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A NOVEL ENZYME MIMIC FOR THIAZOLIUM-CATALYZED α-KETOACID DECARBOXYLATION

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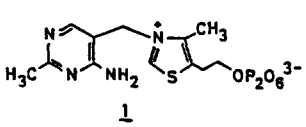
Abstract: The covalent combination of the thiazolium heterocycle of thiamine with macrotricyclic quaternary ammonium receptor units yields the enzyme mimics 3a,b, which show enhanced substrate selectivity and catalytic activity in decarboxylations of α-ketoacids compared to simpler salts lacking the receptor substructure.

In contrast to the great variety of enzyme models for hydrolytic or redox reactions, artificial mimics of biological carbon-carbon bond forming or breaking systems are still rare. A particularly instructive example is provided by thiamin-pyrophosphate (TPP 1)-dependent enzymes which feature a rich chemistry based on the unique carbanion stabilizing properties [1] of the thiazolium substructure of 1. While simple [2,3] and more sophisticated [4,5] models were developed which could promote or slightly accelerate bond breaking like the oxidative decarboxylation of α-oxocarboxylic acids, or bond forming as in benzoin condensations other variants of biological TPP dependent reactions (pyruvate decarboxylase, transketolase, phosphoketolase) resisted modelling so far. The accumulating evidence for the participation of the pyrimidine moiety of 1 [6] and for a distinct steric relationship of the substrate covalently attached to the coenzyme [7] in the initial stages of the catalytic sequences mandates precise control over their relative orientations. A first step in this direction, which met with limited success, involved the covalent combination of thiazolium heterocycles with



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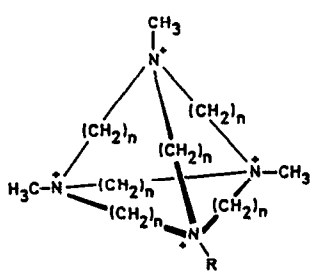
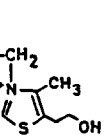


	n	R
2a	6	-CH3
2b	8	
3a	6	-CH2-C6H4-CH2-
3b	8	

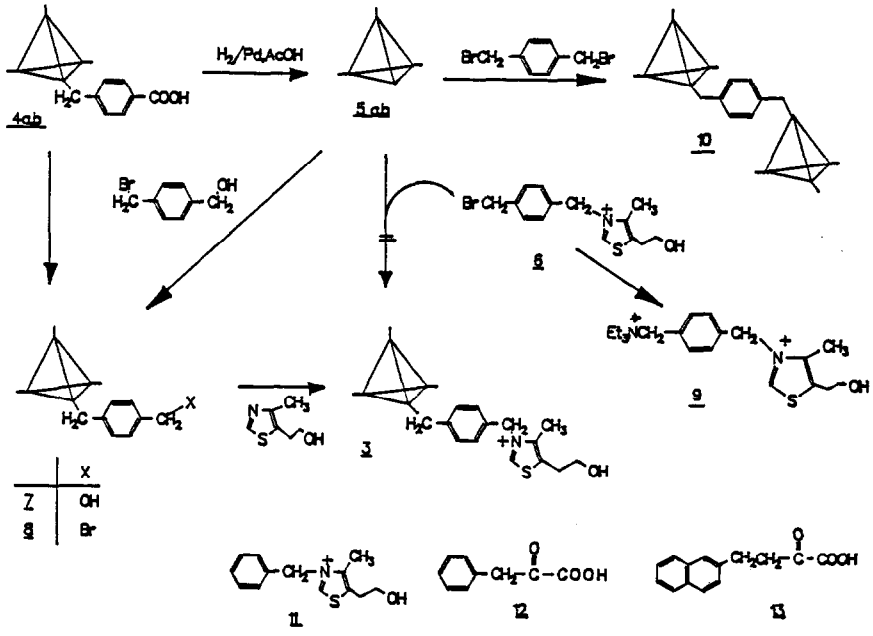


hydrophobic host molecules [4,5]. However, substrate binding into the cavity of the host leading to favorable proximity of the reactive substructure to the catalytically active thiazolium site could be hampered by self saturation i.e. by the penetration of the thiazolium moiety into the cavity resulting in inhibition of substrate binding.

A receptor unit bearing a permanent positive charge like our macrotricyclic quaternary ammonium hosts 2 [8], could avoid this problem. Thus in compound 3 well defined [9] stereochemical relations are set up due to the strong electrostatic repulsion of receptor and catalytic functionalities assisted by a rather rigid linker unit.

This combination may demonstrate additional advantages of its design since positive charges [10] as well as a hydrophobic vicinity of the thiazolium moiety [11] both have been proven beneficial to catalysis, rendering 3a and 3b promising candidates as enzyme models for TPP-dependent reactions. The synthesis of 3 seemed straightforeward starting with the monofunctionalized tetrahedral hosts 4 (Scheme 1) which had been prepared for a different purpose [12]. At that time suitable conditions for the reduction of the

Scheme 1: Series a and b correspond to the substructure 2 with n = 6 or 8, respectively.

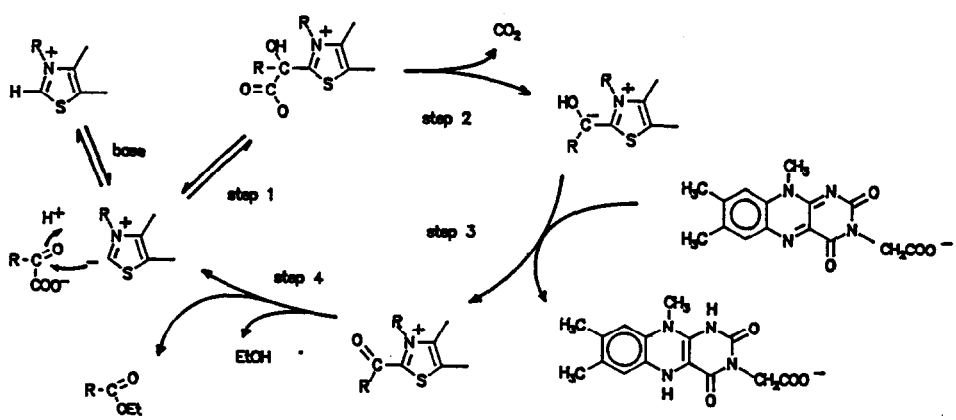


highly charged and in most aprotic solvents totally insoluble carboxylic acid 4 to the corresponding alkohol 7 had not been discovered, so that the cleavage of the benzylammonium bond to produce the tert. amine 5a appeared to be a resonable alternative. Though this conversion was finally achieved by hydrogenolysis, the subsequent quaternization of 5 by 6 failed to yield the target compound 3a, most likely owing to the unfavorable electrostatic repulsion between the reaction partners. As a bypass 5 was cleanly quaternized with 4-bromomethylbenzylalkohol to give 7, which in turn reacted with conc. HBr to yield the benzylic bromide 8. This compound could also be obtained by reaction of xylylene dibromide with 5, but the reaction product had to be separated from 10 by gel filtration, which resulted in partial hydrolysis of 8 to 7. The final step of this sequence used standard procedures to quaternize the commercial thiazole 12 with 8, giving the end product 3a in 32% overall yield. The series b involving the bigger tetrahedral host used the direct reductive transformation of 4b to 7b, which improved the overall yield to 50%.

For comparison purposes thiazolium salt 9 lacking the receptor function while retaining the positive charge nearest to the thiazole was prepared from 6 and triethylamine.

To test the influence of the tetrahedral anchor group on the reactivity of the thiazolium moiety the oxidative decarboxylation of α-oxoacids was probed. This is one of the most simple thiazolium catalyzed reactions following the mechanistic route shown in Scheme 2. In ethanol this reaction does not suffer from the complications due to thiazolium ring opening and it can be easily followed by the absorption change of the flavin [13]. Since decarboxylation, oxidation of the active aldehyde and solvolytic cleavage of the acylthiazole (steps 2-4) are much faster than the initial attack of the catalyst onto the oxoacid, any advantage of the model design should be observable as a rate

Scheme 2



acceleration of this multistep reaction. Relative initial rate data for the hydrophobic oxoacids 12 and 13 are shown in Table 1.

Table 1: Initial rates ($v_{0\ rel}$) for the oxidative decarboxylations of the substrates (50 mM substrate DBU-salt, 5 mM catalyst, 3.3 mM DBU-base 0.61 mM lumiflavin-3-acetic acid in degassed ethanol, T=299K).

catalyst / substrates	11	9	3a	3b
12	1	1.7	1	2.3
13	1	1.7	21	27

These data reveal the expected enhanced catalytic power of the thiazolium salt bearing additional positive charges and a marked dependance on substrate structure. The increased activity of the catalysts possessing an additional receptor function with the larger oxoacid 13 parallels the better matched distance relationship as shown by CPK-models.

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