

Hajos-Parrish reaction mechanism

Hajos, Zoltan George

Biography:

Organic chemist, born 1926 (Budapest, Hungary). MS, Technical University, Budapest, 1947. Ph.D. (Technical Sciences) Technical University, Budapest, 1950. 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.

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.

The carbinolamine mechanism described in both papers has had an unwitting support in a more recent paper entitled "beta-Homoamino acids as catalysts on enantioselective intra- and intermolecular aldol reactions" by Michael Limbach, *Tetrahedron Letters* 47 (2006) 3843-3847. The triketone starting material 2-methyl-2-(3-oxobutyl)-1,3-cyclopentanone gave the expected optically active bicyclic ketol (+)-(3a*S*,7a*S*)-3a,4,7,7a-tetrahydro-3a-hydroxy-7a-methyl-1,5(6*H*)-indanedione with (S)-(-)-proline catalyst. On the other hand, the stereochemical outcome is reversed with ee selectivities of up to 83% by using the homologue amino acid catalysts, such as (S)-(beta)-homoproline, [(pyrrolidine-(2*S*)-yl) acetic acid]. The virtual anomaly can nicely be explained with a top side approach of the bulkier beta amino acids to the above described triketone starting material of reflective symmetry. The top side approach resulted in the formation of an enantiotopic carbinolamine to give the (-)-(3a*R*,7a*R*) bicyclic ketol enantiomer identical to the one obtained with unnatural (R)-(+)-proline.

Since Hajos and Parrish worked at ambient temperature using a catalytic amount (3% molar equiv.) of (S)-(-)-proline they could isolate the optically active intermediate bicyclic ketols 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.

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.

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 H₂¹⁸O 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 H₂¹⁸O 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 ¹⁸O-labeled CO₂ of the sample showed only 7.2% ¹⁸O-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 H₂¹⁸O and 0.03 mmol of (S)-(-)-proline. Mass spectral analysis for ¹⁸O-labeled CO₂ of the optically active bicyclic ketol showed 33.1% ¹⁸O-enrichment.

The asymmetric ring closure of the triketone thus did not confirm ¹⁸O incorporation into the optically active bicyclic ketol in any significant measure (7.2% ¹⁸O-enrichment) thereby contradicting the enamine mechanism. However, the control experiment showed that the optically active bicyclic ketol reaction product incorporated nearly five times more ¹⁸O (33.1% ¹⁸O-enrichment).

It should be emphasized that the ¹⁸O studies have been executed under very similar conditions to the actual asymmetric ring closure experiments always avoiding an overload by H₂¹⁸O. This way Hajos and Parrish tried to keep ¹⁸O 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.

It is highly probable that, **the template mechanism postulated for the amino acid catalyzed intramolecular reactions should also be operational for the intermolecular reactions catalyzed by proline** or other amino acids. Several papers suggested a favorable effect of water in the amino acid catalyzed intermolecular aldol reactions. Postulating an enamine mechanism in

the presence of water is contrary to the requirements of enamine formation. By assuming the template mechanism for the intermolecular aldol reactions it is not necessary to invoke esoteric mechanistic ideas to support the existence of water sensitive enamine intermediates.

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.

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