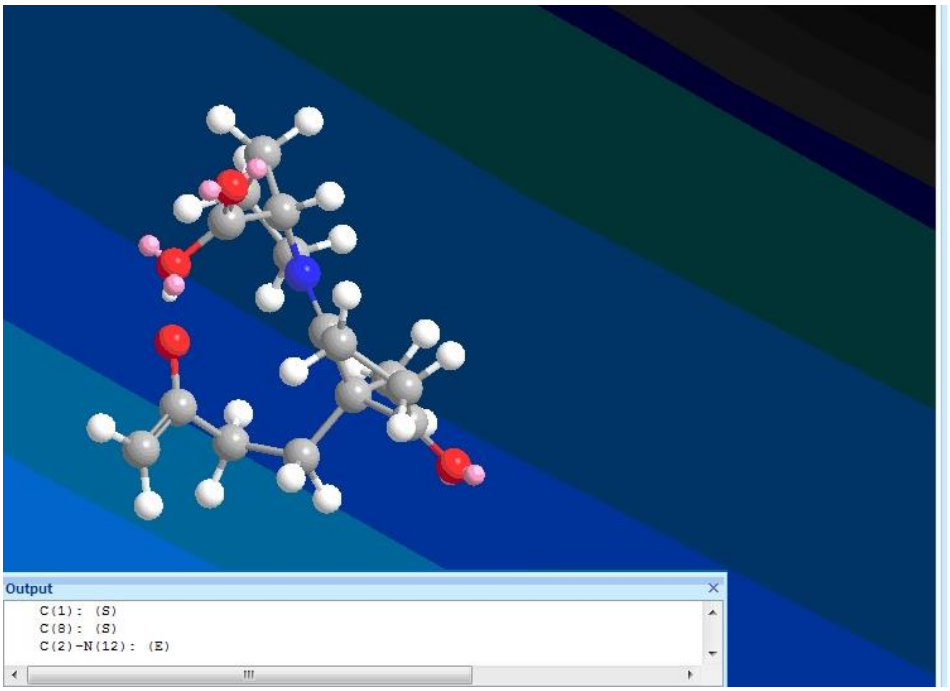
Iteration 137 Heat of Formation: -215.66237 Gradient Norm: 78.872
Heat of Formation: -215.66237 kcal/mole
Gradient Norm: 78.87178

Figure 5. R-iminium-hydroxide-MOPAC-minimized



Iteration 30 Heat of Formation: -182.47340 Gradient Norm: 233.822
Heat of Formation: -182.47340 kcal/mole
Gradient Norm: 233.82169

Figure 6. S-iminium intermediate



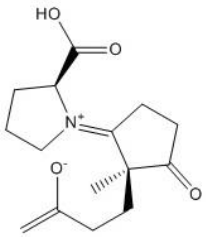
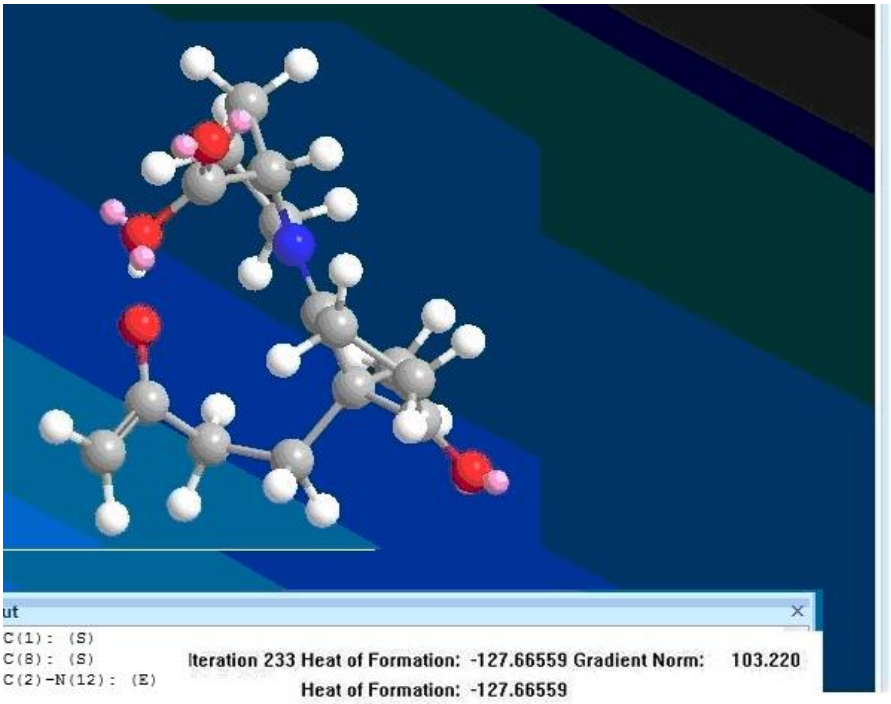


Figure 7. S-iminium-MOPAC-minimization



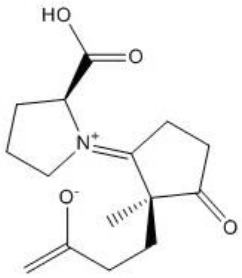
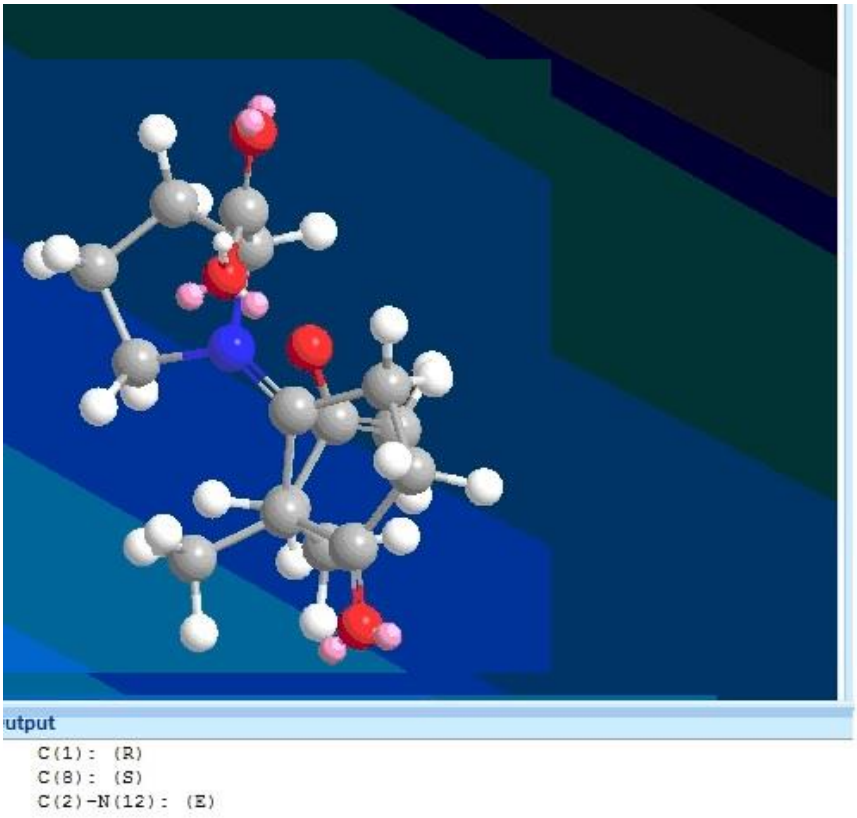


Figure 8. R-Iminium intermediate



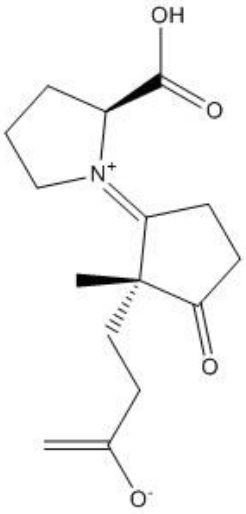
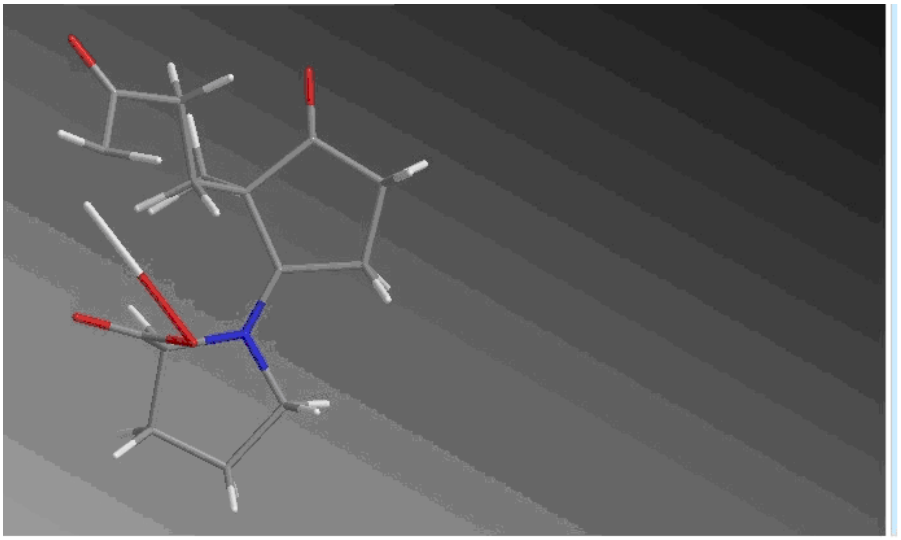


Figure 9. R-Iminium-MOPAC-minimization



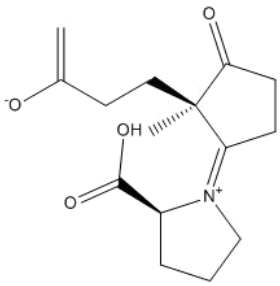
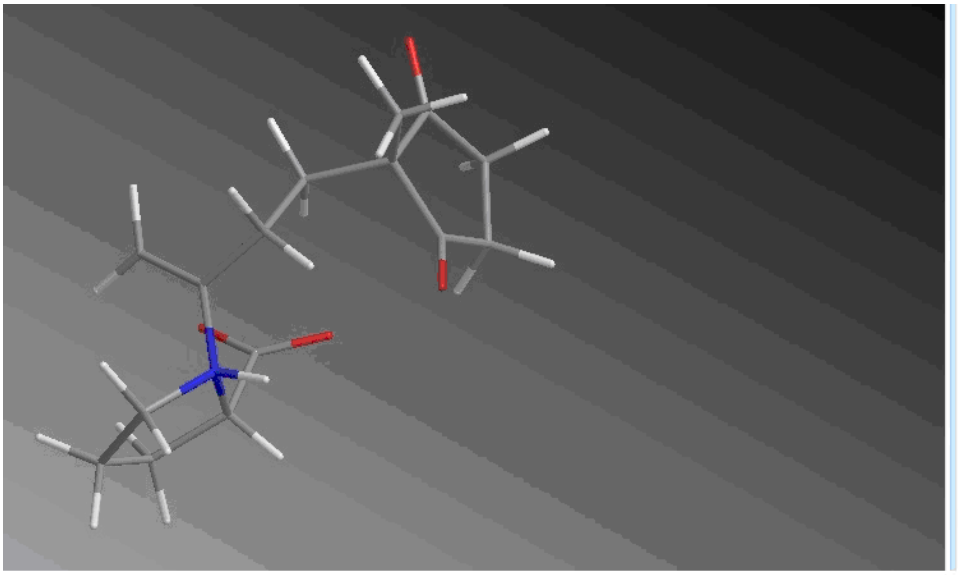
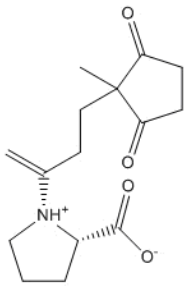


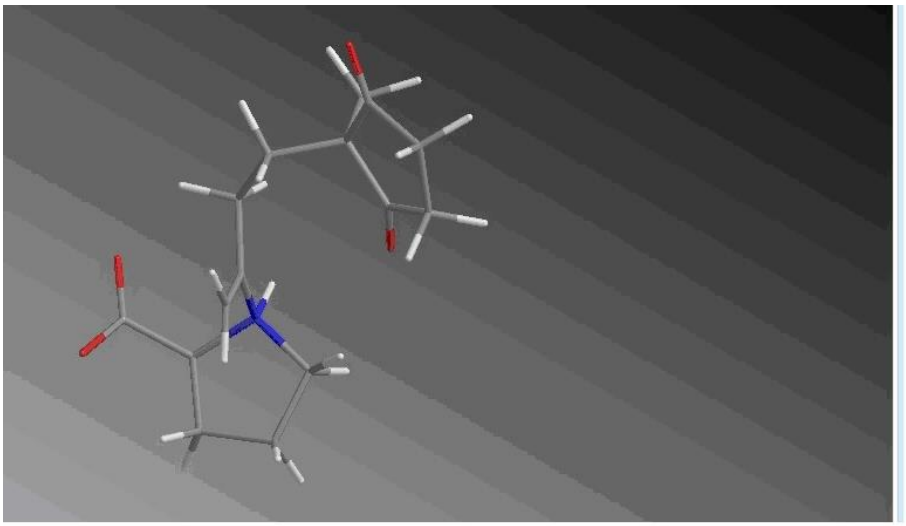
Figure 10 S-enamine-MOPAC minimization.

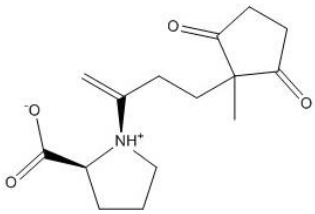




Iteration 94 Heat of Formation: -113.26021 Gradient Norm: 101.330
Heat of Formation: -113.26021 kcal/mole

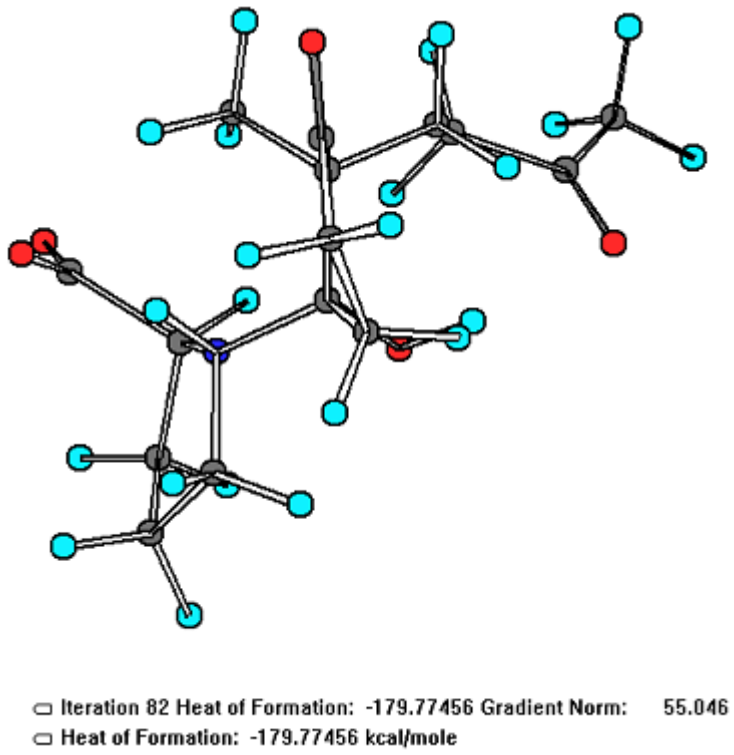
Figure 11. R-enamine-MOPAC-minimization





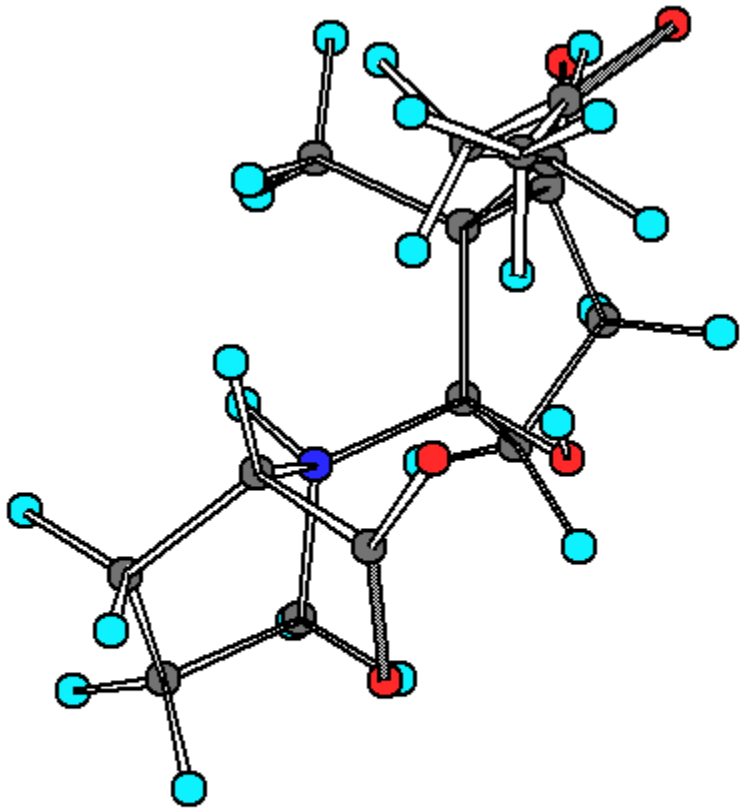
Iteration 186 Heat of Formation: -109.07891 Gradient Norm: 68.153
Heat of Formation: -109.07891 kcal/mole

Figure 12. S-carbinolamine-MOPAC-minimization



Iteration 82 Heat of Formation: -179.77456 Gradient Norm: 55.046
Heat of Formation: -179.77456 kcal/mole

Figure 13. R-carbinolamine-MOPAC-minimization



Iteration 116 Heat of Formation: -175.19526 Gradient Norm: 0.069
Heat of Formation: -175.19526 kcal/mole
Gradient Norm: 0.06892

Figure 14. S-iminium-hydroxide-MM2-minimized

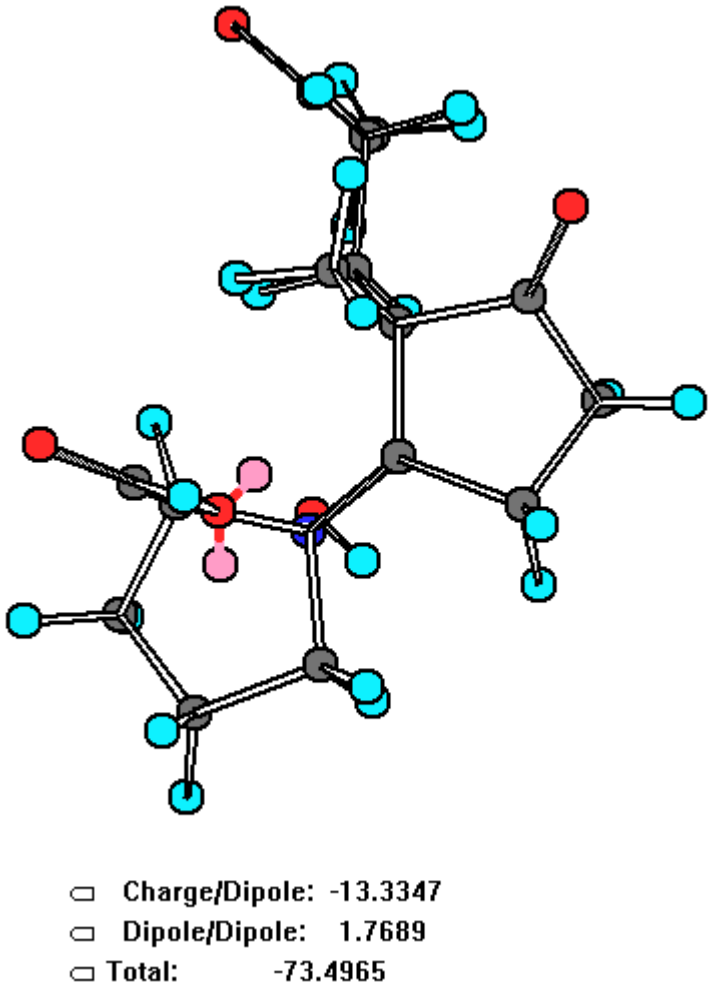
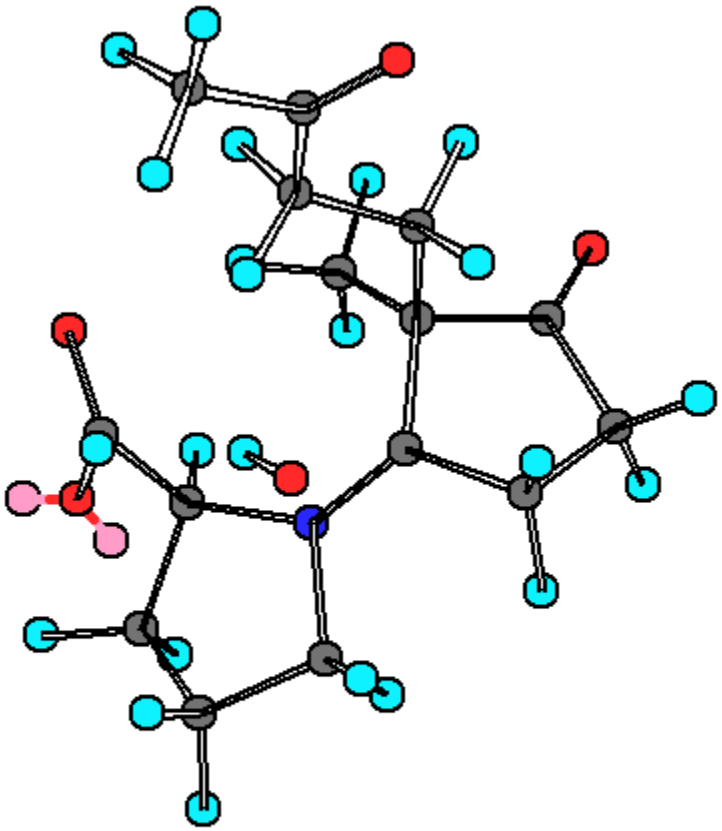
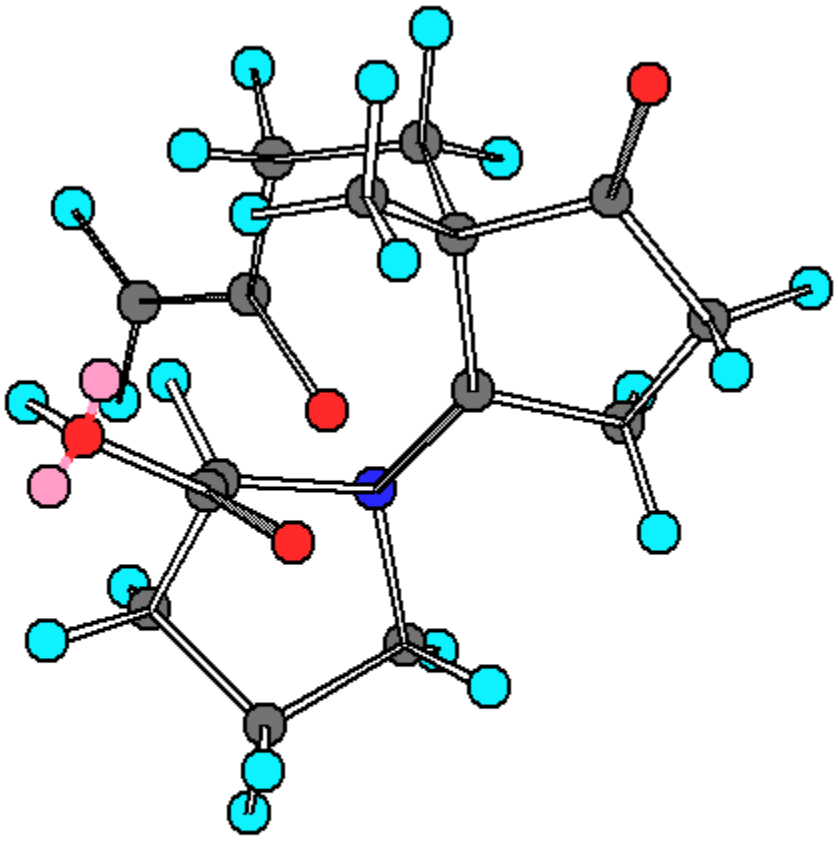


Figure 15. R-iminium-hydroxide-MM2-minimized



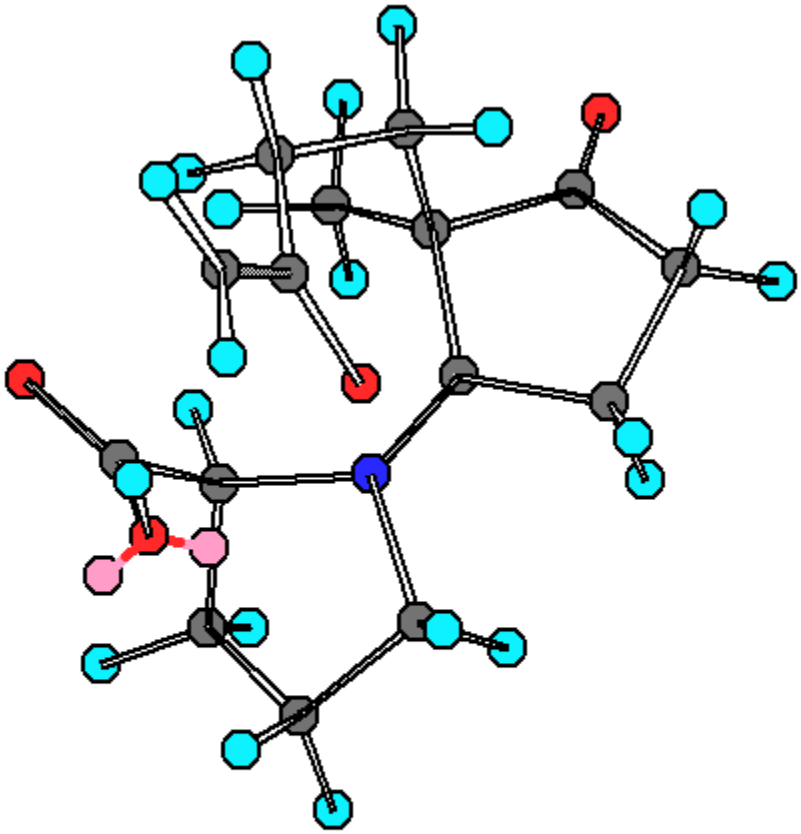
Charge/Dipole: -16.5654
Dipole/Dipole: 0.0306
Total: -70.4948

Figure 16. S-im-MM2-minimized



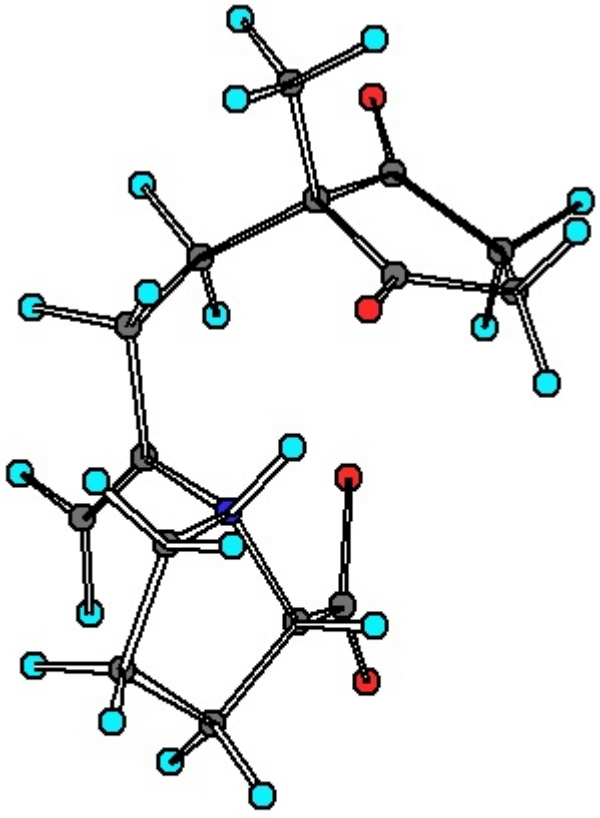
Charge/Dipole: 3.2874
Dipole/Dipole: 4.0974
Total: -53.1383

Figure 17. R-im-MM2-minimized



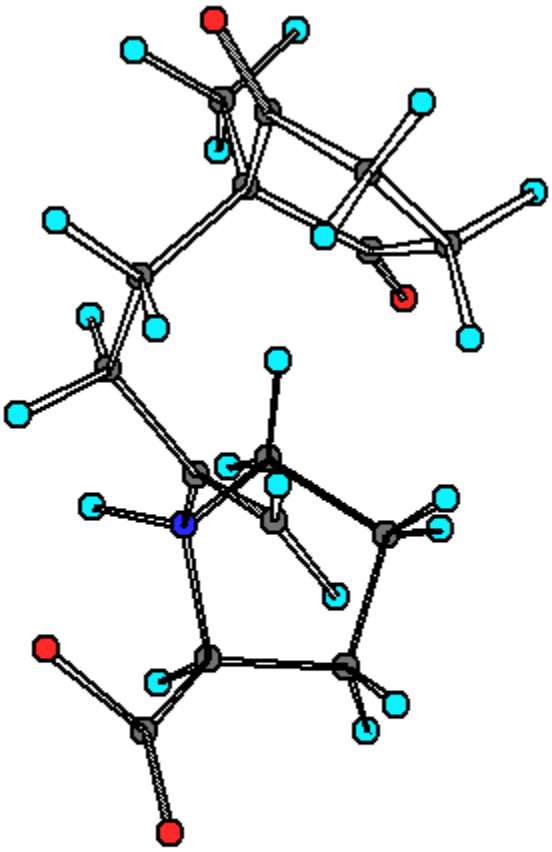
Charge/Dipole: -4.9490
Dipole/Dipole: 1.9455
Total: -58.5160

Figure 18. S-enamine-MM2-minimized



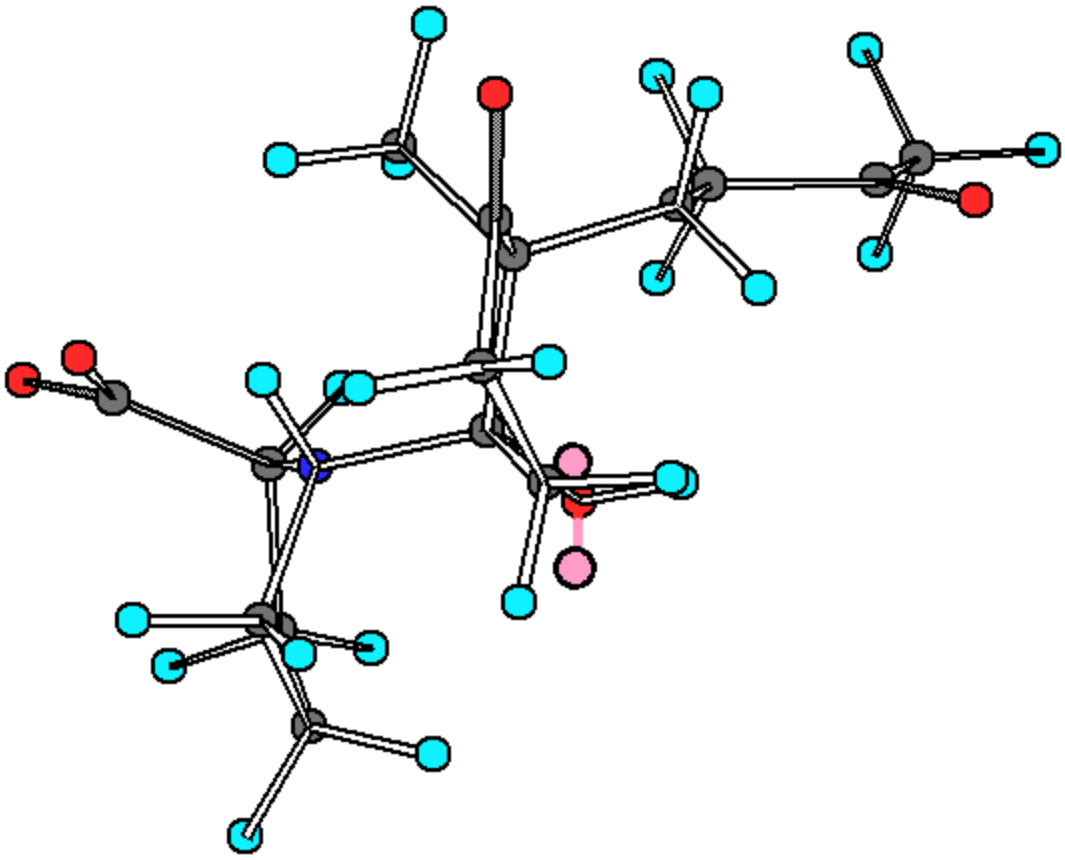
Charge/Dipole: -12.6167
Dipole/Dipole: 3.7590
Total: -58.7288

Figure 19. R-enamine-MM2-minimized



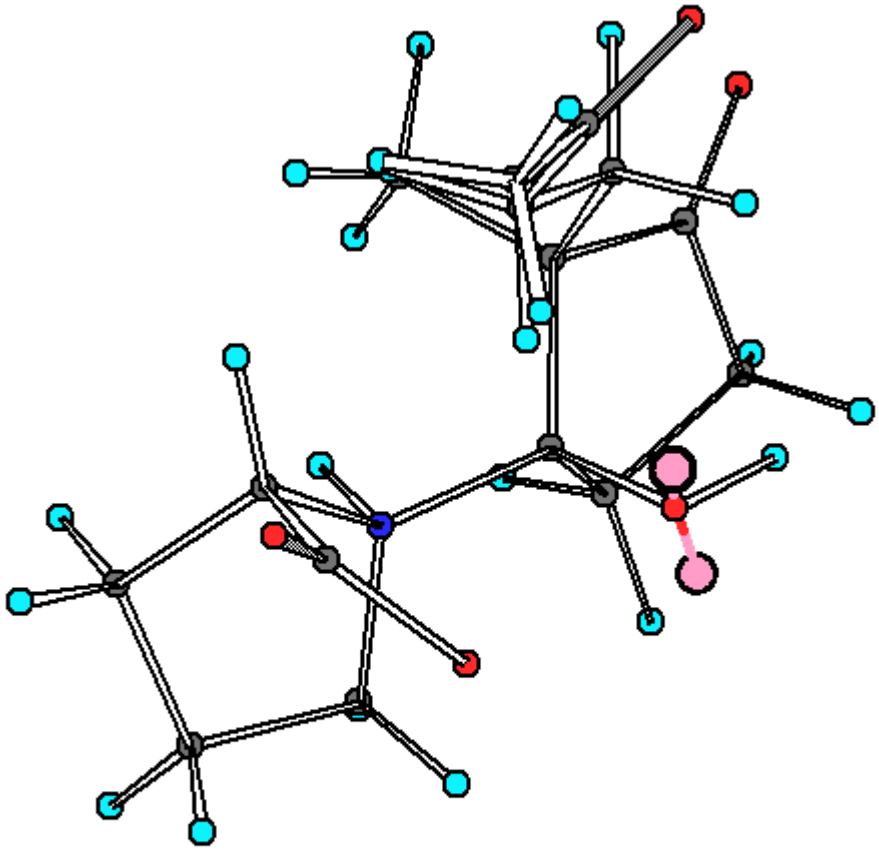
Charge/Dipole: -1.9482
Dipole/Dipole: 3.7028
Total: -51.2820

Figure 20. S-carbinolamine-MM2-minimized



Charge/Dipole: 5.3108
Dipole/Dipole: 1.1103
Total: -36.8186

Figure 21. R-carbinolamine-MM2-minimized

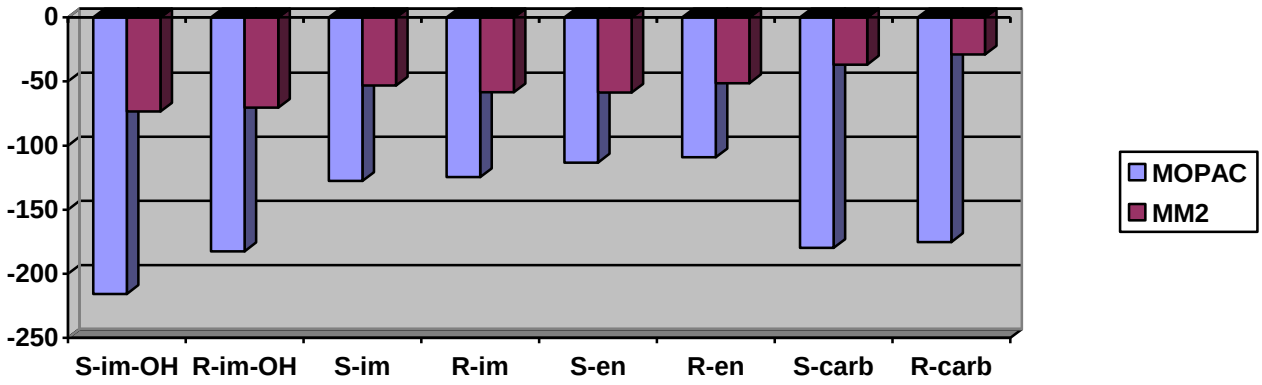


Charge/Dipole: 8.5161
Dipole/Dipole: 1.5924
Total: -28.9576

DISCUSSION

The minimization results have been summarized in Table 1. and in the corresponding Datasheet.

Table 1.



Hajos-new-full-paper-2015.doc - Datasheet

		A	B	C	D	E	F	G	H
		S-im-OH	R-im-OH	S-im	R-im	S-en	R-en	S-carb	R-carb
1	MOPAC	-215.6624	-182.4734	-127.6656	-124.6957	-113.2601	-109.0789	-179.7746	-175.1953
2	MM2	-73.4965	-70.4948	-53.1383	-58.516	-58.7288	-51.282	-36.8186	-28.9576
3									
4									

The MOPAC minimizations thus favor the mechanism with the tautomeric iminium hydroxide intermediate which shows the lowest heat of formation: S-im-OH -215.6624 kcal/mole and R-im-OH -182.4734 kcal/mole. This is in agreement with expectation, because the iminium hydroxide tautomer renders a better interpretation of the side-chain ketone enolization by assuming nucleophilic attack of the hydroxide anion of the iminium hydroxide intermediate rather than the carboxylate anion of the carbinolamine intermediate. The S and the R iminium hydroxide intermediates showed the largest difference in the MOPAC minimizations: 33.19

kcal/mole. This large energy difference explains the excellent stereoselectivity of the (S)-(-)-proline catalyzed intramolecular cyclization reaction.

The data indicate that the tautomeric carbinolamine intermediate showed the second lowest heat of formation of -179.77456 and -175.19526 kcal/mole in the MOPAC (S-carb and R-carb). The difference between the S-carb and R-carb was 4.5793 kcal/mole. The S-carbinolamine appeared to be 66.52 kcal/mole lower than the S-enamine.

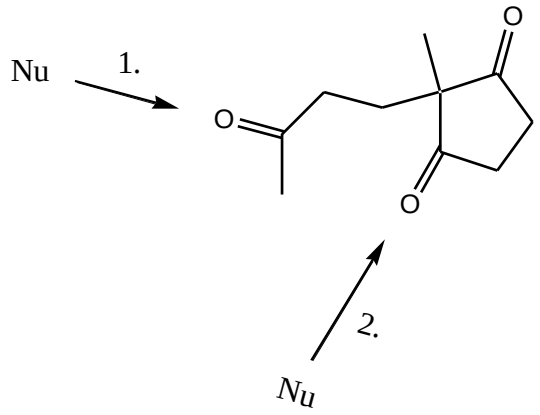
The iminium intermediates formed from the iminium hydroxide intermediate by the loss of water (S-im and R-im) were the third best in the MOPAC at -127.6656 kcal/mole and -124.6957 kcal/mole. The difference between the S-im and R-im was 2.9653 kcal/mole.
The heat of formation MOPAC data of the enamine (S-en and R-en) placed it fourth at -113.2601 and -109.0789 kcal/mole. The difference between the heat of formation of the S-en and R-en energies was found to be the third best at 4.1812 kcal/mole. In summary therefore the MOPAC results showed the following order for the four different intermediates: first and best the S-iminium hydroxide (S-im-OH). second the tautomeric S-carbinolamine (S-carb), third the S-imine (S-im) and fourth the S-enamine (S-en).

The MOPAC study was followed by the MM2 investigation. The MM2 minimizations also favored the tautomeric iminium hydroxide as the best. The MM2 minimized total of the S-im-OH was -73.4965 and -70.4948 for the R-im-OH intermediate. This represents a difference of 3.0017 between the S-im-OH and the R-im-OH . The S-en and R-en intermediates were second best in the MM2 minimization at -58.7288 and -51.2820. The difference between the two is

7.4468. The S-im and R-im intermediates were third best by the MM2 minimization method at -53.1383 of the S-im and -58.5160 of the R-im. This value of -58.5160 was the only result showing some inconsistency: it was by 5.3777 lower than the corresponding S-im MM2 minimized value (-53.1383). The S-en and R-en intermediates were the second best by the MM2 minimization at -58.7288 for the S-en and -51.2820 for the R-en. The difference between the S-en and R-en intermediates was thus 7.4468 favoring the S-en intermediate. The MM2 minimum was -36.8186 for the S-carbinolamine and -28.9576 for the R-carbinolamine intermediate. The difference between S-carb and R-carb was thus 7.8610 in favor of the S-carb. Therefore, the MM2 minimization showed the following order of the four different intermediates : S-im-OH, S-en, S-im and S-carb.

The principles of theoretical organic chemistry suggest preferred attack on the cyclic rather than on the aliphatic carbonyl group of the triketone starting material. Therefore, the reaction mechanism in principle depends upon the consideration whether the side chain aliphatic ketone or the five ring cyclic ketone is the more reactive electrophilic entity facing the nucleophilic secondary amino group of proline. This is then the “Rosetta stone” of the central dogma of the proline catalyzed intramolecular asymmetric cyclization. The enamine mechanism considers the aliphatic side chain ketone the more reactive carbonyl group (site 1., Nu:), while the carbinolamine/imine mechanism assumes attack of the secondary amino group of proline on the cyclic keto group of the triketone starting material (site 2., Nu:). This is shown in Figure 22.

Figure 22. Triketone reaction path possibilities.



The recent paper by Plata and Singleton [16] summarizes the philosophy of scientific interpretation in an excellent fashion by stating: "The computations aid in interpreting observations but fail utterly as a replacement for experiment."

Therefore, the strategy of this investigation has been to abide by the principles of organic chemistry, and then follow with computer assisted modeling and minimization of the intermediates. The well-known Houk-List data are not discussed or disputed, but they were well referenced in this essay. The results of this investigation have to stand by their own merit. Two independent minimization methods, the MOPAC and the MM2 rendered rather similar results thereby fortifying each other's data.

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References

[1] Zoltan G. Hajos and David R. Parrish**,** Asymmetric Synthesis of Bicyclic Intermediates of Natural Product Chemistry**,** J. Org. Chem., 1974, 39, 1615-1621.

[2] Mohammad Movassaghi and Eric N. Jacobsen, The Simplest "Enzyme" *Science,* 6 December 2002, Vol. 298, 1904-1905.

[3] Hans-Detlef Berndt, Paul Buchschacher, Ulrich Eder, Andre Furlenmeier, Andor Furst, Ulrich Kerb, Marcel Muller and Rudolf Wiechert, 18-Nor-14beta-Pregnano-[13,14-f]-Hexahydro-1,4-Oxazapines, United States Patent 3,578,659 May 11, 1971.

[4] Hajos, Zoltan George and Parrish, David Richard, Asymmetrische Synthese polycyclischer organischer Verbindungen, Ger. Pat. DE 2102623, 29, Juli 1971.

[5] Claude Agami, Jacques Levisalles, and Catherine Puchot, A New Diagnostic Tool for Elucidating the Mechanism of enantioselective Reactions. Application to the Hajos-Parrish reaction, J. Chem. Soc., Chem. Communications, 1985, 441-442.

[6] Chemical & Engineering News, SCIENCE & TECHNOLOGY, February 25, 2002**,** Volume 80, Number 8, p. 33.

[7] Paul Ha-Yeon Cheong, Claude Y. Legault, Joann M. Um, Nihan Celebi-Ölcüm, and K. N. Houk, Quantum Mechanical Investigations of Organocatalysis: Mechanisms, Reactivities, and Selectivities, Chem. Rev. 2011, 111, 5042–5137.

[8] page 1619 of ref 1.

[9] Ian K. Mangion, Alan B. Northrup, and David W. C. MacMillan, The Importance of Iminium Geometry Control in Enamine Catalysis: Identification of a New Catalyst Architecture for Aldehyde–Aldehyde Couplings, Angew. Chem. Int. Ed. 2004, 43, 6722 –6724.

[10] Alan Armstrong, Roberto A. Boto, Paul Dingwall, Julia Contreras-Garcia, Matt J. Harvey, Nicholas J. Mason and Henry S. Rzepa, The Houk–List transition states for organocatalytic mechanisms revisited, Chem. Sci., 2014, 5, 2057-2071.

[11] M. J. S. Dewar and W. Thiel. Ground States of Molecules, 39. MNDO Results for Molecules Containing Hydrogen, Carbon, Nitrogen, and Oxygen. *J. Am. Chem. Soc.*, 1977, 99, 4907-4917.

[12] *Computational Chemistry*, David Young, Wiley-Interscience, 2001. Appendix A. A.3.2 page 342.

[13] J. J. P. Stewart. MOPAC: A General Molecular Orbital Package. *Quant. Chem. Prog. Exch.*, 1990, 10, 86.

[14] H. S. Rzepa, M. Y. Yi, M. M. Karelson, and M. C. Zerner. Geometry Optimization at the Semiempirical Self-Consistent-Reaction-Field Level using the AMPAC and MOPAC Programs. *J. Chem. Soc. Perkin Trans. II*, 1991, 5, 635-637.

[15] N.L. Allinger, J.Am.Chem.Soc., 1977, 99, 8127- 8134.

[16] R. Erik Plata and Daniel A. Singleton, Case Study of the Mechanism of Alcohol-Mediated Morita Baylis−Hillman Reactions. The Importance of Experimental Observations, J. Am. Chem. Soc. 2015, 137, 3811−3826.

[17] R. Malathi, D. Rajagopal, Zoltan G. Hajos and S. Swaminathan, Proline-catalysed asymmetric ketol cyclizations: The template mechanism revisited, *J. Chem. Sci.*, 2004. Vol. 116, 159–162.