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A γ-CYCLODEXTRIN THIAZOLIUM SALT HOLOENZYME MIMIC FOR THE BENZOIN CONDENSATION

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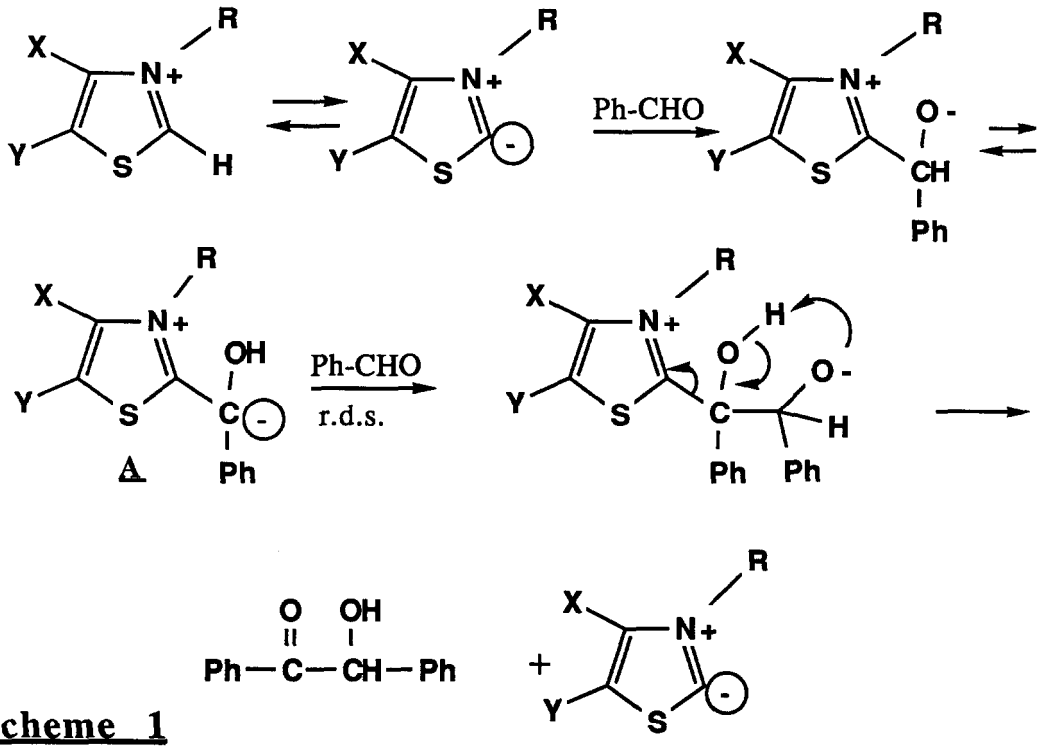
Abstract: *Several thiazolium salts have been attached to a C-6 carbon of γ-cyclodextrin. They catalyze the benzoin condensation of benzaldehyde very effectively.*

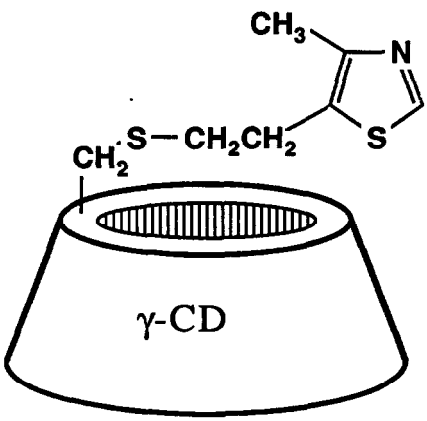
Thiazolium salts can catalyze the benzoin condensation.[1] The mechanism (*Scheme 1*) involves the formation of the C-2 anion in the thiazolium ring, which then acts as a pseudo cyanide anion by the normal mechanism.[2] In fact it was studies on a benzoin-type condensation, as a model for the normal biological reactions catalyzed by thiamine pyrophosphate coenzyme, that led to the elucidation of the biochemical mechanism of thiamine action.[3]

In biochemical reactions, thiamine pyrophosphate is bound noncovalently to apoenzymes; the resulting holoenzymes are involved in many key reactions of metabolism. It was attractive to try to mimic such holoenzymes by covalently linking thiamine or other thiazolium salts to a suitable binding group.

As we have described previously, the linkage of β-cyclodextrin to several thiazolium salts produces catalysts (e.g. 8-10) that indeed use substrate binding to increase their effectiveness.[4] Thiazolium-catalyzed reactions involving a single benzaldehyde molecule were promoted by the binding of the phenyl ring into the cyclodextrin cavity. Both tritium exchange of the aldehyde proton and oxidation of the benzaldehyde to benzoic acid were such promoted reactions, but the β-cyclodextrin catalyst was not very effective at catalyzing the benzoin condensation. Molecular models indicated that the second benzaldehyde could not fit into a β-cyclodextrin cavity already occupied by one phenyl group in the thiazolium adduct A. As we pointed out, better catalysis of the benzoin condensation would require a larger cavity.[4] Subsequently, Diederich prepared a mimic with a thiazolium salt covalently linked to a synthetic binding cavity.[5] He showed that this molecule did indeed show some improvement in the benzoin condensation catalysis, raising the yield from 27% with a simple thiazolium salt to 93% with the salt linked to a binding group.



Scheme 1



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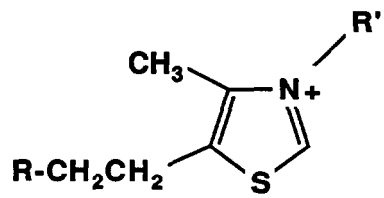

2 R = γ-CD, R' = Et
3 R = γ-CD, R' = CH_2Ph
4 R = γ-CD, R' = CH_2-β-naphthyl
5 R = OH, R' = Et
6 R = OH, R' = CH_2Ph
7 R = OH, R' = $CH_2C_6H_4$-*p*-SO_3-
8 R = β-CD, R' = Et
9 R = β-CD, R' = CH_2Ph
10 R = β-CD, R' = $CH_2C_6H_4$-*p*-SO_3-

We have recently reported that the benzoin condensation of two benzaldehyde molecules is catalyzed by γ-cyclodextrin, but inhibited by β-cyclodextrin.[6] It is also promoted by aqueous solutions known to increase hydrophobic effects, consistent with the prediction that the two phenyl groups can pack together in the transition state for the benzoin condensation.[6] Thus it was attractive to attach a thiazolium salt to γ-cyclodextrin, whose cavity is large enough to accomodate two phenyl groups, to combine the binding and catalytic functions for this reaction. As hoped, such catalysts prove to be particularly effective.

γ-Cyclodextrin was converted to its 6-sulfonate ester with 2-naphthalenesulfonyl chloride, by the procedure of Ueno.[7] Then displacement with 4-methyl-5-(2-mercaptoethyl)thiazole with Cs_2CO_3 in DMF gave the cyclodextrin-thiazole derivative 1 in 53% yield, similar to the results in our earlier β-cyclodextrin work.[4] Again following our earlier work,[4] we converted this to the three thiazolium salts 2-4 by alkylation; the compounds were purified by ion exchange chromatography.[8] For comparison we used the corresponding thiazolium salts 5-7 without a cyclodextrin binding group, and the series 8,9 with a β-cyclodextrin group, both of which we had studied previously.[4] Kinetic studies were performed in aqueous pH 8 phosphate buffer (0.5 M) with 10% added DMSO at 50°. Initially the concentration of benzaldehyde was 100 mM, and of various catalysts 20 mM. Rates were followed by hplc analysis, as we have described,[6] and all reactions were run in triplicate. The reactions under these conditions all proved to be second-order in benzaldehyde, and pseudo-second-order rate constants were obtained.

The kinetic results are listed in Table 1. For simple thiazolium salts the catalysis is more effective with N-benzyl groups [compounds 6 and 7] than with an alkyl group [compound 5]. This inductive effect had been noted by us in our earliest work.[2] Attachment of a β-cyclodextrin group to the thiazolium salts [compounds 8 and 9] leads to about a doubling in the rate. Addition of the larger γ-cyclodextrin group, which can hold both benzaldehydes, increases the rate by about seven fold [compounds 2 and 3] . Although naphthalene groups can bind particularly well into γ-cyclodextrin, the naphthyl catalyst [compound 4] has a rate comparable to that of the benzyl derivative [compound 3]. The Table also shows that most of these thiazolium salts are more effective than is CN^-, the classic benzoin condensation catalyst.

We also examined the effect of added β-cyclodextrin and γ-cyclodextrin on the rates of catalysis by the simple thiazolium salts (5, 6, 7). As we had observed for cyanide catalysis,[6] the β-cyclodextrin was a mild inhibitor while γ-cyclodextrin led to about a two-fold increase in the rate.

We checked the kinetic order more extensively by varying the initial concentrations, not just fitting the kinetic data. With the simple N-benzylthiazolium salt (6), the calculated second-order rate constant stayed constant, within experimental error, over an initial benzaldehyde concentration range of 40 mM to 200 mM. However, with the corresponding γ-cyclodextrin derivative (3) the rate constant of 358 $M^{-1}min^{-1}$ at 40 mM, and 353 at 100 mM, fell to 231 at 150 mM initial benzaldehyde concentration. This is expected if the rate-determining step is reaction of the thiazolium adduct A with another benzaldehyde that can bind into the cyclodextrin cavity; at high benzaldehyde concentration such binding will lead to kinetic saturation, and a less than

second order concentration dependence. The observed kinetic order in catalyst for the three thiazolium salt series all fell in the region 0.5-0.7 when the catalyst concentration was increased from 10 mM to 40 mM. It is not yet clear whether self association is the reason that the kinetic order is apparently less than 1.0 .

Even with a relatively flexible link between the γ-cyclodextrin group and the thiazolium catalytic system, compounds such as 3 are outstanding catalysts for the benzoin condensation. It can be expected that with a more rigid link, and the correct fixed geometry, the catalytic effects could become yet stronger.

Table 1. Rate Constants for the Benzoin Condensation[a]

Catalyst	$10^4\ k_2$[b], $M^{-1}\ min^{-1}$	k_{rel}[c]
thiaz-Et (5)	1.5 ± 0.3	1.00
thiaz-Bn (6)	31 ± 15	20
thiaz-$BnSO_3$ (7)	67 ± 8	45
β-CD-thiaz-Et (8)	2.6[d]	2
β-CD-thiaz-Bn (9)	77 ± 10	50
γ-CD-thiaz-Et (2)	13 ± 2	9
γ-CD-thiaz-Bn (3)	220 ± 28	150
γ-CD-thiaz-Naphth (4)	204 ± 25	140
Cyanide ion	9.1[d]	6

a. Under the conditions described in the text. b. Second order in benzaldehyde. Errors are the standard deviations from three runs. c. Rate constant relative to compound 6. d. Only one run.

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