Comments on Inorganic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713455155

Asymmetric Synthesis. Kinetic Amplification of Enantiomeric Excess

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To cite this Article Bergens, Steven and Bosnich, B.(1987) 'Asymmetric Synthesis. Kinetic Amplification of Enantiomeric Excess', Comments on Inorganic Chemistry, 6: 2, 85 — 90
To link to this Article: DOI: 10.1080/02603598708081854
URL: http://dx.doi.org/10.1080/02603598708081854

Asymmetric Synthesis. Kinetic Amplification of Enantiomeric Excess

The efficiency of an asymmetric synthetic reaction is measured by what is called the enantiomeric excess (e.e.). It is commonly assumed that this is a unique quantity for a given asymmetric reaction under specified conditions. The purpose of this Comment is to show that this is not necessarily so, and that, under certain circumstances, e.e. is an elusive quantity which continuously changes with the extent of reaction.

Asymmetric synthesis is the preferred transformation of an achiral substrate possessing enantiotopic faces, groups or atoms into one enantiomer of the product. Consider the pairs of reactions in Fig. 1. One pair involves a ketonic and the other an olefinic substrate. Attack by X on the ketone can occur in two ways, either from the "top" (a) or from the "bottom" (b) side of the ketonic face leading, respectively, to the R- and S-enantiomers of the product. Similarly, overall (catalytic stepwise) *cis*-addition of hydrogen to the olefinic faces ((c) and (d)) leads to the respective enantiomers of the reduced product. The ketonic and olefinic faces are equivalent but not identical in the sense that addition to the respective faces leads to molecules of opposing chirality. These faces are said to be enantiotopic. In the absence of a chiral environment, the enantiotopic faces will react at the same rates ($k_1 = k_2$; $k_3 = k_4$) leading to equal concentrations of the enantiomeric pairs. If, however, the ketonic and olefinic substrates are in a chiral environment, for example, by being bound to a chiral complex, the enantiotopic

Comments Inorg. Chem.
1987, Vol. 6, No. 2, pp. 85–90
0260-3594/87/0602-0085/$15.00/0

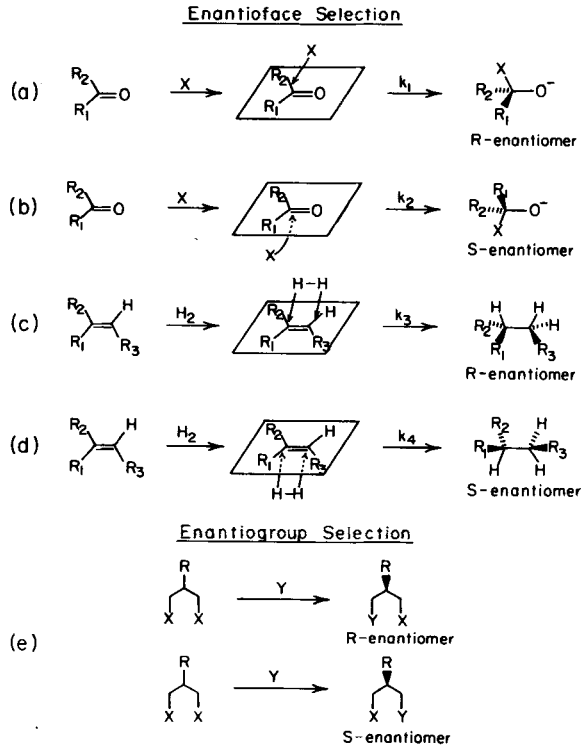

FIGURE 1 Examples of enantioselective reactions.

faces are no longer identical. Under such circumstances the substrate-chiral complex aggregate becomes diastereomeric; the reactivity of the enantiotopic faces is no longer the same because energetically unequal diastereomeric transition states are formed. It follows that because $k_1 \neq k_2$ and $k_3 \neq k_4$, the respective enantiomers are produced in unequal amounts, that is, an asymmetric synthesis has been contrived. The e.e. of an asymmetric synthesis is defined as %e.e. = |%R − %S|; note that when R − S is 50% − 50%, %e.e. = 0, corresponding to an achiral synthesis.

It is clear that for substrates with enantiotopic faces the e.e. remains constant throughout the reaction, the ratio of enantiomers remains constant from beginning to end. But is this the case when we perform an asymmetric synthesis on substrates possessing en-

antiotopic groups or atoms (Fig. 1(e))? In many cases the surprising answer is no! This fact is not commonly recognized and it is the purpose of this Comment to explain and draw attention to this curious circumstance.

ASYMMETRIC SYNTHESIS WITH ENANTIOTOPIC GROUPS OR ATOMS

Consider the simple proton-for-deuterium exchange reaction where the two protons are enantiotopic. We take the case of glycine (Fig. 2) which has a direct biological analogy[1] and a cobalt(III) synthetic analog which we described recently.[2] If the α-glycine protons are exchanged in a chiral environment, such as an enzyme[1] or a chiral metal complex,[2] $k_1' \neq k_2'$. Assuming that $k_1' > k_2'$, the R-chiral glycine will be produced at a greater rate than the S-enantiomer and, were the reaction completely specified by the scheme in Fig. 2, the e.e. at any time during the reaction would be a constant value determined by the values of k_1' and k_2'. A moment's reflection, however, leads to the realization that the asymmetric proton exchange will not stop at the two enantiomers but will continue and finally produce dideuterated glycine ($H_2NCD_2CO_2H$), as shown in the scheme in Fig. 3.

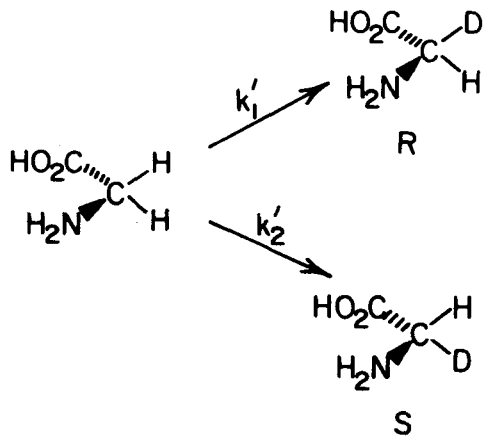

FIGURE 2 Asymmetric synthetic scheme for the production of chiral glycine.

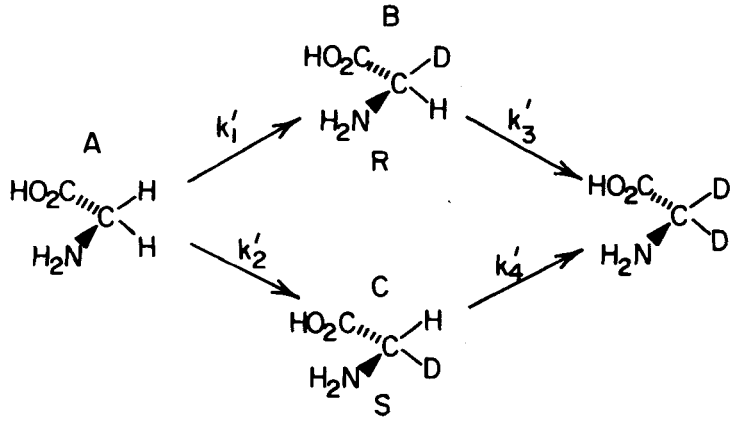

FIGURE 3 Proton exchange sequence for the enantioselective production of chiral glycine.

As before, we assume $k_1' > k_2'$. In general the chiral bias which makes $k_1' > k_2'$ will also make $k_4' > k_3'$ because the hydrogen atom which is exchanged via k_1' is in the same site as the hydrogen atom that is exchanged via k_4'. In the jargon of the trade, the k_1' and k_4' paths both refer to diastereotopic pro-R protons. The consequences of these relationships are that R-chiral glycine ($H_2NCDHCOOH$) is initially produced faster than the S-enantiomer ($k_1' > k_2'$, but as the reaction proceeds, the S-enantiomer is removed faster than its R-antipode ($k_4' > k_3'$). Thus, one enantiomer, in this case the R-isomer, continuously increases in concentration over the other as the reaction proceeds. In principle we can obtain chiral glycine to any degree of optical purity provided we are prepared to sacrifice chemical yield. The greater the disparity between the appropriate rate constants, the less of the material we need to sacrifice for a desired optical purity.

So what is the e.e. of such an asymmetric reaction? An e.e. can only be specified if values of the rate constants are determined and the extent of reaction is specified. It follows that the e.e. of such a reaction has no meaning in the conventional sense. The literature contains many examples where e.e.'s are quoted for asymmetric reactions which fit the scheme in Fig. 3. Some of these values look impressive until one recognizes the amplifying effects

of certain parallel-consecutive reactions. Indeed, as we now show, even a difference of 5 in the respective rate constants can generate highly pure enantiomers with tolerable chemical yields.

The kinetic equations appropriate for the scheme in Fig. 3 have been determined.[2,3,4] They are:

$$[B] = \frac{k_1'[A]_0}{k_3' - (k_1' + k_2')} (e^{-(k'_1+k'_2)t} - e^{-k'_3 t})$$

$$[C] = \frac{k_2'[A]_0}{k_4' - (k_1' + k_2')} (e^{-(k'_1+k'_2)t} - e^{-k'_4 t})$$

We take a simple example to illustrate the kinetic amplification effect: taking $k_1' = k_4' = 1 \times 10^{-3}\ s^{-1}$, $k_2' = k_3' = 2 \times 10^{-4}\ s^{-1}$ and $[A]_0 = 1$ molar, the variation of [B], [C] and [D] with time is shown in Fig. 4. Even with the modest difference of 5:1 in the rate constants the ratio of R:S isomers dramatically changes with time giving almost pure B early in the reaction. In essence

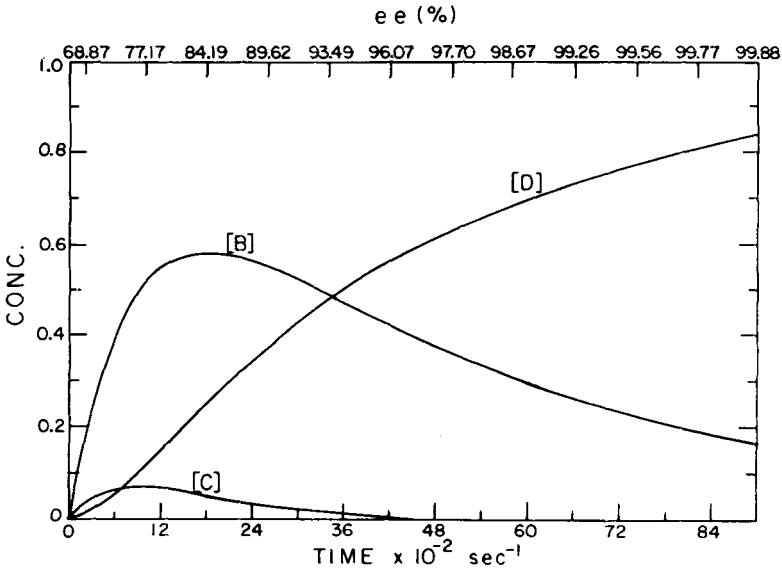

FIGURE 4 Variation of the concentrations of B and C (Fig. 3) with time with a 5:1 ratio of k_1':k_2' and also k_4':k_3'. [D] is the concentration of the dideuterated product.

the scheme in Fig. 3 is an asymmetric synthesis (k_1', k_2') followed by a reinforced kinetic resolution[5] (k_3', k_4') and is more effective than the latter in that the enantiomers, B and C, are in unequal concentrations.

The crucial assumption is that if $k_1' > k_2'$, then $k_4' > k_3'$ because reaction occurs at the same chiral site for k_1' and k_4' and for k_2' and k_3'. We suspect that many asymmetric syntheses involving enantiotopic groups or atoms will obey this scheme although it is easy to conceive of special circumstances where, for example, k_3' and k_4' effectively do not operate. Indeed many enzymes carry out asymmetric syntheses on enantiotopic atoms or groups where the k_3' and k_4' steps appear to be effectively shut down but for others, for example, certain hydrolytic enzymes, the scheme in Fig. 3 applies.[3]

We believe the comments adumbrated here represent a central concept in asymmetric synthesis.

Acknowledgment

We have been supported by grants from the Natural Sciences and Engineering Research Council of Canada.

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References

1. P. M. Jordan and M. Akhtar, Biochem. J. **116**, 277 (1970).
2. Z. Dokuzovic, N. K. Roberts, J. F. Sawyer, J. Whelan and B. Bosnich, J. Amer. Chem. Soc. **108**, 2034 (1986).
3. Y. F. Wang, C. S. Chen, G. Girdaukas and C. J. Sih, J. Amer. Chem. Soc. **106**, 3695 (1984).
4. There is a misprint in equation (6) of Ref. 2; k_2 should be replaced by k_4 in the last exponential.
5. A. Horeau, Tetrahedron **31**, 1307 (1975).
6. *Asymmetric Catalysis*, ed. B. Bosnich (Martinus Nijhoff Publishers, Boston, 1986), p. 111.