Hajos-Parrish reaction mechanism

Hajos, Zoltan George

Biography:

Organic chemist, born 1926 (Budapest, Hungary). Ph.D. (Technical Sciences) Technical University, Budapest, 1950. MS, Technical University, Budapest,1947. Assistant Professor Technical University, Budapest, Hungary 1948-1957. Research scientist Princeton University, Princeton, NJ 1957-1960; Hoffmann-La Roche, Inc. Nutley, NJ 1960-1970; University of Vermont, Burlington, VT 1972-1973; University of Toronto, Ontario, Canada 1973-1974; R.W.Johnson Pharmaceutical Research Institute, Raritan, NJ 1975-1990.

He received a Certificate of Merit, an Iron Award from the Technical University on May 22, 2013 in recognition of Sixty Five years of professional service.

Achievements include publications and patents in the field of total and asymmetric synthesis of medicinal-organic compounds. Heterogeneous catalysis; Inhibitor Effect in Autoxidation Processes; Hydrolysis and Esterification catalysed by Ion Exchange Resins; Stereospecific preparation of glycosides from sugar acetates; Amino acid catalyzed asymmetric syntheses of chiral synthons. Synthesis of hydrophenanthrenes, steroidal hormones, heterocyclics, (i.e. tetrahydrofuran derivatives, dioxanes and purines). Author: Aldol and Related Reactions pp. 1-84 in Techniques and Applications in Organic Synthesis, Vol.1, Carbon-Carbon Bond Bond Formation. Robert L. Augustine, Editor, Marcel Dekker Inc., New York and Basel, 1979. Lectures at the 145th, 148th, 150th National ACS meetings, and at the Gordon Research Conferences in Natural Product Chemistry in 1970 and at the Research Conference on Heterocyclic Compounds in 1989. Citizen of the U.S.A. Married to Katherine Birnbaum. Emeritus Member of the American Chemical Society and of the Society of the Sigma Xi.

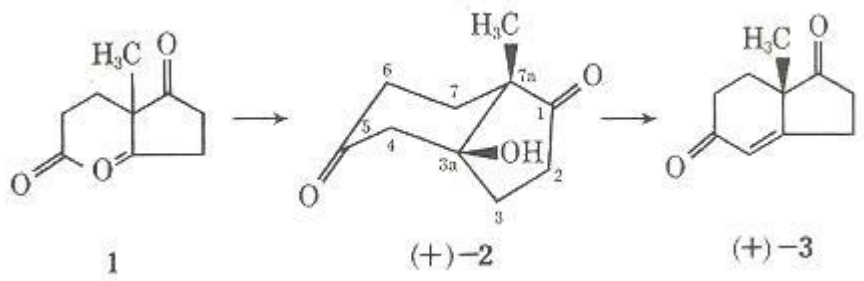
An essay by Zoltan Hajos entitled **Proline Catalyzed Asymmetric Cyclization.Theory of the Reaction mechanism** can be found on the ChemWeb Preprint server under http://www.sciencedirect.com/preprintarchive/article/B7J22-4DNMR08-22/2/7e47d5d0bd80be28df693b74ec631b3e Chemistry Preprint Archive, Volume 2002, Issue 9, September 2002, Pages 84-100. It is an extension of the original publication on **Asymmetric Synthesis of Bicyclic Intermediates of Natural Product Chemistry** by Zoltan G. Hajos and David R. Parrish, J.Org.Chem. **1974**, 39, 1615-1621.

On March 17, 2014 an article appeared in C&ENews by Jean-Francois Tremblay about the award Benjamin List received. In it Tremblay wrote: "Throughout the 20th century, scientists published papers that mentioned examples of catalysis using small organic molecules, including amines. **In particular, pharmaceutical industry groups led by Zoltan Hajos**, who was then at Roche in Nutley, N.J., and Rudolf Wiechert of Schering AG in Berlin, described the use of proline for certain asymmetric intramolecular aldol reactions. But the reactions' mechanics were ill defined, and they therefore had been widely viewed as exotic exceptions."

Hajos and Parrish proposed two reaction mechanisms [enamine and carbinolamine (imine) mechanism]. Of these the enamine mechanism became more widely accepted [ref. Wiener, J.J.M. Amer. Chem. Soc., Div. of Org. Chem. 2001 Fellowship Award Essay "Enantioselective Catalysis by Simple Chiral Amines: The Search for a General Strategy"]. The experimental results in the Hajos laboratory with ^{18}O labeled water suggested the imine

mechanism to be more likely [ref. J. Org. Chem. **1974**, 39, 1619 and 1621.] Therefore, the statement that the ”reactions’ mechanics were ill defined” should be reconsidered in this context.

Hajos and Parrish needed the starting material triketone **1** for their asymmetric synthesis. The synthesis of **1** has been described by them in J.Org.Chem., **1974**, 39, pp 1612-1615. Another Hajos and Parrish paper in J.Org.Chem., **1974** 39, 1615-1621 describes that starting with the triketone **1** and executing the experiments at ambient temperature using a catalytic amount (3% molar equiv.) of (S)-(-)-proline Hajos and Parrish could isolate the optically active intermediate bicyclic ketol **(+)-2** a prerequisite of elucidating the reaction mechanism. This was most likely the reason for Professor Claude Agami to call the reaction the Hajos-Parrish reaction in his paper in J.Chem.Soc., Chemical Commun., **1985**, 441-442. Compound **(+)-2** could be converted to its dehydration product **(+)-3** in excellent chemical and optical yield.



The last few lines of the Hajos and Parrish **1974** paper read: "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." This has been referred to in a publication by Mohammad Movassaghi and Eric N. Jacobsen of the Department of Chemistry and Chemical Biology, Harvard University, Cambridge, MA 02138, USA: The Simplest "Enzyme" *Science*, 6 December **2002**, Vol. 298, 1904-1905.

The intermediate of the carbinolamine mechanism put forward by Hajos in 1974 is shown in Figure A. The stereochemical assignment of the carbinolamine substituents has been changed as suggested by Professor Michael Jung. The carbinolamine is tautomeric to the iminium hydroxide intermediate shown in Figure B. Enolization of the side chain methyl ketone caused by the iminium hydroxide would then be followed by ring closure to the above shown ketol product (+)-**2** under the influence of a catalytic amount of (S)-(-)-proline.

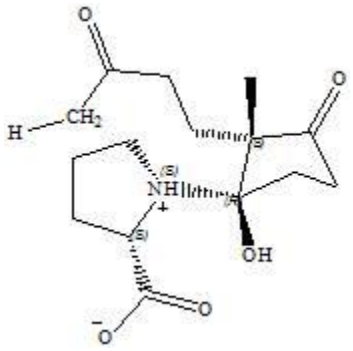


Figure A

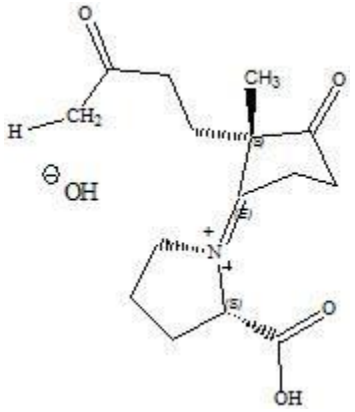


Figure B

Minimization studies of the iminium hydroxide intermediate using the CambridgeSoft Corporation's Chem3D MM2 energy minimization menu based on Allinger's Molecular Mechanics force field version2 showed a difference of 2.6932 kcal/mole in favor of this 2(S)-intermediate over the one with the 2(R)-configuration.

Pengxin Zhou, Long Zhang, Sanzhong Luo, and Jin-Pei Cheng obtained excellent results using the simple chiral primary amine t-Bu-CH(NH2)-CH2-NEt2.TfOH for the synthesis of both the Wieland-Miescher ketone and the Hajos-Parrish ketone as well as their analogues. ("Asymmetric Synthesis of Wieland-Miescher and Hajos-Parrish Ketones Catalyzed by an Amino-Acid-Derived Chiral Primary Amine" Zhou, P.; Zhang, L; Luo, S; Cheng, J.-P., J.Org.Chem. **2012**, 77, 2526 to 2530).This supports the iminium mechanism, because it is textbook chemistry that primary amines form imines rather than enamines with carbonyl compounds; cf. http://en.wikibooks.org/wiki/Organic_Chemistry/Amines

According to Professor David C. MacMillan [“The advent and development of organocatalysis" David C. MacMillan, NATURE Vol 455|18 September 2008, p.304.] “current interest in organocatalysis is focused on asymmetric catalysis with chiral catalysts and this particular branch is called asymmetric organocatalysis or enantioselective organocatalysis. Between 1968 and 1997, there were only a few reports of the use of small organic molecules as catalysts for asymmetric reactions (the Hajos–Parrish reaction probably being the most famous)." The Hajos-Parrish reaction is thus a representative example of **organocatalysis.**

In order to establish whether or not an enamine mechanism was operational Hajos and Parrish executed the proline catalyzed asymmetric ring closure in the presence of $H_2{}^{18}O$ as follows.

The triketone starting material 2-Methyl-2-(3-oxobutyl)-1,3-cyclopentanedione (1.0 mmol) has been stirred under argon at RT for 1 week in 1.0 mL acetonitrile containing 40 mg of $H_2{}^{18}O$ and (S)-(-)-proline(0.03 mmol). The optically active bicyclic ketol(+)-(3aS,7aS)-3a,4,7,7a-Tetrahydro-3a-hydroxy-7a-methyl-1,5(6H)-indandione was isolated in 22% yield by preparative thin layer chromatography. Mass spectral analysis for ^{18}O-labeled CO_2 of the sample showed only 7.2% ^{18}O-enrichment. In a highly important control experiment 1.0 mmol of the optically active bicyclic ketol reaction product was stirred under argon at RT for 1 week in 1.0 mL acetonitrile containing 40 mg of $H_2{}^{18}O$ and 0.03 mmol of (S)-(-)-proline.

Mass spectral analysis for ^{18} O-labeled CO_2 of the optically active bicyclic ketol showed 33.1% ^{18}O-enrichment.

The asymmetric ring closure of the triketone thus did not confirm ^{18}O incorporation into the optically active bicyclic ketol in any significant measure (7.2% ^{18}O-enrichment) thereby contradicting the enamine mechanism. However, the control experiment showed that the optically active bicyclic ketol reaction product incorporated nearly five times more ^{18}O (33.1% ^{18}O- enrichment). It should be emphasized that the ^{18}O studies have been executed under very similar conditions to the actual asymmetric ring closure experiments always avoiding an overload by $H_2{}^{18}O$.This way Hajos and Parrish tried to keep ^{18}O incorporation into the reaction product at a minimum (for more details see J.Org.Chem., **1974**, 39, pages 1619 and 1621).

In the aforementioned ChemWeb preprint article it was emphasized that there is no problem to accept the enamine mechanism for the antibody catalyzed enantioselective Robinson annulation. It is well known that, antibody catalyzed reactions may proceed contrary to the small molecule catalyzed reactions. Antibodies for instance catalyze ring closures in formal violation of Baldwin's rules.

Further calculations after the ChemWeb publication using the CambridgeSoft Corporation's Chem3D MM2 energy minimization menu based on Allinger's Molecular Mechanics force field version2 led to the conclusion that the template mechanism gives lower energy levels than either the carbinolamine or the enamine pathways. Due to this realization a cooperation has been established resulting in a paper entitled **"Proline-catalysed asymmetric ketol cyclizations: The template mechanism revisited."** (R. Malathi, D. Rajagopal, Zoltan G. Hajos and S. Swaminathan, *J. Chem. Sci.*, Vol. 116, No. 3, May **2004,** pp. 159-162.Indian Academy of Sciences.) Modeling was done using Builders software in INSIGHT II. The models were minimized using force field CFF91 using DISCOVER software.

A preprint by Zoltan Hajos entitled **"Amino Acid Assisted Chemical Catalytic Computing Device"** can be located on the ChemWeb Preprint server under http://www.sciencedirect.com/preprintarchive/article/B7J22-4D5K021-2/2/de2189148a7ca02ca87ea9e6072862ad. Chemistry Preprint Archive, Volume 2004, Issue 2, February 2004, Pages 15-21. It describes the concept of an amino acid assisted Chemical Catalytic Computing Device (CCCD). The technical design of a prototype CCCD will have to involve the know-how of nanotechnology and combinatorial devices.