Bioorganic & Medicinal Chemistry Letters, Vol.3, No.8, pp. 1637-1642, 1993
Printed in Great Britain

0960-894X/93 $6.00 + .00

HYDRIDE TRANSFER VERSUS ELECTRON TRANSFER IN THE BAKER'S YEAST REDUCTION OF α-HALOACETOPHENONES

Luis M. Aleixo, Márcia de Carvalho, Paulo José Samenho Moran* and J. Augusto R. Rodrigues*

Universidade Estadual de Campinas, Instituto de Química
13.081 Campinas, SP, Brazil

(*Received in USA 29 March* 1993)

Abstract: The baker's yeast reduction of α-iodoacetophenone gave acetophenone. Some evidence for a free radical chain process in this reduction was obtained by addition of DNB which not only provoked a decrease in the formation of acetophenone but also allow the appearance of the enzyme-controlled formation of (-)-(R)-2-iodo-1-phenylethanol.

The baker's yeast (*Saccharomyces cerevisiae*) reduction of ketones have been used to obtain important chiral building blocks useful for stereoselective organic synthesis.[1] In view of the great importance of these microbiological reduction processes involving baker's yeast,[2] the mechanisms of these reactions is of current interest.

Tanner at al[3] have used, α-fluor-, α-chloro- and α-bromoacetophenone as a mechanistic probe, in the reduction reactions of NADH-dependent horse liver alcohol dehydrogenase (NADH/HLDH), which enables differentiation between reduction processes which proceed via hydride transfer (H^-) or by a multistep electron transfer (e^-, $H\cdot$ or e^-, H^+, e^- as has been suggested[4]). The use of the α-haloketone as a mechanistic probe has also been applied in the reduction of β-halogen-substituted 1,2-dioxetanes by 1,4-dihydronicotinamides[5] and in a mechanistic study of halide elimination of the ketyl radical.[6]

Acetophenone is the reduction product obtained by electron transfer while halohydrin is obtained by the hydride transfer process. Optically active halohydrin is obtained when an enzyme mediate a hydride transfer process. No free radical reduction was observed which did not involve carbon-halogen bond cleavage.[3]

In this work the baker's yeast reduction of α-iodoacetophenone is

investigated and the results are discussed in the light of the above mentioned concepts.

While the reduction of α-iodoacetophenone gave acetophenone and (-)-1-phenylethanol (Figure 1), the reduction of α-fluor-, α-chloro- and α-bromoacetophenone gave the corresponding (-)-halohydrins.[7]

Taking into account that the production of acetophenone may be by a free radical chain process, we decided to investigate in more detail the baker's yeast reduction of α-iodoacetophenone with the addition of a small quantity of m-dinitrobenzene (DNB), a reagent frequently used as an inhibitor of this mechanism. In duplicate experiments the production of acetophenone was partially inhibited by DNB, giving 9-15% yield while the production of the corresponding (-)-iodohydrin was 15-17% (Figure 1)[8]. The (-)-(S)-1-phenylethanol was probably produced by a baker's yeast reduction of part of the acetophenone produced in this reaction.

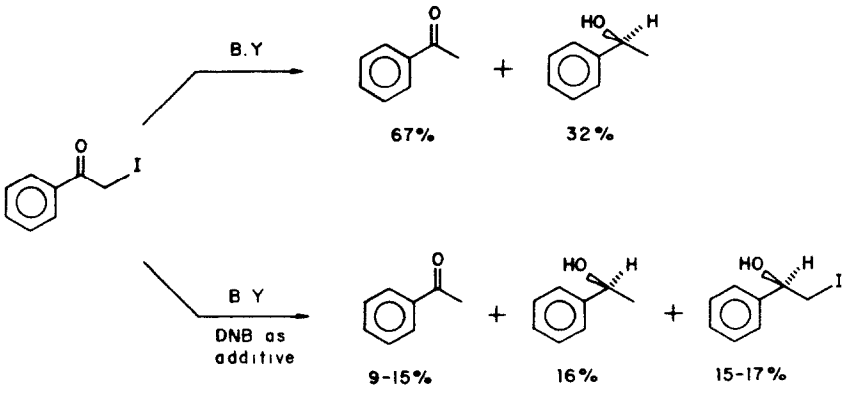

Figure 1. Isolated products from Baker's Yeast (B.Y) reductions of α-iodoacetophenone with and without the addition of DNB.

The enantioselectivity of the baker's yeast reduction of α-iodoacetophenone was determined by conversion of the isolated (-)-(R)-2-iodo-1-phenyethanol in the corresponding (+)-epoxide.[9] The

optical purity was 87%, based on the absolute rotation of the (+)-epoxide reported in the literature.[10]

The addition of DNB not only provoked a decrease in the formation of acetophenone but also allows the appearance of the enzyme-controlled formation of the (-)-(R)-2-iodo-1-phenylethanol. Since the DNB has no influence on the enzyme-controlled formation of the halohydrin,[3c] it seems that there is competition between the hydride transfer and the free radical chain processes in the baker's yeast reduction of α-iodoacetophenone. This competitive reaction system was also observed in the reduction of α,α-dichloroacetophenone by NADH/HLADH system.[3c]

A general competition reaction system may be proposed for the baker's yeast reduction of α-haloacetophenones (Figure 2), although there are several hundreds of enzymes[1a] in the whole cell from which some active oxiredutases have been isolated.[11]

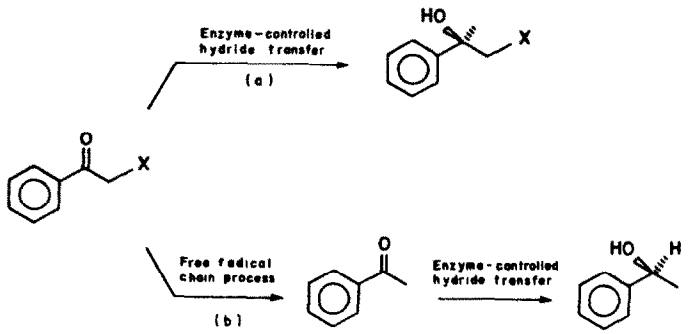

Figure 2. General competition reaction system proposed for the Baker's Yeast (B.Y.) reduction of α-haloacetophenones. Path a : enzyme mediated hydride transfer process, mainly for X = F, Cl, Br. Path b : free radical chain process, mainly for X = I.

For the α-fluor-, α-chloro- and α-bromo-acetophenone substrates the enzyme-controlled hydride transfer process, path a, takes place to yield only optically active halohydrins (no acetophenone was isolated or even detected by ^1H nmr spectra of the extracted material).[7] On the other hand, for the α-iodoacetophenone substrate, the free radical chain process, path b, takes place to yield acetophenone and (-)-1-phenylethanol. When the baker's yeast reduction of α-iodoacetophenone occurs with addition of DNB, this additive lowers the rate of the free radical chain process and thus the enzyme-controlled hydride transfer process, path a, become competitive. In this case the reaction yields products from both pathways, i.e., optically active iodohydrin, acetophenone and (-)-1-phenylethanol.

The free radical chain process takes place for the baker's yeast reduction of α-iodoacetophenone even though, in the α-bromoacetophenone reduction, the enzymatic complex of baker's yeast has more reduction power than that for the NADH/HLDH system by the hydride transfer mechanism.[3c,7]

The electrolytic reduction at a dropping mercury electrode of the α-iodoacetophenone was compared to the other α-haloacetophenones, see Table I, in order to understand the difference in behavior of the α-iodoacetophenone in the baker's yeast reduction.

Table I. Polarographic Half-Wave Potentials of α-haloacetophenone in Acetonitrile

ketone	$E_{1/2}$ /V
α-iodoacetophenone	- 0.33[a]
α-bromoacetophenone	- 0.66[a]; - 0.78[b]
α-chloroacetophenone	- 1.32[a]; - 1.49[b]
α-fluoracetophenone	- 1.85[b]

a - (Ag/AgCl sat) electrode as reference[12]
b - ($Ag/AgClO_4$, 0.1 M) electrode as reference[3b]

The magnitude of the half-wave potentials for reduction at mercury suggests that in the heterogeneous media the α-iodoacetophenone is a better electron acceptor than the other α-haloacetophenones which is in accordance with the mechanism proposed by Rubinstein and Kariv[13] involving the addition of an electron to a delocalized orbital on the carbonyl and halogen of the α-haloketones to form the anion radical. Thus molecules with low lying σ^* orbitals like the α-iodoketones should reduce most easily.

It is interesting to note that among the α-haloacetophenones, only α-iodoacetophenone has an appropriate reduction potential for reduction by a free radical chain process in a living system such as baker's yeast. Therefore α-iodoacetophenone may be used as a probe to investigate the performance of electron acceptors or radical inhibitors in this media.

Acknowledgement. We thank FAPESP and PADCT for financial support and CNPq for fellowship for M. Carvalho. We are very grateful to Dr. R.E. Bruns for his assistance in the elaboration of the manuscript.

References and Notes

1. (a) Servi, S.; *Synthesis*, **1990**, 1; (b) Santaniello, E.; Ferraboschi, P.; Grisenti, P.; Manzocchi, A. *Chem. Rev.*, **1992**, 92, 1071.
2. (a) Csuk, R.; Glanzer, B. I. *Chem. Rev.*, **1991**, 91, 49; (b) Faber, K. *Biotranformation in Organic Chemistry*, Springer-Verlag, Berlin, **1992**, pp 135-168.
3. (a) Tanner, D. D.; Singh, H. K.; Kharrat, A.; Stein, A. R. *J. Org. Chem.*, **1987**, 52, 2142; (b) Tanner, D. D.; Singh, H. K. *J. Org. Chem.*, **1986**, 51, 5182; (c) Tanner, D. D.; Stein, A. R. *J. Org. Chem.*, **1988**, 53, 1642; (d) Tanner, D. D.; Kharrat, A. *J. Org. Chem.*, **1988** 53, 1646.
4. (a) Ohno, A.; Kito, N. *Chem. Lett.* **1972**, 369; (b) Ohno, A.; Yamamoto, H.; Oka, S. *J. Am. Chem. Soc.*, **1981**, 103, 2041.
5. Adam, W.; Heil, M.; Hutterer, R. *J. Org. Chem.*, **1992**, 57, 4491.
6. Tanner, D. D.; Chen, J. J.; Chen, L.; Luelo, C. *J. Am. Chem. Soc.*, **1991**, 113, 8074.
7. Carvalho, M.; Okamoto, M. T.; Moran, P. J. S.; Rodrigues, J. A. R.; *Tetrahedron*, **1991**, 47, 2073.

8. **Baker's yeast reduction of α-iodoacetophenone with addition of m-dinitrobenzene.** DNB (218 mg, 1.30 mmol) was added with stirring at 30 °C to a mixture of baker's yeast (222 g) and water (127 ml). The ketone (1.56 g, 6.34 mmol) was added 30 minutes later and the stirring was continued at 30 °C for 24 hours. After this period the reaction mixture was saturated with sodium chloride and the products were extracted with chloroform in a liquid-liquid extractor during 48 hours. The following products were isolated by silica gel column chromatography using chloroform as eluent: **(-)-(R)-2-iodo-1-phenylethanol** (229 mg, 0.923 mmol, 15%), oil, $[\alpha]_D^{25}$ -34.0° (c 2.4, $CHCl_3$) (lit. $[\alpha]_D^{25}$ +36.3° (c 5.29, $CHCl_3$), S configuration, Soai, K.; Yamanoi, T.; Hikima, H. *J. Organomet. Chem.*, **1985**, 290, C23); I.R. (film) 3380, 3020, 2960, 1490, 760, 700 cm -1 ; NMR (80 MHz, CCl_4) δ 2.5 (br s, 1H, OH), 3.25 (dd, 1H, J = 8 and 12 Hz, CH_2), 3.45 (dd, 1H, J = 4,4 and 12 Hz, CH_2), 4.7 (dd, 1H, J = 4.4 and 8 Hz, CH), 7.25 (s, 5H, Ph); m/z (%) 248 (M^+, 14), 121 (100), 107 (98), 77 (96), 43 (56). **Acetophenone** (69.89 mg, 0.582 mmol, 9.2%), oil, spectral data were identical with that of the authentic sample. **1-phenylethanol** (122.3 mg, 1.00 mmol, 15.8%), oil, spectral data were identical with that of the authentic sample.
9. **Epoxidation of (-)-(R)-2-iodo-1-phenylethanol.** Iodohydrin (200 mg, 0.806 mmol) dissolved in 0.8 ml of ether was added to 11 ml of 2M NaOH aqueous solution at 22 °C. After stirring for 1 hour the mixture was saturated with Na_2SO_4 and extracted with pentane (3 x 5 ml) to give (+)-(R)-stirene oxide after solvent evaporation (63.3 mg, 0.527 mmol, 65%), oil, $[\alpha]_D^{25}$ + 38.8° (c 3.1, C_6H_6) (lit.[10] $[\alpha]_D^{25}$ + 42.2 (c 3.09, C_6H_6), NMR (80 MHz, CCl 4) δ 2.75 (dd, 1H, J = 3 and 6 Hz, CH_2), 3.10 (dd, 1H, J = 4 and 6 Hz, CH_2), 3.85 (dd, 1H, J = 3 and 4 Hz, CH), 7.40 (s, 5H, Ph).
10. (a) Imuta, M.; Kawai, K.; Ziffer, H. *J. Org. Chem.*, **1980**, 45, 3352; (b) Berti, G.; Bottari, F.; Ferrarini P. L.; Macchia, B. *J. Org. Chem.*, **1965**, 30, 4091.
11. (a) Furuichi, A.; Akita, H.; Matsukura, H.; Oishi T.; Horikoshi, K. *Agric. Biol. Chem.*, **1985**, 49, 2563; (b) Shieh, W. R.; Gopalan, A. S.; Sih, C.J.; *J. Am. Chem. Soc.*, **1985**, 107, 2993; (c) Nakamura, K.; Kawai, Y.; Nakajima, N.; Ohno, A. *J. Org. Chem.*, **1991**, 56, 4778; (d) Nakamura, K.; Kawai, Y.; Miyai, T.; Honda, S.; Nakajima, N.; Ohno, A. *Bull. Chem. Soc. Jpn.*, **1991**, 64, 1467.
12. The current-voltage curves for the polarographic reductions of the ketones were obtained with a Princeton Applied Research Model 264A. The solutions consist of anhydrous acetonitrile containing $(Bu)_4N^+ClO_4^-$ (0.1 M) and the reactant (0.01 M).
13. Rubinstein, I.; Kariv, E. *Tetrahedron*, **1976**, 32, 1487.