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Polymer-bound Thiamine models

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SUMMARY

This thesis describes the synthesis of various polymer-bound Thiazolium salts, which can serve as models of the coenzyme thiamine. The catalytic activity of these polymers (**1**) and their low molar mass analogues were examined in the condensation of benzaldehyde to benzoin (Scheme 1), which was selected as a model reaction of thiamine mediated carbon-carbon bond formation. It was our aim to obtain an insight into the effects of the polymer support, the structure of the immobilized thiazolium moiety and the employed reaction conditions, in order to develop a polymer-bound thiazolium salt with both high catalytic activity and catalyst stability in carbon-carbon bond formation processes. A valuable spin-off of this study was the insight gained in the mechanism of thiazolium salt-catalyzed acyloin condensation reactions.

In **Chapter 1**, the subject of this thesis is discussed in the broader context of polymeric models of reactive biological systems, and the possible polymer effects are considered. Furthermore, the potential scope of synthetic applications of thiazolium salts in preparative chemistry is presented.

Since it was our aim to study the role of the polymer support on the activity of the pendant thiazolium salt moieties into detail, the mechanism of the model reaction was studied. In **Chapter 2**, the kinetic results of the benzoin condensation reaction are discussed. They indicate that the only role of the cocatalyst is to generate the thiazolium ylid, which is the true catalytically active species. In later experiments (Chapter 3), this idea was verified by the fact that a polymer-bound thiazolium salt (**1a**), upon pretreatment with a cocatalyst solution, exhibited undiminished catalytic activity in the absence of the basic cocatalyst. Furthermore, it was found that thiazolium ylids of the low molar mass model of **1a** (P= Ph) tend to dimerize, to yield the so called ylid "dimers", which have a higher catalytic activity than the corresponding "monomers". It was found that the extent of ylid

dimerization is critically dependent upon the nature of the substituent bound to the nitrogen of the thiazole heterocycle. For example, it was found that N-alkyl thiazolium salts (1b, 1d, P = Ph) did not dimerize under the employed reaction conditions (Chapters 4-5).

In Chapter 3, the immobilization of thiazolium salts on macroporous styrene-divinylbenzene copolymers is described. These supports were selected because of their facile chemical modification, permanent porosity (independent of the employed reaction medium) and commercial availability. When such a support was loaded with 0.40 mmol Thiazolium salt (Th)/g (a low degree of functionalization), it was found that the catalytic sites were isolated, thereby preventing possible ylid dimerization. This was considered as one of the reasons of the nearly two-fold decrease in activity of such a polymer (1a) with respect to its low molar mass analogue. A second reason for the observed lower activity of 1a had its origin in steric hindrance of the polymeric carrier on the supported reaction.

In Chapter 4, it is shown that the extent of site isolation could be decreased by increasing the degree of catalyst loading, whereby the extent of ylid dimerization on the polymer support increased. The steric influence of the polymeric carrier could be diminished by immobilizing the thiazolium salt moieties via a spacer chain (1c, 1d). Attachment of thiazolium salts to flexible linear polystyrenes was thought to serve both purposes simultaneously. Contrary to expectation, it was found that the catalytic activity of the polymers in these experiments decreased rather than increased. These results could be explained by invoking the assumption that the polymer-bound intramolecular ylid dimers are inactivated by entropic stabilization of a non-catalytic dimeric intermediate. This hypothesis was confirmed in a low molar mass model study. Consequently, it was concluded that the prevention of polymer-bound ylid dimer formation is a prerequisite for designing active polymer-bound thiamine models. In agreement with the aforementioned, it was found that immobilization of a thiazolium salt via a spacer chain is only advantageous if the immobilized thiazolium salt is not prone to ylid dimerization (1d).

Chapter 5 describes a simple and efficient new method for immobilization of such a thiazolium salt on macroporous polystyrene resins via a dimethylene spacer (1b). This method involves a selective hydrobromination of pendant unreacted vinyl groups which are present on this class of polymer-supports. Polymeric catalysts of these type had a activity which was nearly equal to that of the low molar mass analogue, demonstrating that the negative steric influence of the polymer support can be effectively reduced by a spacer-chain linkage.

The stability of two selected macroporous polystyrene-bound thiazolium salts in the batch-wise reutilization experiments or in the continuous production of benzoin in a steady-state flow stirred-tank reactor, is discussed in Chapter 6.

The stability of 1a (low Th content) in such experiments was disappointing. This is most probably due to a side reaction involving the hydroxyethyl group of the thiazole heterocycle, since, when the hydroxyl function of the catalytic moieties was protected as an ether, as in 1d, the stability of the polymeric catalyst was markedly improved. Preliminary results have shown that, once the immobilized thiazolium salts of type 1d are converted into the corresponding ylids, the continuous production of benzoin could, in principle, be performed in the absence of cocatalyst. It can therefore be concluded that immobilized thiazolium salts like 1d are promising catalysts for the continuous production of acylolins at very low base concentrations.