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A thermodynamic study of ketoreductase-catalyzed reactions 3. Reduction of 1-phenyl-1-alkanones in non-aqueous solvents

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Abstract

The equilibrium constants K for the reactions (1-phenyl-1-alkanone + 2-propanol = 1-phenyl-1-alkanol + acetone) in the solvents *n*-pentane and *n*-hexane have been determined by using gas chromatography at the temperature 298.15 K. The 1-phenyl-1-alkaones included in this study were: 1-phenyl-1-ethanone, 1-phenyl-1-propanone, 1-phenyl-1-butanone, 1-phenyl-1-pentanone, 1-phenyl-1-hexanone, and 1-phenyl-1-heptanone. The equilibrium constants for the reaction involving 1-phenyl-1-ethanone were measured in the solvent *n*-hexane as a function of temperature (288 K to 308 K). The calculated thermodynamic quantities for the 1-phenyl-1-ethanone reaction at $T = 298.15$ K are: $K = 0.2177 \pm 0.0018$; the standard molar Gibbs free energy change, $\Delta_r G^\circ_m = (3.78 \pm 0.02)$ kJ · mol^{-1}, the standard molar enthalpy change, $\Delta_r H^\circ_m = (4.53 \pm 0.87)$ kJ · mol^{-1}, and the standard molar entropy change, $\Delta_r S^\circ_m = (2.5 \pm 2.9)$ J · K^{-1} · mol^{-1}. The equilibrium constants of 1-phenyl-1-alkanone with an odd number of carbons in alkyl side chain are higher than the equilibrium constants of the preceding 1-phenyl-1-alkanone having an even number of carbons in the side chain and follow a zig-zag pattern with increasing carbon number in the alkyl side chain.
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1. Introduction

In recent years, the use of biocatalysis for organic synthesis [1,2] in non-aqueous media has become an attractive alternative to traditional chemical synthetic methods. The use of enzyme-catalyzed reactions has made it possible to obtain desired stereoselective products which are useful intermediates in the pharmaceutical, agrochemical, and perfume industries [3–5]. Lipase-catalyzed reactions in organic solvents have been used for the stereoselective resolution of racemic mixtures [4,6–8]. Ketoreductase catalyzed reduction of carbonyl groups [9–16] have been used for the synthesis of chiral secondary alcohols which are useful intermediates for pharmaceuticals, agrochemicals, and liquid crystals.

There have been several studies from our laboratory dealing with the thermodynamics of enzyme-catalyzed reactions in organic solvents [17–22]. The thermodynamic results obtained in these studies are essential for the basic understanding of the energetics of these reactions and also for the practical utilization of enzyme-catalyzed reduction reactions of 1-phenyl-1-alkanone in non-aqueous solvents.

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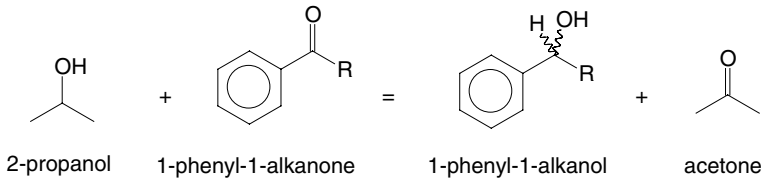

FIGURE 1. The structures of the substances involved in the reduction of 1-phenyl-1-alkanones {reactions (1) to (6)}, where R = CH_3, C_2H_5, C_3H_7, C_4H_9, C_5H_{11}, or C_6H_{13}.

In the present investigation, we report results of equilibrium measurements for the following ketoreductase-catalyzed reduction of 1-phenyl-1-alkanone reactions (see figure 1).

1-phenyl-1-ethanone(soln) + 2-propanol(soln) = 1-phenyl-1-ethanol(soln) + acetone(soln), (1)

1-phenyl-1-propanone(soln) + 2-propanol(soln) = 1-phenyl-1-propanol(soln) + acetone(soln), (2)

1-phenyl-1-butanone(soln) + 2-propanol(soln) = 1-phenyl-1-butanol(soln) + acetone(soln), (3)

1-phenyl-1-pentanone(soln) + 2-propanol(soln) = 1-phenyl-1-pentanol(soln) + acetone(soln), (4)

1-phenyl-1-hexanone(soln) + 2-propanol(soln) = 1-phenyl-1-hexanol(soln) + acetone(soln), (5)

1-phenyl-1-heptanone(soln) + 2-propanol(soln) = 1-phenyl-1-heptanol(soln) + acetone(soln). (6)

Here "soln" denotes the organic solvent, *n*-pentane or *n*-hexane, have been used in this study.

A small amount of β-nicotinamide-adenine dinucleotide (reduced), {NAD(red)} is required for catalytic activity of this ketoreductase. As described in our previous papers [21,22], the ketoreductase catalyzed reactions proceed in two steps. In the first step, the 1-phenyl-1-alkanone is reduced to the corresponding 1-phenyl-1-alkanol and NAD(ox). Then in the second step, the NAD(red) is regenerated by reduction of NAD(ox) in presence of 2-propanol:

1-phenyl-1-alkanone(soln) + 2NAD(red) = 1-phenyl-1-alkanol(soln) + 2NAD(ox) (7)

2NAD(ox) + 2-propanol(soln) = 2NAD(red) + acetone(soln). (8)

Thus, the combination of equations (7) and (8) leads to an overall reaction for the reduction of the 1-phenyl-1-alkanone:

1-phenyl-1-alkanone(soln) + 2-propanol(soln) = 1-phenyl-1-alkanol(soln) + acetone(soln). (9)

The principal aim of this study was to determine the equilibrium constants for the above 1-phenyl-1-alkanone reactions as a function of the number of carbons in the alkyl chain. The chirality of these reactions has also been investigated. The chiral analysis of the 1-phenyl-1-alkanols in reactions (1) to (6) showed that the 1-phenyl-1-alkanols produced in these reduction reactions were racemic mixtures (equal mole fractions) of both the (*R*)-(+)-1-phenyl-1-alkanol and the (*S*)-(−)-1-phenyl-1-alkanol.

2. Experimental

2.1. Materials

The substances used in this study, their Chemical Abstract Service (CAS) registry numbers, empirical formulae, molar masses, sources, and purities as determined by gas chromatography (g.c.) are given in table 1. The mass fraction of water listed in table 1 for the compounds involved in these reactions and the internal standard, 1-hexanol were determined by Karl Fischer titration [23]. The enzyme used in this study was ketoreductase (EC 1.1.1.2) from BioCatalytics, Inc., Pasadena, CA. This enzyme was prepared from a recombinant bacterial source and gene expressed in *E. coli* and required NAD(red) catalytic activities.

2.2. Chromatography and quantitative analysis

The quantitative analysis of the reactants and products was carried out by using a Hewlett-Packard (HP) 5890 g.c. (Agilent Technologies, Wilmington, DE, USA),[1] equipped with a flame ionization detector (FID) and a fused silica Phenomenex ZB-FFAP capillary column (30 m long, 0.53 mm i.d., 0.53 μm thick film coating). The injector and detector temperatures were 523 K and 543 K, respectively; the head pressure of the helium carrier gas was $P = 283$ kPa. The initial column temperature of 313 K was held for 3 min and then raised to $T = 513$ K at a rate of $0.333\ \mathrm{K \cdot s^{-1}}$ and held at $T = 513$ K for 5 min. Under these conditions, the chromatographic peaks of the compounds of interest and the internal standard were well separated.

Enantioselective separation of the (*R*)-(+)-1-phenyl-1-alkanol and (*S*)-(−)-1-phenyl-1-alkanol was carried out with another HP 5890 g.c. equipped with an FID and a fused silica γ-cyclodextrintrifluoroacetyl capillary column

[1] Certain commercial equipment, instruments, or materials are identified in this paper to specify the experimental procedures adequately. Such identification is not intended to imply recommendation or endorsement by the National Institute of Standards and Technology, nor is it intended to imply that the materials or equipment identified are necessarily the best available for the purpose.

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