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ASYMMETRIC AUTOCATALYSIS: FACTS AND FANCY*

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ABSTRACT

Apparently no definitive experiments have ever been reported which could be defined as asymmetric autocatalysis. This paper discusses the design of several experiments which might lead to asymmetric autocatalytic reactions. The implications of this novel type of asymmetric synthesis are evaluated.

INTRODUCTION

We define asymmetric autocatalysis as the process whereby a chiral reaction product is the catalyst in its own formation from achiral reactants. The reaction is shown schematically in Fig. 1.

Autocatalysis is an important catalytic variant with, unfortunately, too few examples in the organic literature. In the inorganic realm the well-known formation of rust, the oxidation of iron to iron oxide, is perhaps one of the most common and important examples of autocatalysis [1]. The kinetic complexity of this reaction is exemplified by recent work [2].

*Dedicated to my dear father-in-law, Dr. Maurits Dekker, in honor of his 90th birthday. A patient great grandfather to our grandchildren, a generous grandfather to our children, an understanding and supportive father to my wife and me for 45 years. I wish him many more years of health and happiness with his wife, family, and friends.

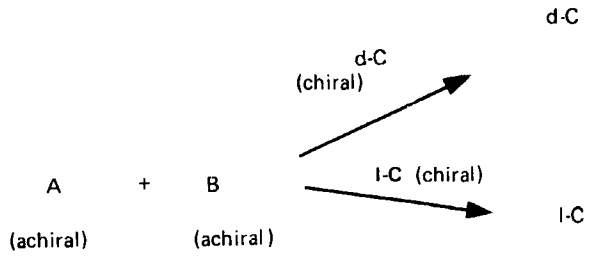


FIG. 1.

A classical autocatalytic organic reaction is, of course, the hydrolysis of esters to form acids and alcohols. The organic acid formed (acetic acid, when methyl acetate is hydrolyzed) is the catalyst for the hydrolysis of the ester [3].

One very recent example of the importance of autocatalysis in polymerization reaction is found in the work of C. A. A. van Boekel, G. M. Visser, R. Hegstrom, and J. H. van Boom who studied the association of oligonucleotides (G. M. Visser, Dissertation, Leiden, 1986).

DISCUSSION

Frank, in a seminal paper, derived kinetic expressions for autocatalytic reactions in which one enantiomeric product catalyzes its own formation while the antipode inhibits the formation of its antipode. This may seem like a very strange sentence, but an examination of a possible experiment might clarify the confusion. Suppose (see Fig. 2) we allow the naphthol **1** to react with the imine **2**. This reaction, first recorded by Betti [5], produces an adduct **3**, which, of course, is racemic. Its chirality is due to the stereocenter formed by the addition of the carbon of the aromatic ring to the carbon of the imine. In Frank's scenario, the first requirement for successful autocatalysis lies in the ability of the product, in our case the adduct **3**, to catalyze the addition reaction.

A first clue that this reaction might show autocatalysis is found in the original paper. Betti writes that the reaction goes spontaneously: "Quantita eqimoleculari di beta-naftolo e di benzalanalina si sciolgono a freddo nella

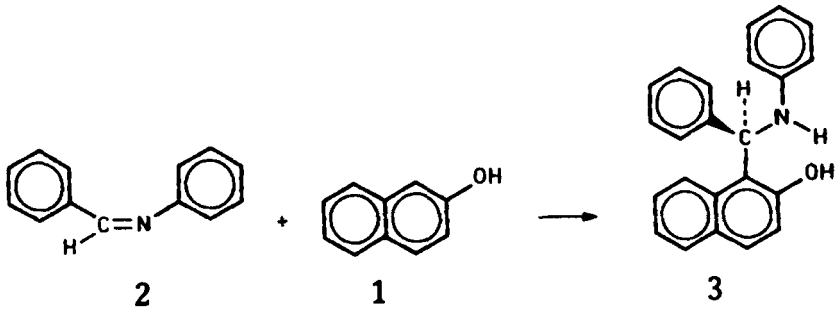


FIG. 2.

minima quantita di benzina; si lascia in riposo alla temperatura dell'ambiente per diversi giorni (remember this is July 1900 in Florence, Italy, no air conditioning. I estimate a room temperature of 30°C) dopo i quali comincia a formarsi un deposito che, *lenta da prima* (emphasis added), diviene poi a mano piu rapido (Slowly at first, later on faster . . .)." It is clear from this detailed experimental description that Betti mixed equimolar quantities of the naphthol and the imine in a small quantity of petroleum ether (benzina is not benzene), and the product formed slowly at first, and faster as the reaction proceeded. An even stronger clue to the catalytic nature of this addition reaction is found in the following sentence from the same paper: "Per mezzo dell'aggiunta di una goccia (one drop) di piperidina pare che reazione si effetui piu rapidamente ma non porta a resultati diversi." Addition of one drop of piperidine speeds up the reaction without changing the results.

We have here, then, a base-catalyzed addition reaction in which the catalyst could be the starting material (the Schiff's base or imine is weakly basic), or it could be the product (a secondary amine, probably more basic than the imine).

We (Dr. Wiero Menge carried out the experiments described in this paper) repeated Betti's experiments with essentially the same results. Essentially but not entirely. The adduct **3** could be identified completely by standard spectroscopic techniques and proved to have the structure assigned to it by Betti. However, we discovered that when we purified the starting materials rigorously, thus eliminating the last traces of aniline from the Schiff's base (which is prepared from aniline and benzaldehyde), the reaction did not really go spontaneously until a drop of piperidine was added. We have to conclude that the spontaneity of the reaction as observed and described by Betti might have

been due to traces of aniline present in the starting product. However, the base catalysis by piperidine was confirmed, and this encouraged us to try an experiment in which asymmetric autocatalysis would play a role.

The reasoning Frank followed, and which led him to conclude that asymmetric autocatalysis (or spontaneous asymmetric synthesis, as Frank calls the process) "is a natural property of life, which may be present in simpler autocatalytic systems. A laboratory demonstration is not necessarily impossible" [4], can be summarized thus: "When, in a reaction between two achiral reactants, a product is formed that is chiral, the two enantiomers are formed in equal amounts. Even when the enantiomers are catalysts in their own formation, the natural tendency will be that, as one enantiomer is formed, catalyzed by itself, the other enantiomer will be formed, statistically speaking, in exactly the same amounts. However, and this is the crucial difference, now suppose that the catalysis is more complex. Suppose the enantiomer that catalyzes its own formation inhibits the reaction which forms the other enantiomer. The word 'inhibit' must be properly interpreted. I do not imply that the inhibition stops the reaction entirely. All that is meant is that the rate of the reaction for the production of enantiomer **S** catalyzed by enantiomer **S** is faster than the rate of the reaction to form enantiomer **R** catalyzed by enantiomer **S**."

Frank reasons further: "If the reaction described above is allowed to proceed for a long time, the possibility increases that, at a certain moment, 10 molecules of enantiomer **S** and 11 molecules of enantiomer **R** are present in the reaction mixture. If the conditions of catalysis and inhibition prevail, the following will occur: Since more molecules of enantiomer *S* are present, the reaction forming enantiomer **S** is accelerated, while at the same time the reaction which forms enantiomer **R** is slowed down. Both phenomena are the result of two mutually reinforcing events. More enantiomer **S** is formed, not only because more **S** is present, but also because less **R** (its inhibitor) is present. Conversely, less enantiomer **R** will be formed, not only because less **R** is present, but also because more **S** (its inhibitor) is acting on the system. The 'instability' in the system, well familiar to students of 'chaos' phenomena, is an inherent property of the system and is the result of the normal fluctuations in reaction rates." The conclusions drawn by Frank are now seen to be entirely warranted, and his statement that "a laboratory demonstration is not impossible," is a challenge to every red-blooded synthetic organic chemist.

Having summarized Frank's work and laid the basis for experimental tests, I want to summarize our attempts, unsuccessful thus far, to provide data supporting these thought experiments.

Four factors mitigate against early success in the search for an asymmetric

autocatalytic system. (a) The human experimenter is in no position to wait 1000 years for the statistically possible but nevertheless unlikely event of fluctuations in the reaction rates causing the autocatalysis to "take off." (b) Although finding a catalyst for a given reaction (for example, the Betti reaction described above) is certainly within our present expertise, finding an asymmetric catalyst is an order of magnitude more difficult. However, in this respect our earlier experience with asymmetric catalysis stood us in good stead [6]. (c) Finding a satisfactory asymmetric catalyst is clearly a necessary but not sufficient condition for asymmetric autocatalysis. The desired catalyst must also be the product of the reaction being studied. (d) Even having found an autocatalytic system, of which exceedingly few examples occur in the organic literature, the last requirement, i.e., that the catalyst must show inhibition properties, might discourage any but the most optimistic researchers.

Having formally retired as Professor of Organic Chemistry a year ago, and through the kindness and generosity of my colleagues having been allowed to continue to do research and obtain grants, I felt I was in the perfect position to try this long shot. After all, a rapid stream of "Communications to the Editor," needed to obtain tenure, is at present not my most important worry.

The Betti Reaction

As mentioned under (a) above, waiting will get us nowhere. Thus the experimental design to prove asymmetric autocatalysis must begin with separately prepared, enantiomerically enriched product as catalyst for its own formation. In the Betti reaction this means that we needed enantiomerically enriched adduct **3**. We reasoned that this adduct **3**, produced as a racemate in the piperidine-catalyzed reaction (see Fig. 2), might very well be produced in optically active form by using a chiral amine as catalyst instead of the achiral piperidine.

This reasoning proved correct. When the reaction shown in Fig. 2 was carried out in the presence of brucine (an optically active naturally occurring alkaloid), optically active adduct **3** was obtained after several crystallizations. This seems to be, inter alia, the first example of asymmetric catalysis in the reaction of a carbon nucleophile with an imine. The enantiomerically enriched material was used as a catalyst in the reaction of beta-naphthol, **1**, with the imine **2**. However, no enrichment of the product was observed. No definite proof either of autocatalysis or of asymmetric induction was obtained. We must conclude that the reaction shown in Fig. 2, although cata-

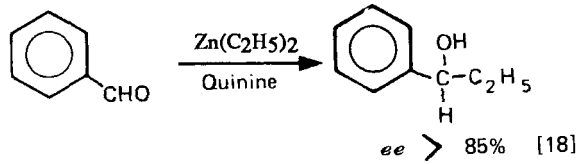
lyzed by piperidine, is not noticeably catalyzed by the phenolic amine **3**. A rationale is provided by the observation that the product, although formally an amine, suffers from the disadvantage of having a phenolic (and therefore an acidic) functional group positioned in such a way that the basic properties of the amine might well be negated through hydrogen bonding with the phenolic hydroxyl group.

The Diethylzinc Reaction

After Mukaiyama [7] showed that diethylzinc gave chiral alcohols when added to aldehydes in the presence of chiral ligands, and Oguni [8] discovered a catalytic variation of this reaction by using camphor derivatives and palladium as chiral catalysts, we found that the easily available cinchona alkaloids (e.g., quinine, cinchonidine) produced the alcohols in high yield and with an enantiomeric excess (*ee*) exceeding 90% (see Fig. 3a) [6].

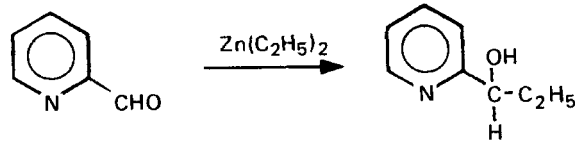
It does not take a great leap of the imagination to adapt this reaction from producing alcohols to preparing amino alcohols (see Reaction 3b). At present we are studying the two reactions shown in Fig. 3b. Both reactions are cata-

3a.



ee > 85% [18]

3b.



3c.

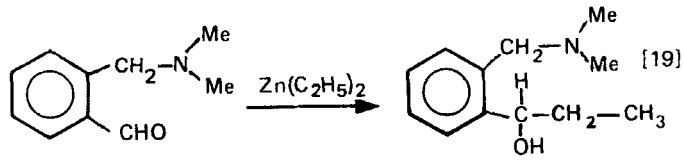


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FIG. 3.

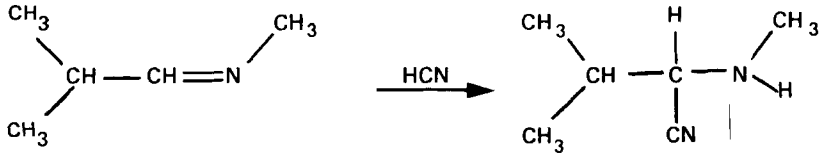

FIG. 4.

lyzed by hydroxyamines. Furthermore, the products, chiral hydroxyamines, can be prepared in optically active form either through classical resolution or through asymmetric catalysis by using the quinine catalysis as shown earlier. Once again, although no clear demonstration of autocatalysis has yet been obtained, the system holds considerable promise.

The HCN Reaction

The addition of HCN to imines (Fig. 4) is in many ways similar to the addition of beta-naphthol to the imine (Fig. 2). The product in this case, however, is an aminonitrile, a natural precursor to amino acids. In terms of an "origin of life" or "origin of optical activity" argument, the HCN reaction is a formidable candidate. After all, the prebiotic "soup" may well have contained (achiral) amines and aldehydes in addition to HCN. Thus, the spontaneous formation of imines, followed by the addition of HCN to form aminonitriles and thence to amino acids, provides a convenient scenario for the production of chiral building blocks for living organisms. We are studying this addition reaction in the system shown in Fig. 4. A considerable barrier to the success of this study lies in the fact that the products, the aminonitriles, are easily racemized.

The Origin of Life

Experiments designed to prove the existence of asymmetric autocatalysis are manifestly important in the ongoing arguments concerning the "origin of optical activity." The feeling is widespread that an answer to that question will also provide insight into the question of the origin of life. The question has intrigued chemists for generations. Calvin [9], Rutten [10], Bonner [11], and very recently Mason [12] made valuable contributions to answering the problem. Experiments by Ollis [13] and Havinga [14] on the spontaneous resolution of racemates as well as those of Addadi, Lahav, and coworkers [15]

have provided new insights into this intriguing question. A paper by Kagan [16] and, very recently, one by Oguni [17] on amplifying phenomena in asymmetric syntheses have important implications for research in the area.

It is hoped that this discussion, incomplete as it is, and raising more questions than it answers, will stimulate organic chemists to investigate the fascinating problem of asymmetric autocatalysis.

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REFERENCES

[1] E. Gossart, *C. R. Acad. Sci., 23,* 21 (1847).
[2] M. Orbane and I. R. Epstein, *J. Am. Chem. Soc., 104,* 5918 (1982).
[3] See, for example, S. Glasstone, *Textbook of Physical Chemistry,* Van Nostrand, New York, 1946, pp. 1061, 1078.
[4] F. C. Frank, *Biochim. Biophys. Acta, 11,* 459 (1953).
[5] M. Betti, *Gazz. Chim. Ital., II,* 301 (1900).
[6] H. Wynberg, "Asymmetric Catalysis by Alkaloids," in *Topics in Stereochemistry* (E. Eliel, S. H. Wilen, and N. L. Allinger, eds.), Wiley-Interscience, New York, 1986, p. 87.
[7] T. Mukaiyama, K. Soai, T. Sato, H. Shimizu, and K. Suzuki, *J. Am. Chem. Soc., 101,* 1455 (1979).
[8] N. Oguni, T. Omi, Y. Yamamoto, and A. Nakamura, *Chem. Lett.,* p. 841 (1983).
[9] M. Calvin, *Chemical Evolution,* Clarendon, London, 1969.
[10] M. G. Rutten, *The Origin of Life,* Elsevier, Amsterdam, 1971.
[11] W. A. Bonner, "The Origins of Molecular Chirality," in *Exobiology* (C. Pennamperuma, ed.), North-Holland, Haarlem, 1972.
[12] S. F. Mason, *Nature, 314,* 400 (1985), and earlier papers.
[13] W. Baker, B. Gilbert, and W. D. Ollis, *J. Chem. Soc.,* p. 1443 (1952).
[14] E. Havinga, *Biochim. Biophys. Acta, 13,* 171 (1954).
[15] Z. Berkovitch-Yellin, J. van Mil, L. Addadi, M. Idelson, M. Lahav, and L. Leiserowitz, *J. Am. Chem. Soc., 107,* 3111 (1985).

[16] C. Puchot, O. Samuel, E. Dunanch, S. Zhao, C. Agami, and H. B. Kagan, *Ibid., 108,* 2353 (1986).
[17] N. Oguni and T. Kaneko *Ibid. 110,* 7877 (1988).
[18] H. Wynberg and A. Smaardijk, *J. Org. Chem., 52,* 135 (1987).
[19] Unpublished experiments with W. Menge.

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