270 MHz NMR ($CDCl_2$) δ 7.40-7.30 (5 H, m), 6.64 (1 H, d, J = 15.4 Hz), 6.43 (1 H, d, J = 15.4 Hz), 4.83 (1 H, dd, J = 8.4, 5.5 Hz), 4.65 (1 H, d, J = 11.0 Hz), 4.61 (1 H, d, J = 11.0 Hz), 3.47 (1 H, dd, J = 10.5, 1.1 Hz), 2.79 (1 H, dq, J = 10.5, 7.1 Hz), 2.62-2.48 (1 H, m), 1.94 (1 H, s), 1.82-1.62 (3 H, m), 1.49-1.19 (2 H, m), 1.33 (3 H, s), 1.32 (3 H, d, J = 6.8 Hz), 1.20 (3 H, d, J = 7.1 Hz), 1.05 (3 H, d, J = 6.5 Hz), 0.89 (3 H, t, J = 7.4 Hz).

***d,l*-Methynolide (38).** Enone alcohol **36** (3.4 mg, 0.0085 mmol) was debenzylated according to the method of Yonemitsu et al.[15c] with 2,6-dichloro-2,5-dicyano-1,4-benzoquinone (DDQ, 12 mg) and water (0.03 mL) which were combined in CH_2Cl_2 (0.6 mL). After stirring for 4 h, 1,4-cyclohexadiene (0.1 mL) was added to convert the excess DDQ into the dihydroquinone. The reaction mixture was diluted with ether (20 mL) and washed with saturated $NaHCO_3$ (5 × 3 mL) to remove the hydroquinone. Purification by preparative thin-layer chromatography (30% ethyl acetate-hexane) gave synthetic *d,l*-methynolide (2.0 mg, 77%).

38. Solid, mp dec 189-194 °C (crystallized from ether-hexane); MS, no peak match, parent; M - H_2O, 294.1827, calcd = 294.1831, error = 1.4 ppm formula = $C_{17}H_{28}O_5$; IR (neat, cm^{-1}) OH, 3620, C=O, 1745, C=O, 1705, C=C-C=O, 1645; 500 MHz NMR ($CDCl_3$) δ 6.59 (1 H, d, J = 16.3 Hz), 6.34 (1 H, d, J = 16.3 Hz), 4.78 (1 H, dd, J = 11.2, 2.2 Hz), 3.58 (1 H, d, J = 10.3 Hz), 2.61 (1 H, dq, J = 10.3, 6.9 Hz), 2.60-2.51 (1 H, m), 1.99 (1 H, s), 1.91 (1 H, ddq, 14.2, 2.2, 6.9), 1.68-1.48 (3 H, m), 1.40-1.15 (2 H, m), 1.38 (3 H, s), 1.34 (3 H, d, J = 6.9 Hz), 1.20 (3 H, d, J = 6.9 Hz), 1.01 (3 H, d, J = 6.3 Hz), 0.91 (3 H, t, J = 7.3 Hz).

***d,l*-C_{10}-*epi*-Methynolide (37).** Hydroxy enone benzyl ether **35** (2.4 mg, 0.0062 mmol) was debenzylated under exactly the same conditions as described for debenzylation of **36**. The product was purified by PTLC (30% ethyl acetate-hexane) to give *d,l*-C_{10}-*epi*-methynolide (1.3 mg, 68%).

37. Solid, mp 165-166 °C (crystallized from ether-hexane); MS, exact mass calcd for $C_{17}H_{28}O_5$ = 312.1929, found 312.1923, error = 2 ppm; IR (neat, cm^{-1}) OH, 3460, C=O, 1720, 1650; 500 MHz NMR ($CDCl_3$, ppm) 6.67 (1 H, d, J = 15.3 Hz), 6.46 (1 H, d, J = 15.3 Hz), 4.86 (1 H, dd, J = 8.1, 5.8 Hz), 3.58 (1 H, br d, J = 10.4 Hz), 2.67 (1 H, dq, J = 10.4, 6.8 Hz), 2.56 (1 H, ddq, J = 6.9, 3.6, 7.1), 1.95 (1 H, br s), 1.82-1.74 (2 H, m), 1.67-1.49 (2 H, m), 1.52-1.32 (2 H, m), 1.36 (3 H, s), 1.33 (3 H, d, J = 6.8 Hz), 1.23 (3 H, d, J = 7.1 Hz), 1.01 (3 H, d, J = 5.9 Hz), 0.91 (3 H, t, J = 7.4 Hz).

Acknowledgment. This work was supported by the National Science Foundation.

Catalytic Cyclophanes. 4. Supramolecular Catalysis of Benzoin Condensations by a Thiazolium Cyclophane[1,2]

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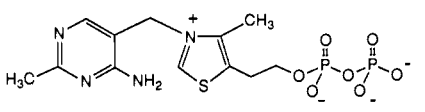
Abstract: As a model for thiamine pyrophosphate dependent ligases, the thiazolium-bridged cyclophane **1** was prepared in a 14-step synthesis. Compound **1** was designed to catalyze the benzoin condensation, and its macrocyclic cavity provides in aqueous and organic solutions a binding site for the two benzaldehyde molecules that react to give benzoin. In macrobicycle **1**, the thiazolium residue is connected to the binding site by two side arms, which limits the number of unproductive conformations of the catalytic residue. As a catalyst for the benzoin condensation, **1** is superior to the thiazolium derivative **3** without a macrocyclic binding site. For benzoin condensations catalyzed by **1**, high turnovers and very high yields in benzoin formation, catalysis of the back reaction, and sigmoid saturation kinetics plots suggesting the formation of a 1:2 Michaelis-Menten complex are observed. The surprisingly high catalytic activity of the thiazolium-bridged diphenylmethane spacer **2** is best explained by its potential for binding benzaldehyde at its niche binding site. The thiazolium-catalyzed benzoin condensation is investigated as a function of solvent polarity, of base concentration, and of buffer strength. Cyclophane **1** catalyzes the furoin condensation. Specific large enhancements of the H/D-exchange rate at C-2′ of the thiazolium ring in **1** are observed in aqueous buffers. They are best explained by a micropolarity effect of the cavity of **1** on the (kinetic) acidity of the proton at this position.

In recent years, novel reagents and catalysts for chemical processes have been developed by covalently anchoring coenzymes and coenzyme analogues to the binding sites of cyclodextrins,[3a] synthetic receptors,[3b-e] and semisynthetic enzymes.[4] Thiamin pyrophosphate (TPP, **1**)[5] participates as the essential cofactor in



TPP

numerous enzymatic reactions involving formation and breakage of carbon-carbon bonds, e.g., in the transketolase-catalyzed formation and cleavage of carbohydrates in the pentose phosphate pathway.[6] Since the pioneering work of Breslow in the 1950s,[7] it is well established that the catalytic action of TPP is mainly due to the thiazolium ring and that simple thiazolium ions catalyze many of the enzymatic transformations, e.g., acetoin condensations, in the absence of the enzymes.[8-11] The pyrophosphate part of

(1) Dedicated to the memory of Professor Emil T. Kaiser.

(2) For parts 1-3 in this series, see: (a) Preliminary communication of parts of this work: Lutter, H.-D.; Diederich, F. *Angew. Chem.* **1986**, *96*, 1125-1127; *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 1125-1127. (b) Diederich, F.; Schürmann, G.; Chao, I. *J. Org. Chem.* **1988**, *53*, 2744-2757. (c) Jimenez, L.; Diederich, F. *Tetrahedron Lett.* **1989**, *30*, 2759-2762.

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Scheme I

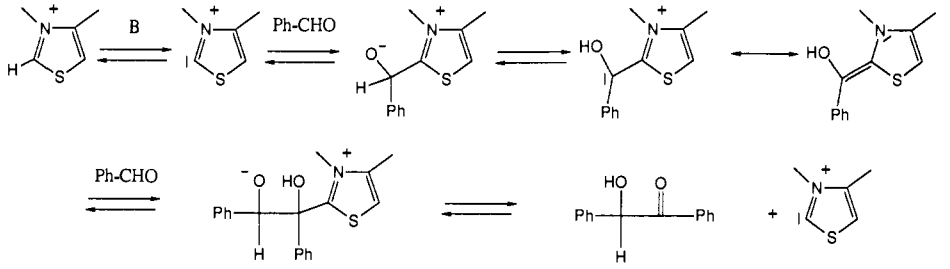
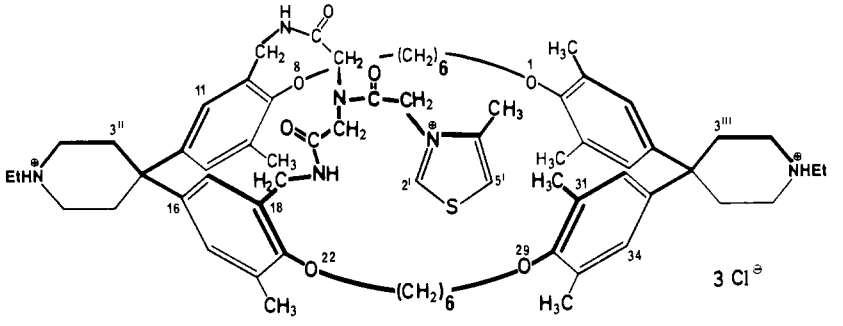
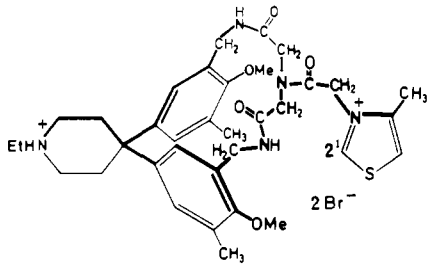


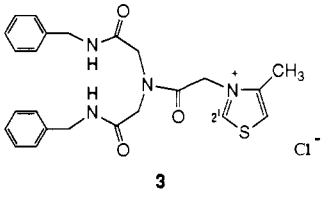
Chart I



1[19]



2



3

TPP is mainly responsible for the binding of the cofactor via Mg^{2+} complexes to the enzyme active sites, while the role of the pyrimidine ring still remains unclear.[5,7b,12,13] The pyrimidine ring could activate the enzyme-bound coenzyme through desolvation by preventing water from penetrating into the active site. It has been shown that the activity of TPP analogues very strongly depends on the polarity of the environment and that catalyzed reactions proceed faster in solvents less polar than water.[14,15]

Since the formation and cleavage of carbon–carbon bonds are key conversions in organic chemistry, we became interested in exploring the supramolecular catalysis of the benzoin condensation (Scheme I[16]) by the novel thiazolium-functionalized cyclophane **1**.[2a] Previously, thiazolium micelles[17] and thiazolium cyclodextrins[18] had been investigated as synthetic catalysts with a binding and reactive site. With its long C_6 chains between the two diphenylmethane spacers, compound **1** provides a binding cavity large enough to incorporate the two benzaldehyde molecules that react to give benzoin. A thiazolium residue is connected by two side arms to the macrocyclic binding site. The double fixation atop the cavity was designed to ensure the location of the catalytic residue in favorable proximity to the aldehyde molecules in the supramolecular complex and to limit its number of unproductive conformations. Compounds **2** and **3** without macrocyclic binding sites were designed to analyze in comparative studies the specific activation of the thiazolium ring at the apolar macrocyclic binding site of cyclophane **1**. In **2** and **3**, the thiazolium rings are subject to the same electronic activation as in **1**.

In this paper, the synthesis of the thiazolium derivatives **1–3** is described. The activities of these compounds in benzoin condensations are compared under a variety of reaction conditions. Cyclophane **1** is shown to be a very efficient model for TPP-dependent ligases. H/D-exchange studies demonstrate a specific activation of the thiazolium ring by the apolar binding site of **1**.

Synthesis and Characterization of the Thiazolium Derivatives 1–3. For the preparation of macrobicyclic derivative **1**, the dibromo[8.1.8.1]tetraoxaparacyclophane **4**[2b] was allowed to react with copper(I) cyanide in dimethylformamide to give the dinitrile **5** (86%) which was reduced (BH_3·THF) to the corresponding tetramine **6** (86%). Cyclization of **6** and the bis(pentafluorophenyl ester) **7**[2b] afforded the macrobicyclic system **11** in 23% yield.

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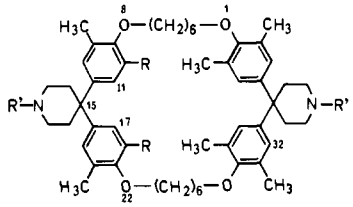
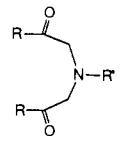
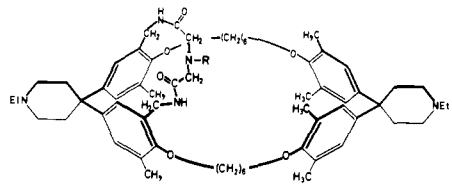
(19) The numbering of the atoms in the drawings is used in the description of the ^1H NMR spectra in the Experimental Section. This numbering differs from the numbering used in the systematic nomenclature of the macrobicycles.



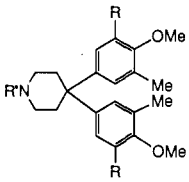
	R	R' [19]
4	Br	Ac
5	CN	Ac
6	CH_2NH_2	Et

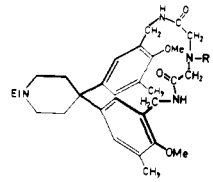


	R	R'
7	C_6F_5O	$COOCH_2C_6H_5$
8	$C_6H_5CH_2NH$	$COOCH_2C_6H_5$
9	$C_6H_5CH_2NH$	H
10	$C_6H_5CH_2NH$	$COCH_2Br$



	R [19]
11	$COOCH_2C_6H_5$
12	H
13	$COCH_2Br$





	R	R'
14	Br	Ac
15	CN	Ac
16	CH_2NH_2	Et

	R
17	$COOCH_2C_6H_5$
18	H
19	$COCH_2Br$

Catalytic deprotection (H_2, Pd/C, 10%) yielded the triamine **12** (95%). The reaction of **12** with α-bromoacetyl bromide gave the bromomethyl derivative **13** (37%). Reaction of the dihydrobromide of **13** with an excess of 4-methylthiazole followed by ion-exchange chromatography (Cl^-) afforded the target molecule **1** (77%) which was analyzed as a dihydrate. The macromonocyclic comparison compound **2** and the nonmacrocyclic derivative **3** were obtained in similar reaction sequences (**14** → **19** → **2** and **8** → **10** → **3**, respectively).

The ^1H NMR spectra (500 MHz) of **1** in Me_2SO-d_6 at T = 303 K correspond to a mixture of an unknown number of conformers since the rotations around the three amide bonds and the chair inversions of the two protonated spiro piperidinium rings with equatorially positioned *N*-ethyl groups are slow. At T = 418 K, the rotations around the amide bonds and the chair inversions are fast on the NMR time scale, and a considerably simpler spectrum corresponding to one homogeneous compound is obtained. The contour plot of a 2D NOESY ^1H NMR experiment (500 MHz, Me_2SO-d_6, T = 303 K) indicates the location of the thiazolium ring on the cavity side in proximity to the tetramethyl-substituted diphenylmethane unit. Revealing connectivities are observed between 2′-*H*, 5′-*H*, and 4′-CH_3 of the thiazolium ring and 31,35-CH_3, 32,34-*H*, and NCH_2CH_3 of the diphenylmethane unit (for numbering, see formula **1**).

Benzoin Condensations Catalyzed by the Thiazolium Derivatives 1–3 in Methanol. As previously observed by others,[7,9] we found the thiazolium-catalyzed benzoin condensations to be extraordinarily sensitive to reaction parameters such as solvent polarity or the nature and strength of buffers. We observed the highest conversions of benzaldehyde to benzoin in methanol solutions of low ionic strength.

The reaction in the presence of **1–3** and other nonmacrocyclic thiazolium salts was studied by ^1H NMR (500 MHz). For kinetic analysis, the decrease in integrated intensity of the singlet for the aldehyde proton of benzaldehyde at δ = 9.97 and the increase in integrated intensity of the isolated doublet at δ = 7.93 for the aromatic protons ortho to the carbonyl group of benzoin were monitored relative to an internal standard. The evaluation of the plots of benzaldehyde disappearance and of benzoin formation versus time led to identical results, which shows that the rate of H/D exchange of the aldehydic proton via the enamine intermediate known as active aldehyde (Scheme I) is slow as compared to the rate of benzoin formation. The increase in intensity of the benzoin methine proton at δ = 6.15, however, cannot be considered for evaluation of the rate of benzoin formation, since it exchanges, presumably thiazolium catalyzed (Scheme I), with the deuterated solvent. Alternatively, the course of the reaction was followed by using medium-pressure chromatography (MPLC). Aliquot samples were taken at various reaction times from the reaction mixture, and their reactant and product contents were analyzed by standardized computing integration. The kinetic results obtained by NMR and MPLC were in good agreement.

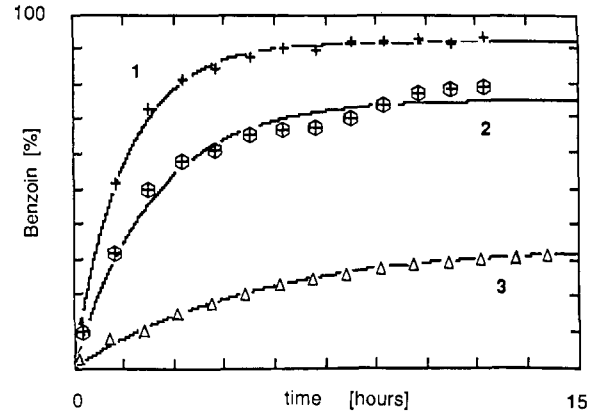


Figure 1. Increase in benzoin versus time followed by ^1H NMR. [Catalyst] = 20 mM, [ArCHO] = 0.4 M, [NEt_3] = 60 mM, T = 323 K in methanol-d_4.

Figure 1 shows the plots of product formation versus time for benzoin condensations catalyzed by **1–3** in methanol-d_4 in the presence of triethylamine as base ([benzaldehyde] = 0.4 M, [NEt_3] = 60 mM, [catalyst] = 20 mM, T = 323 K, under N_2). The experimental data obtained with **1** and **2** are best evaluated by assuming that the reactions are first-order in benzaldehyde (Figure 1). The fitting of the experimental data for **1** to a first-order rate law is valid over several half times up to conversions of 80%. The observed first-order rate constant for the reaction in the presence of **1** is calculated as $k_{obsd} = 1.9 \times 10^{-4}$ s^{-1} and for the reaction in the presence of **2** as $k_{obsd} = 9.7 \times 10^{-5}$ s^{-1}. The evaluation by fitting the experimental data of Figure 1 for **1** and **2** to a second-order rate law provides less significant results. A comparison of the initial rates (V_{init}(**1**) = 7.3×10^{-5}, V_{init}(**2**) = 3.5×10^{-5}, V_{init}(**3**) = 6.5×10^{-6} $M \cdot s^{-1}$) shows the catalytic advantages of macrobicyclic and macromonocyclic thiazolium salts **1** and **2** over the nonmacrocyclic derivative **3**. Under the given conditions, **1** is 11 times and **2** is 5 times more active than **3**. No benzoin condensation is observed in the absence of **1–3**. Other nonmacrocyclic thiazolium derivatives, e.g., 3-benzyl- and 3-phenacylthiazolium bromide or the natural coenzyme TPP, are less efficient catalysts than **1** or **2**.

The quantitative workup after 12 h of the benzoin condensation catalyzed by **1**, using preparative MPLC, afforded unchanged catalyst and analytically pure benzoin in 93% isolated yield. The reaction in the presence of **2** led to 74% isolated yield of benzoin after 12 h, and the reaction catalyzed by **3** afforded a 27% yield of benzoin.

The catalytic advantage of macrocycle **1** over thiazolium salt **3** shows the importance of collecting and orienting reacting partners by complexation prior to the catalytic event. In dimethyl sulfoxide, saturation kinetics are observed with a maximum velocity of benzoin formation at [benzaldehyde] ≈ 3 M. The sigmoidal plot of initial rates versus substrate concentration is shown in Figure 2 for the reaction in Me_2SO at T = 318 K ([**1**] = 20 mM, [NEt_3] = 0.16 M, and [$NEt_3H^+Cl^-$] = 0.1 M). The experimental data could neither be fitted to a pure 1:1 Michaelis–

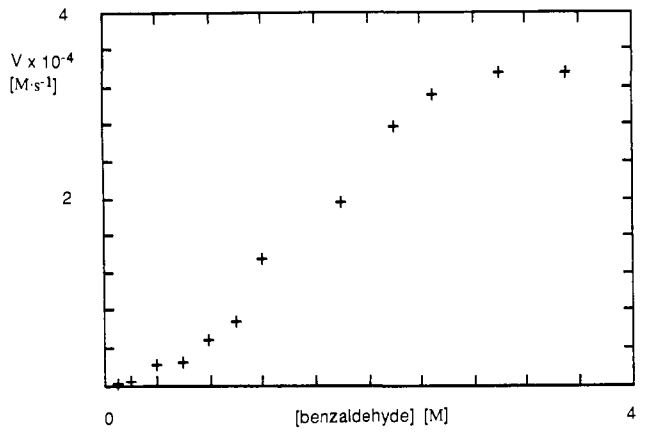


Figure 2. Plot of initial rates versus substrate concentration for the benzoin condensation catalyzed by **1** in Me_2SO, T = 318 K, [**1**] = 20 mM, [NEt_3] = 100 mM, [$NHEt_3^+Cl^-$] = 160 mM.

Menten kinetics nor be fitted to a kinetics that involves the formation of a pure 1:2 Michaelis–Menten complex. From the observed $V_{max} \approx 3.4 \times 10^{-4}$ M·s^{-1}, a catalytic turnover of $\approx$1 min^{-1} can be calculated. The saturation binding curve in methanol takes a very similar sigmoidal shape as in Me_2SO; however, due to the more limited solubility of benzaldehyde, the maximum rate V_{max} is not observed.

^{1}H NMR binding studies (500 MHz, T = 323 K) in methanol-d_4 in the absence of base to prevent the benzoin condensation provide additional evidence for host–guest interactions being involved in the catalytic process. Upon addition of benzaldehyde (c = 0.1–1.6 M), the signal for 4,5-H of **1** (c = 0.02 M) moves upfield by 0.14 ppm to δ = 1.39 and the signal for 3,6-H moves upfield by 0.12 ppm to δ = 1.67 ppm. From the concentration ranges in which ground-state binding and saturation kinetics are observed, it is obvious that the binding of one and/or two benzaldehydes to the cavity of **1** is only very weak in organic solvents. This is in agreement with recent data on the binding of neutral benzene derivatives by cyclophane hosts in methanol and dimethyl sulfoxide.[20]

The surprise, at first, was the very good catalytic performance of **2**, lacking the macrocyclic binding and reactive site of **1** (Figure 1). We explained the considerable activity of **2**, comparable to the activity of **1**, by the fact that this macromonocycle, according to CPK model examinations, can provide a niche binding site for benzaldehyde. This assumption is supported by the observation in methanol of a curvature, characteristic of 1:1 Michaelis–Menten kinetics, in the plot of the initial rates of benzoin formation as a function of benzaldehyde concentration (see below). Also, host–guest interactions are supported by qualitative ^{1}H NMR binding studies. In methanol-d_4 with [**2**] = 20 mM and [benzaldehyde] = 1.5 M, the aromatic signals of **2** show weak but significant downfield shifts ($\Delta\delta \approx$–0.07 ppm), and the resonances of the diphenylmethane methyl protons move upfield ($\Delta\delta \approx$ 0.04 ppm). In contrast, no signs for complexation are obtained with the nonmacrocyclic system **3**. The plot of the initial rates of benzoin formation as a function of benzaldehyde concentration in the presence of **3** in methanol gives a straight line. Also, no signal shifts are observed for protons of **3** in the ^{1}H NMR spectra of solutions containing a large excess of benzaldehyde.

The experimental data suggest that complexation not only provides a catalytic advantage to the thiazolium derivative **1** with its macrocyclic cyclophane binding site but also to **2** with its interesting niche-type binding site.

Solvent and Buffer Effects on the Benzoin Condensation Catalyzed by the Thiazolium Derivatives 1–3. The rate of the benzoin condensation catalyzed by **1–3** in methanol was found to be very strongly dependent on the concentration of triethylamine. As an example, the initial rate for the reaction catalyzed by **2** in methanol at T = 318 K increases in a nearly linear way from $V_{init} = 3.3 \times 10^{-6}$ M·s^{-1} at [NEt_3] = 0.02 M to $V_{int} = 1.6 \times 10^{-4}$ M·s^{-1} at [NEt_3] = 1.2 M. A similarly strong rate dependency on the base concentration had been previously noted by Tagaki et al.[9] Under the base-optimized conditions, the initial rate for the reaction catalyzed by **2** in methanol at T = 318 K was studied as a function of substrate concentration. Figure 3 shows the observed Michaelis–Menten kinetics, and the kinetic parameters were calculated as $V_{max} = 8.8 \times 10^{-4}$ M·s^{-1}, $k_{cat} = 2.7$ min^{-1}, and $K_M = 1.7$ M.[21]

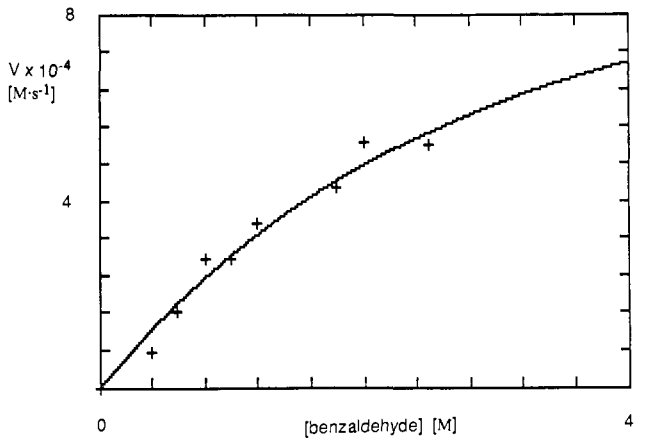


Figure 3. Plot of initial rates versus substrate concentration for the benzoin condensation catalyzed by **2** in methanol, T = 318 K, [**1**] = 20 mM, [NEt_3] = 1.2 M.

Table I. Initial Rates (V_{init}) for Benzoin Condensations in Solvents of Different Polarity, [1] = 20 mM, [Benzaldehyde] = 0.4 M, T = 318 K

solvent	V_{init}, M·s^{-1}
aq phosphate buffer[a]/methanol (40:60 v/v)	1.8×10^{-6}
methanol[b]	9.1×10^{-6}
DMF[b]	1.1×10^{-5}
Me_2SO[b]	1.7×10^{-5}

[a] pH 8.00, I = 0.2 M. [b] [Et_3N] = 160 mM, [$Et_3NH^+Cl^-$] = 100 mM.

A high conversion of benzaldehyde to benzoin as described above is only obtained if the ionic strength of the methanolic reaction solution is low. When the condensations in the presence of **1** or **2** are executed in methanol containing a triethylamine/triethylammonium buffer or a phosphate buffer with ionic strengths $\geq$0.1 M, the initial rates and the degree of conversion to benzoin decrease. Even after 18 h, condensations catalyzed by **1** in methanolic buffers never afforded yields of benzoin that exceeded 60%. A decrease in the efficiency of thiazolium-catalyzed benzoin condensations upon increasing the ionic strength of ammonium buffers had previously been observed by Tagaki et al.[9] Recently, Kool and Breslow described divergent salt effects on the rates of cyanide-catalyzed benzoin condensations in aqueous and organic solutions, which they explained by salting out/in effects on the hydrophobically stacked transition state for the cyanohydroxybenzyl anion attack at the second benzaldehyde molecule.[22]

The activity of simple thiazolium salts in the benzoin condensation increases with decreasing polarity of the solvent.[14,17b] Reactions catalyzed by **1**, however, could possibly benefit from an increase in solvent polarity since the complexation of aldehydes will be strengthened in polar protic, especially aqueous solvents. Enhanced proximity and orientation effects in more stable supramolecular complexes could lead to increasing rates of benzoin

(20) (a) Ferguson, S. B.: Seward, E. M.; Diederich, F.; Sanford, E. M.; Chou, A.; Inocencio-Szweda, P.; Knobler, C. B. *J. Org. Chem.* **1988**, *53*, 5593–5595. (b) Sanford, E. M.; Diederich, F. Unpublished results.

(21) It would have been of interest to compare the maximum velocities for **1** and **2** under these base-optimized conditions. Unfortunately, the material quantities of **1** at the time when we studied the base optimization for reactions with **2** did not allow us to make this worthwhile comparison.

(22) Kool, E. T.; Breslow, R. *J. Am. Chem. Soc.* **1988**, *110*, 1596–1597.

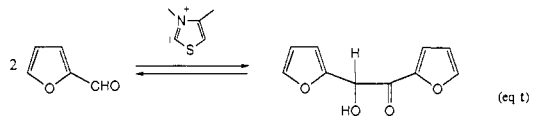
Table II. Observed First-Order Rate Constants for H/D Exchange at C-2′ of Thiazolium Ions Determined by 500-MHz ^{1}H NMR in Deuterated Buffers, T = 303 K

buffer, pD	1	2	3	3-benzylthiazolium bromide
DCl/KCl, 1.8	1.48×10^{-3}	4.88×10^{-5}	2.25×10^{-5}	
phosphate, 5.2	too fast	3.36×10^{-3}	2.45×10^{-3}	
citric acid (3.4)/methanol (60:40 v/v)	7.33×10^{-4}	2.28×10^{-4}	1.95×10^{-4}	5.93×10^{-5}

formation in protic solvents. To test this hypothesis, the benzoin condensation was investigated in solvents of different polarity. The measured initial rates are shown in Table I and decrease with increasing solvent polarity. Polarity effects on the activity of the thiazolium residue seem to be more important than the higher degree of orientation and proximity provided by strengthened complex formation in protic solvents.

Benzaldehyde Formation by Cleavage of Benzoin Catalyzed by Cyclophane 1. Specific changes of the cyclophane ^{1}H NMR resonances, e.g., upfield shifts of the C_6-bridge protons, indicate that benzoin (c = 0.2 M), expectedly, binds to the cavity of **1** (c = 20 mM) in methanol-d_4 and Me_2SO-d_6. We were unable to observe the catalysis of the reverse reaction, the formation of benzaldehyde from benzoin, in pure methanol with triethylamine as the base. Under these conditions, the thermodynamic equilibrium presumably is too far on the benzoin side as indicated by the isolated 93% yield of benzoin in the reaction catalyzed by **1**. The formation of benzaldehyde through cleavage of benzoin is, however, observed under conditions where the thermodynamic equilibrium is not as far on the benzoin side. As an example, with [**1**] = 20 mM and [benzoin] = 0.8 M in Me_2SO containing [NEt_3] = 0.16 M and [$NHEt_3^+Cl^-$] = 0.1 M at T = 318 K under Ar, the formation of benzaldehyde in 15% yield is observed after 24 h. Under these conditions, the reaction starting from benzaldehyde leads to a 50% yield of benzoin after 24 h. The reverse reaction, yielding benzaldehyde from benzoin, is slow, and at longer reaction times, the formation of benzil as a side product interferes with the monitoring of the benzaldehyde formation. The formation of benzil from benzoin is not mediated by the thiazolium derivative and is observed even in pure Me_2SO and ammonium buffer under rigorously anaerobic conditions. A Swern-type oxidation mechanism possibly is operative.[23] It is noteworthy that, to our knowledge, the formation of benzaldehyde from benzoin catalyzed by TPP model systems had previously not been described.[13]

Furoin Condensation Catalyzed by 1. The cyclophane **1** is a very good catalyst for the furoin condensation (eq 1). For a reaction with [2-furaldehyde] = 1 M, [Et_3N] = 1 M, and [**1**] = 20 mM in Me_2SO at T = 318 K under Ar, MPLC analysis gave



V_{init} = 6.7×10^{-4} M·s^{-1} as the initial rate of furoin formation. After 2 h, a 38% yield of furoin was isolated by preparative MPLC from the reaction mixture. The increasing formation of two nonidentified side products interfered with the monitoring of the furoin formation beyond a reaction time of 2 h.

Kinetic Acidities of the Thiazolium Ions in 1–3: A Strong Micropolarity Effect. A large macrocyclic effect on the kinetic acidity of the proton 2′-H of the thiazolium ring of **1** was observed in comparative studies with **1–3**.[24-26] The rates of H/D exchange at C-2′ of the thiazolium rings of **1–3** (c = 20 mM) in aqueous buffers were monitored by 500-MHz ^{1}H NMR spectroscopy following procedures described by Breslow[7] and later by Haake et al.[24] Table II shows the observed first-order rate constants for the H/D exchange in different buffers at various pDs. Figure 4 shows the fitting to a first-order rate law of the experimental data obtained for the H/D exchange in a KCl/DCl buffer at pD = 1.80, T = 303 K.

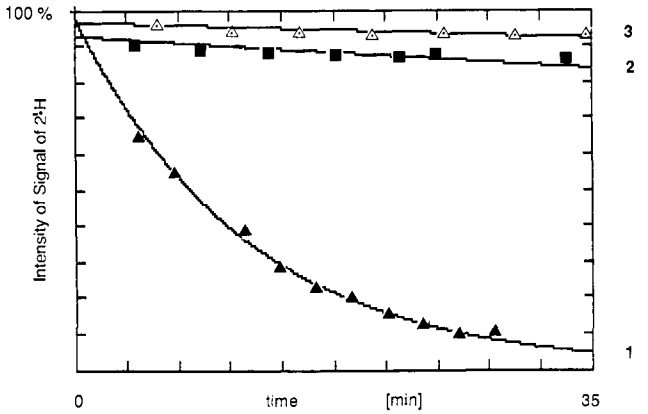


Figure 4. H/D-exchange rates at C-2′ of the thiazolium rings in **1–3** (c = 20 mM) in a KCl/DCl buffer, pD = 1.8, T = 303 K, monitored by 500-MHz ^{1}H NMR. The observed intensity of the NMR signal for 2′-H is plotted as a function of time.

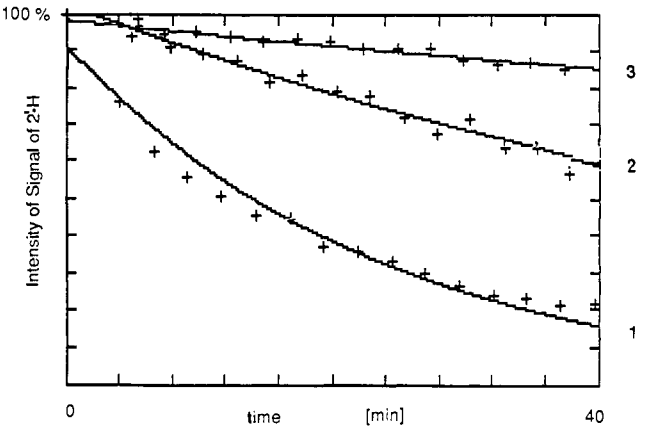


Figure 5. H/D-exchange rates at C-2′ of the thiazolium rings in **1–3** (c = 20 mM) in aqueous citrate buffer, pD = 3.4/methanol (60:40 v/v), T = 303 K, monitored by 500-MHz ^{1}H NMR. The observed intensity of the NMR signal for 2′-H is plotted as a function of time.

At pD = 1.80, the rate for the H/D exchange at C-2′ of the thiazolium ring of **1** is 30 times faster than the exchange rate of **2** and 65 times faster than the exchange rate of **3**. Such large differences in H/D-exchange rates have previously neither been observed in studies with simple thiazolium salts of different steric and electronic activation[7,9,25] nor been observed in studies of micellar thiazolium derivatives.[9] We explain the enhanced rate of H/D exchange by a micropolarity effect of the cavity of **1** on the acidity of 2′-H of its thiazolium ring. The *ionic* thiazolium salt is stabilized by a polar environment, e.g., by the aqueous buffer. The *neutral* ylide, however, formed upon deprotonation (Scheme I), is stabilized by the less polar microenvironment provided by the macrocyclic binding cavity of **1**. This stabilization of the conjugate base leads to an enhanced acidity of 2′-H at the macrobicyclic thiazolium ring, which is also reflected in the product-resembling transition state of the deprotonation. A similar ylide stabilization is not present in **2** or **3**, and the kinetic acidities of the thiazolium protons at C-2′ in these compounds are reduced.

(23) Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165–185.
(24) Haake, P.; Bausher, L. P.; Miller, W. B. *J. Am. Chem. Soc.* **1969**, *91*, 1113–1119.
(25) (a) Zoltevicz, J. A.; Sridharan, S. *J. Org. Chem.* **1978**, *43*, 3785–3787. (b) Gallo, A. A.; Sable, H. Z. *J. Biol. Chem.* **1976**, *251*, 2564–2570.
(26) For the observation of a macrocyclic effect of H/D-exchange rates, see: Vögtle, F.; Müller, W. M. *Angew. Chem.* **1984**, *96*, 711–712; *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 712–714.

That the polarity of the cavity microenvironment is at the origin of the enhanced kinetic acidity observed for the thiazolium ring of **1** is shown in studies where the polarity difference between the binding site and the surrounding solution is reduced due to the addition of 40% (v/v) methanol to the aqueous buffer (Figure 5). In the deuterated citric acid buffer (pD 3.4)/methanol-d_4 (60:40 v/v) system, the rate of H/D exchange observed for **1** is only 3.2 times faster than the rate observed for **2** and 3.8 times faster than the rate observed for **3**. Our findings on specific H/D-exchange rates in the series **1–3** have, in the meanwhile, been further supported by experiments with a new thiazolium-functionalized cyclophane, nonrelated to **1**, and the corresponding nonmacrocyclic comparison compounds.[2c,27]

Lienhard et al.[14] have shown that the rates of TPP-catalyzed reactions are much faster in environments less polar than water since the relevant reaction transition states are less polar than the ground states and, hence, are more stabilized in less polar environments. Jencks proposed that the transfer of TPP from aqueous solution to an apolar enzyme active site could be sufficient to account for much or for all of the observed enzymatic rate advantage.[15] One of the advantages provided by a less polar environment is the enhancement of the acidity of the thiazolium ring. Specific changes in pK_a values have been recognized as catalytic mechanisms at enzyme active sites.[28] Our studies suggest that a part of the catalytic advantage of the cyclophane **1** over nonmacrocyclic thiazolium derivatives, e.g., **3**, could result from a higher percentage of active ylide present in a buffer at a given pH. They indicate that an enzymatic catalytic mechanism such as a specific change in pK_a can be realized in synthetic biomimetic catalysts.

Conclusions. The thiazolium-bridged cyclophane **1** is a very efficient, highly stable catalyst for the benzoin condensation and is superior to the nonmacrocyclic derivative **3**. Compound **1** exhibits a large number of features typical for TPP-dependent enzymes, e.g., high catalytic turnover, sigmoid saturation kinetics suggesting the formation of a 1:2 Michaelis–Menten complex, catalysis of forward and back reactions, and, dependent on the reaction conditions, then clean formation of the desired product in very high yield. The surprisingly high catalytic activity of the thiazolium derivative **2** is explained by its potential for binding benzaldehyde at its niche-type binding site. Correspondingly, 1:1 Michaelis–Menten-type kinetics are observed in reactions catalyzed by **2**. The rates of thiazolium-catalyzed benzoin condensations increase with decreasing solvent polarity and with increasing concentration of base. Large salt effects on rates are observed, and the presence of ammonium and phosphate buffers leads to a considerable decrease in catalytic efficiency of thiazolium derivatives. Cyclophane **1** also catalyzes the furoin condensation. A strong micropolarity effect of the apolar binding cavity of **1** on the kinetic acidity of 2′-H of the thiazolium ion is observed in H/D-exchange studies. A similar effect was not detectable with the nonmacrocyclic thiazolium derivatives **2** and **3**. Micropolarity effects at active sites are believed to be at the origin of the activation of TPP by holoenzymes. Our study shows that we can mimic enzymatic catalytic mechanisms such as pK_a changes in supramolecular catalysis.

Experimental Section

General. One-dimensional ^{1}H NMR was carried out on Bruker WP80, HX360, and AM500 spectrometers. Two-dimensional COSY and NOESY spectra were obtained at 500 MHz. All spectra of the macromonocyclic and macrobicyclic structures were evaluated with the help of COSY spectra. All δ values (ppm) in the spectra to characterize new compounds refer to Me_4Si as internal standard. If not stated otherwise, the spectra were recorded at 303 K. EI mass spectra (70 eV) were carried out on a Du Pont CEC 21-492 instrument. FAB spectra (matrix: *m*-nitrobenzyl alcohol) were recorded on AEI MS 902 and VG FAB-SE spectrometers. Melting points (uncorrected) were measured on a Büchi (Dr. Tottoli) apparatus. IR spectra were recorded on a Beckman IR-4240 instrument. Elemental analysis was performed at the Max-Planck-Institut für Medizinische Forschung, Heidelberg. Analytical thin-layer chromatography (TLC) on silica gel was performed on SI microcards, Riedel deHaen; TLC on alumina was performed on Polygram-Alox N/UV_{254} cards, Macherey-Nagel. The following packing materials were used in column chromatography: E. Merck silica gel 60, 0.063–0.2 mm, for gravity chromatography; E. Merck silica gel 60, 0.04–0.063 mm, for flash chromatography at ≈1 bar. For medium-pressure liquid chromatography (MPLC) at 15–20 bar and flow rate of 35–40 mL·min^{-1}, thick glass columns were packed with silica gel, 0.012–0.021 or 0.020–0.045 mm, from Labomatic. The columns were packed either by following a wet[29] or by a dry[30] packing procedure. Product fractions in analytical MPLC separations were detected quantitatively with the Chromatopac C-R3A computing integrator, Shimadzu.

Materials. For synthesis, reagents were purchased and were used without further purification unless otherwise specified. Chloroform ($CHCl_3$), dimethylformamide (DMF), and dioxane were purified for cyclization reactions by stirring over basic alumina, activity I, from E. Merck under N_2 followed by filtration. Chloroform saturated with ammonia was prepared as a chromatographic eluant by extracting concentrated NH_4OH with chloroform and drying the resulting chloroform solution over sodium sulfate. For catalytic runs, benzaldehyde, 2-furaldehyde, and acetaldehyde were distilled under Ar. The solvents used in kinetic runs analyzed by MPLC were distilled under mild conditions under Ar from Mg (methanol), from CaH_2[dimethyl sulfoxide (Me_2SO)], and from BaO (DMF). Degassed, doubly distilled water was used for the preparation of aqueous solutions. Highest quality deuterated solvents were purchased from Aldrich and used in kinetic NMR runs without further purification.

Deuterated buffers for measurements of H/D exchange were prepared by freeze-drying 20 mL of the aqueous buffer solution followed by three cycles of adding D_2O (99.8 atom % D) and freeze-drying. After the last freeze-drying, 20 mL of D_2O (99.98 atom % D) was added to the residue. The following buffers were used: pH 4.8, standard acetate buffer, E. Merck; pH 3.0, citric acid/sodium hydroxide/sodium chloride buffer, E. Merck; pH 1.4, potassium chloride/deuterium chloride prepared according to Clark and Lubs[31] (25 mL of 0.2 N KCl, 26.6 mL of 0.2 N DCl, and D_2O to give a total volume of 100 mL).

Synthesis. 1′,1″-Diacetyl-10,18-dibromo-14,20,31,35,39,41-hexamethyldispiro[1,8,22,29-tetraoxa[8.1.8.1]paracyclophane-15,4′:36,4″-bispiperidine] (4). A total of 11.02 g (30 mmol) of 1-acetyl-4,4-bis(4-hydroxy-3,5-dimethylphenyl)piperidine[32] and 10.75 g (30 mmol) of cesium carbonate was dissolved in 200 mL of methanol, and the solvent was evaporated in vacuo. After the addition of 225 mL of dry DMF to the residue, 50 mL of solvent was removed under reduced pressure. The remaining solution was transferred under Ar into 2.5 L of dry DMF, and 22.03 g (30 mmol) of 1-acetyl-4,4-bis[3-bromo-4-(6-chlorohexoxy)-5-methylphenyl]piperidine[2b] was added. The mixture was stirred under Ar for 9 days at 60 °C. The solvent was removed in vacuo, and 200 mL of $CHCl_3$ was added to the residue. The cesium salts were removed by filtration, and the solution was evaporated to dryness. Flash chromatography [SiO_2; $CHCl_3$/methanol (100:0.75) afforded the product which was recrystallized from methanol: 3.7 g (12%) of **4**, mp 310 °C dec; IR (KBr) ν 1640 (C=O) cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.5–1.7 (m, 8 H, 4-H, 5-H), 1.75–1.95 (m, 8 H, 3-H, 6-H), 2.07 (s, 3 H, $NCOCH_3$), 2.09 (s, 3 H, $NCOCH_3$), 2.18 (s, 12 H, $ArCH_3$), 2.23 (s, 6 H, $ArCH_3$), 2.25–2.35 (m, 8 H, 3′-H, 3″-H), 3.55–3.65 (m, 8 H, 2′-H, 2″-H), 3.71 (t, J = 6.3 Hz, 4 H, 2-H), 3.85 (t, J = 6.2 Hz, 4 H, 7-H), 6.77 (s, 4 H, 32-H), 6.87 (s, 2 H, 13-H), 7.15 (s, 2 H, 11-H); MS, m/z (relative intensity) 1026 (20, M^+), 255 (100). Anal. Calcd for $C_{56}H_{72}Br_2N_2O_6$ (1029.0): C, 65.36; H, 7.05; Br, 15.53; N, 2.72. Found: C, 65.10; H, 6.89; Br, 15.72; N, 2.64.

1′,1″-Diacetyl-10,18-dicyano-14,20,31,35,39,41-hexamethyldispiro-[1,8,22,29-tetraoxa[8.1.8.1]paracyclophane-15,4′:36,4″-bispiperidine] (5). A mixture of 3 g (2.9 mmol) of **4** and 0.59 g (6.7 mmol) of CuCN in 15 mL of dry DMF was heated under Ar to reflux for 35 h. After the mixture was cooled to 20 °C, 100 mL of CH_2Cl_2 was added, and the inorganic salts were removed by filtration. The organic solution was extracted four times with concentrated NH_4OH followed by water and dried over sodium sulfate. The solvent was distilled off and the product was purified by flash chromatography on silica gel [CH_3Cl/methanol (100:1)] followed by recrystallization from methanol: 2.3 g (86%) of **5**, mp 329–330 °C; IR (KBr) ν 2240 (CN), 1640 (C=O) cm^{-1}; ^{1}H NMR

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(31) *Laborprodukte für die* Praxis; E. Merck: Darmstadt, 1983; p 136.
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(33) (a) Vögtle, F. *Chem.-Ztg.* **1972**, *96*, 396–403. (b) Vögtle, F. *Chem. Ind. (London)* **1972**, 346.

(360 MHz, Me_2SO-d_6, T = 350 K) δ 1.4–1.6 (m, 8 H, 4-H, 5-H), 1.6–1.85 (m, 8 H, 3-H, 6-H), 1.91 (s, 3 H, $NCOCH_3$), 1.94 (s, 3 H, $NCOCH_3$), 2.14 (s, 12 H, $ArCH_3$), 2.18 (s, 6 H, $ArCH_3$), 2.2–2.45 (m, 8 H, 3′-H, 3″-H), 3.25–3.50 (m, 8 H, 2′-H, 2″-H), 3.72 (t, J = 6.3 Hz, 4 H, 2-H), 3.99 (t, J = 6.2 Hz, 4 H, 7-H), 6.89 (s, 4 H, 32-H), 7.48 (s, 2 H, 13-H), 7.50 (s, 2 H, 11-H); MS, m/z (relative intensity) 920 (100, M^+). Anal. Calcd for $C_{58}H_{72}N_4O_6$ (921.2): C, 75.62; H, 7.88; N, 6.08. Found: C, 75.41; H, 7.91; N, 6.03.

10,18-Bis(aminomethyl)-1′,1″-diethyl-14,20,31,35,39,41-hexamethyldispiro[1,8,22,29-tetraoxa[8.1.8.1]paracyclophane-15,4′:36,4″-bispiperidine] (6). A total of 15.6 mL (15.6 mmol) of a 1 M solution of borane in THF was added under Ar to a solution of 1.8 g (1.95 mmol) of **5** in 10 mL of THF. The mixture was heated under Ar to reflux for 15 h. The solution was cooled to 20 °C, and the excess of borane was hydrolyzed by adding carefully a mixture of water/THF (1:1). After the solvents were removed in vacuo, the residue was dissolved in 50 mL of ethanol and 1.5 mL of concentrated sulfuric acid, and the mixture was heated to reflux for 30 min. The solution was neutralized by the addition of 2 N NaOH, and the solvent was evaporated under reduced pressure. Upon addition of 10 mL of 2 N NaOH to the residue, the product precipitated and was collected by filtration. The solid product was washed with water until the washing liquors showed a neutral pH. Drying at 70 °C/10^{-3} Torr afforded 1.5 g (86%) of **6** as a white powder which was used for the subsequent amide cyclization without further purification: mp 142–143 °C; IR (KBr) ν 3500–3300 (N–H) cm^{-1}; ^1H NMR (360 MHz, Me_2SO-d_6, T = 350 K) δ 0.9–0.95 (m, 6 H, NCH_2CH_3), 1.45–1.5 (m, 8 H, 4-H, 5-H), 1.7–1.75 (m, 8 H, 3-H, 6-H), 2.10 (s, 18 H, $ArCH_3$), 2.1–2.2 (m, 4 H, NCH_2CH_3), 2.2–2.35 (m, 16 H, 2′-H, 2″-H, 3′-H, 3″-H), 3.5–3.7 (m, 12 H, 2-H, 7-H, $ArCH_2NH_2$), 6.86 (s, 4 H, 32-H), 6.89 (s, 2 H, 13-H), 7.16 (s, 2 H, 11-H); HRMS, m/z (M^+, $C_{58}H_{84}N_4O_4$) calcd 900.6492, obsd 900.6475.

40′-[(Benzyloxy)carbonyl]-13′,16′:18′,21′-dietheno-1,1″-diethyl-3′,14′,20′,31′,48′,51′-hexamethyldispiro[piperidine-4,17′-[5,12,22,29]tetraoxa[37,40,43]triazatetracyclo[31.13.1.0^{4,45}.0^{30,35}]heptatetraconta-1′,3′,13′,15′,18′,20′,30′,32′,34′,45′-decaene-47′,4″-piperidine]-38′,42′-dione (11). A solution of 0.20 g (0.22 mmol) of **6** in 50 mL of degassed, dry dioxane and a solution of 0.132 g (0.22 mmol) of the bis(pentafluorophenyl ester) **7**[2b] in 50 mL of the same solvent were added dropwise and synchronously under Ar to 250 mL of dioxane heated to reflux. A high-dilution apparatus described by Vögtle[33] was used in this procedure. After the addition, stirring under reflux was continued for 4 h. The solvent was removed in vacuo, and the residue was partitioned between CH_2Cl_2 and 2 N NaOH. The aqueous layer was extracted with two portions of CH_2Cl_2, and the combined organic phases were dried over sodium sulfate. Evaporation of the solvent afforded a crude product which was chromatographed (MPLC) on silica gel from ethyl acetate/triethylamine/methanol (100:5:30). Recrystallization from ether and drying at 303 K/10^{-3} Torr afforded 57.3 mg (23%) of colorless **11**: mp 230 °C dec; IR (KBr) ν 3240 (N–H), 1710, 1665 (C=O) cm^{-1}; ^1H NMR (360 MHz, Me_2SO-d_6, T = 350 K) δ 1.0–1.25 (m, 6 H, NCH_2CH_3), 1.35–1.6 (m, 8 H, 4-H, 5-H), 1.6–1.95 (m, 8 H, 3-H, 6-H), 2.13 (s, 12 H, $ArCH_3$), 2.15 (s, 6 H, $ArCH_3$), 2.2–2.55 (m, 20 H, NCH_2CH_3, 2′-H, 2″-H, 3′-H, 3″-H), 3.55–3.75 (m, 8 H, 2-H, 7-H), 4.15 (s, 4 H, CH_2NCH_2), 4.26 (s, 4 H, $ArCH_2$), 5.04 (s, 2 H, $COCH_2Ar$), 6.89 (s, 6 H, 13-H, 32-H, 34-H), 6.91 (s, 2 H, 11-H), 7.15–7.35 (m, 5 H, $OCH_2C_6H_5$), 8.93 (m, 2 H, NH); MS (FAB), m/z (relative intensity) 1132 (83, M^+), 1024 (100, $M^+ - C_7H_7O$). Anal. Calcd for $C_{70}H_{93}N_5O_8$ (1132.6): C, 74.24; H, 8.28; N, 6.18. Found: C, 74.18; H, 8.30; N, 6.46.

13′,16′:18′,21′-Dietheno-1,1″-diethyl-3′,14′,20′,31′,48′,51′-hexamethyldispiro[piperidine-4,17′-[5,12,22,29]tetraoxa[37,40,43]triazatetracyclo[31.13.1.0^{4,45}.0^{30,35}]heptatetraconta-1′,3′,13′,15′,18′,20′,30′,32′,34′,45′-decaene-47′,4″-piperidine]-38′,42′-dione (12). A solution of 1.5 g (1.32 mmol) of **11** in 100 mL of ethanol was stirred for 14 h at 20 °C in a hydrogen atmosphere (4 bar) in the presence of 100 mg of palladium (10%) on charcoal. The catalyst was removed by filtration and washed twice with ethanol. The solvent was evaporated in vacuo, and the product was obtained by chromatography (MPLC) on silica gel from chloroform, saturated with ammonia/methanol (100:10). Recrystallization from ether afforded 1.25 g (95 %) of colorless **12**: mp 135 °C; IR (KBr) ν 1670 (C=O) cm^{-1}; ^1H NMR (360 MHz, Me_2SO-d_6) δ 0.97 (t, J = 7.1 Hz, 6 H, NCH_2CH_3), 1.5–1.6 (m, 8 H, 4-H, 5-H), 1.65–1.85 (m, 8 H, 3-H, 6-H), 2.10 (s, 12 H, $ArCH_3$), 2.14 (s, 6 H, $ArCH_3$), 2.2–2.45 (m, 20 H, NCH_2CH_3, 2′-H, 2″-H, 3′-H, 3″-H), 3.16 (s, 4 H, CH_2NCH_2), 3.64 (t, J = 6.1 Hz, 4 H, 7-H), 3.66 (t, J = 6.2 Hz, 4 H, 2-H), 4.25–4.3 (m, 4 H, $ArCH_2$), 6.86 (s, 4 H, 32-H, 34-H), 6.96 (s, 2 H, 13-H), 7.03 (s, 2 H, 11-H), 8.20 (t, J = 6.0 Hz, 2 H, NH); MS (FAB), m/z (relative intensity) 998 (100, M^+). Anal. Calcd for $C_{62}H_{87}N_5O_6 \cdot H_2O$ (1016.4): C, 73.26; H, 8.83; N, 6.89. Found: C, 73.29; H, 9.14; N, 7.08.

40′-(Bromoacetyl)-13′,16′:18′,21′-dietheno-1,1″-diethyl-3′,14′,20′,31′,48′,51′-hexamethyldispiro[piperidine-4,17′-[5,12,22,29]tetraoxa[37,40,43]triazatetracyclo[31.13.1.0^{4,45}.0^{30,35}]heptatetraconta-1′,3′,13′,15′,18′,20′,30′,32′,34′,45′-decaene-47′,4″-piperidine]-38′,42′-dione (13). A solution of 60 mg (0.29 mmol) of α-bromoacetyl bromide in 5 mL of dry $CHCl_3$ was added dropwise at 20 °C under Ar to a solution of 200 mg (0.2 mmol) of **12** in 2 mL of dry $CHCl_3$. The reaction was stirred for 2 h, after which 50 mL of $CHCl_3$ was added. The organic solution was extracted with 2 N NaOH and dried over sodium sulfate. The solvent was evaporated in vacuo, and the residue was chromatographed (MPLC) on silica gel from chloroform, saturated with NH_3/methanol (100:15). Recrystallization from ether/n-heptane afforded 83 mg (37%) of colorless **13**: mp 265 °C; IR (KBr) ν 1665 (C=O) cm^{-1}; ^1H NMR (500 MHz, Me_2SO-d_6) δ 0.97 (m, 6 H, NCH_2CH_3), 1.4–1.6 (m, 8 H, 4-H, 5-H), 1.65–1.8 (m, 8 H, 3-H, 6-H), 2.10 (s, 12 H, $ArCH_3$), 2.14 (s, 6 H, $ArCH_3$), 2.2–2.85 (m, 20 H, NCH_2CH_3, 2′-H, 2″-H, 3′-H, 3″-H), 3.55–3.75 (m, 8 H, 2-H, 7-H), 4.10 and 4.19 (2 s, 4 H, CH_2NCH_2), 4.2–4.25 (m, 4 H, $ArCH_2$), 4.39 (s, 2 H, CH_2Br), 6.83 (s, 2 H, 32-H), 6.89 (s, 2 H, 34-H), 6.91 (s, 2 H, 13-H), 6.96 (s, 2 H, 11-H), 8.69 (t, J = 5.5 Hz, 1 H, NH), 9.16 (t, J = 5.5 Hz, 1 H, NH); MS (FAB), m/z (relative intensity) 1120 (100, $M^+ + H$). Anal. Calcd for $C_{64}H_{88}BrN_5O_7$ (1119.4): C, 68.77; H, 7.92; Br, 7.14; N, 6.26. Found: C, 68.39; H, 7.82; Br, 7.29; N, 6.00.

13′,16′:18′,21′-Dietheno-1,1″-diethyl-3′,14′,20′,31′,48′,51′-hexamethyl-40-(4-methylthiazolium-3-ylacetyl)dispiro[piperidinium-4,17′-[5,12,22,29]tetraoxa[37,40,43]triazatetracyclo[31.13.1.0^{4,45}.0^{30,35}]heptatetraconta-1′,3′,13′,15′,18′,20′,30′,32′,34′,45′-decaene-47′,4″-piperidinium]-38′,42′-dione Trichloride (1). A solution of 70 mg (0.07 mmol) of **12** and 20 mg (0.09 mmol) of α-bromoacetyl bromide in 1 mL of dry chloroform was stirred at 20 °C under Ar. After stirring was continued for 2 h, ether was added, and the precipitated dihydrobromide of **13** was collected by filtration. The product was washed several times with ether and dried for 2 h at 20 °C/10^{-3} Torr. Without further purification, the dry dihydrobromide of **13** was added to 1 mL of 4-methylthiazole, and the mixture was stirred at 20 °C under Ar for 48 h. The viscous pale-yellow solution was diluted with 2 mL of methanol, and precipitation of the product was induced by addition of acetone. The crystallization of **1** as the dihydrobromide was completed upon addition of ether. For ion exchange, the dihydrobromide was chromatographed on Dowex ion-exchange resin (1 × 8, Cl^-) from doubly distilled water. Two recrystallizations from acetone/ether/n-hexane and drying for 3 days at 80° C/10^{-3} Torr afforded 67 mg (77%) of **1** as hygroscopic colorless solid which was analyzed as a dihydrate: mp 265 °C dec; IR (KBr) ν 1670 (C=O) cm^{-1}; ^1H NMR (500 MHz, Me_2SO-d_6) δ 1.15–1.25 (m, 6 H, $N^+CH_2CH_3$), 1.45–1.6 (m, 8 H, 4-H, 5-H), 1.6–1.85 (m, 8 H, 3-H, 6-H), 2.11 (s, 6 H, 14-CH_3), 2.16 (s, 12 H, 31-CH_3, 35-CH_3), 2.31 (s, 3 H, 4′-CH_3), 2.3–2.35 (m, 4 H, 3″-H_{ax}, 3‴-H_{ax}), 2.55–2.8 (m, 4 H, 3″-H_{eq}, 3‴-H_{eq}), 2.85–3.15 (m, 8 H, $N^+CH_2CH_3$, 2″-H_{ax}, 2‴-H_{ax}), 3.4–3.5 (m, 4 H, 2″-H_{eq}, 2‴-H_{eq}), 3.55–3.75 (m, 8 H, 2-H, 7-H), 4.1–4.55 (m, 8 H, CH_2NCH_2, $ArCH_2NH$), 5.3–6.15 (m, 2 H, CH_2–thiaz), 6.8–7.05 (m, 8 H, 11-H, 13-H, 32-H, 34-H), 7.98 (s, br, 1 H, 5′-H), 8.68, 8.82, 9.26, 9.35 (4 t, 2 H, NH), 10.12 (s, 1 H, 2′-H); MS (FAB) for $C_{68}H_{95}Cl_3N_6O_7S$ (1244.6), m/z (relative intensity) 1139.8 (34, $M^+ - 3Cl$), 1138.8 (68, $M^+ - 3Cl - H$), 1137.8 (100, $M^+ - 3Cl - 2H$), 1136.8 (68, $M^+ - 3Cl - 3H$). Anal. Calcd for $C_{68}H_{95}Cl_3N_6O_7S \cdot 2H_2O$ (1283.0): C, 63.66; H, 7.78; Cl, 8.29; N, 6.55; S, 2.50. Found: C, 63.79; H, 7.90; Cl, 8.49; N, 6.45; S, 2.41.

[(Benzyloxy)carbonyl]bis[(*N*-benzylcarbamoyl)methyl]amine (8). A solution of 1.08 g (10 mmol) of benzylamine in 10 mL of ether was added dropwise at 20 °C to a stirred solution of 3.0 g (5 mmol) of the bis(pentafluorophenyl ester) **7**.[2b] The precipitation of the product from the reaction mixture was completed after 30 min. The product was collected by filtration, washed with 10 mL of ether, and dried for 12 h at 20 °C/10^{-3} Torr: 1.86 g (84%) of **8**, mp 137 °C; IR (KBr) ν 1640 (C=O) cm^{-1}; ^1H NMR (80 MHz, Me_2SO-d_6) δ 4.03 (s, br, 4 H, $NCOCH_2$), 4.2–4.35 (m, 4 H, $ArCH_2N$), 5.07 (s, 2 H, OCH_2), 7.2–7.35 (m, 15 H, ArH), 9.10 (t, J = 6.6 Hz, 2 H, NH); MS, m/z (relative intensity) 445 (6, M^+), 310 (48 $M^+ - C_8H_7O_2$), 91 (100, C_7H_7). Anal. Calcd for $C_{26}H_{27}N_3O_4$ (445.2): C, 70.08; H, 6.11; N, 9.43. Found: C, 70.12; H, 5.82; N, 9.50.

Bis[(*N*-benzylcarbamoyl)methyl]amine (9). A solution of 1.3 g (2.9 mmol) of **8** in 100 mL of ethanol was stirred for 6 h at 20 °C in a hydrogen atmosphere (4 bar) in the presence of 400 mg of palladium (10%) on charcoal. The catalyst was removed by filtration. The residue, obtained by evaporation of the solvent in vacuo, was chromatographed on silica gel from ethyl acetate/methanol (10:0.5). Recrystallization from methanol/ether afforded 0.80 g (88%) of **9** as colorless microcrystals: mp 66 °C; IR (KBr) ν 1640 (C=O) cm^{-1}; ^1H NMR (80 MHz, Me_2SO-d_6) δ 2.85–3.5 (s, 4 H, $NCOCH_2$), 4.25–4.35 (m, 4 H, $ArCH_2N$), 7.1–7.5 (m, 10 H, ArH), 8.40 (t, J = 6.5 Hz, 2 H, NH); MS, m/z (relative intensity) 312 (6, $M^+ + H$), 311 (2, M^+), 91 (100, C_7H_7). Anal. Calcd for $C_{18}H_{21}N_3O_2$ (311.1): C, 69.42; H, 6.80; N, 13.49.

Found: C, 69.70; H, 6.90; N, 13.17.

N,N-Bis[(N-benzylcarbamoyl)methyl]bromoacetamide (10). A solution of 0.7 g (3.5 mmol) of α-bromoacetyl chloride in 5 mL of dry $CHCl_3$ was added dropwise under Ar at 20 °C to a stirred solution of 1.0 g (3.2 mmol) of **9** and 0.45 mL of triethylamine in dry $CHCl_3$. After 1 h, the solvent was evaporated in vacuo, and the crude product was chromatographed on silica gel from ethyl acetate. The solvent of the combined product fractions was removed in vacuo to leave a residual volume of 10 mL from which pure **10** started crystallizing out. The crystallization process was completed by keeping the solution overnight at 0 °C. The crystals were collected by filtration, and drying at 60 °C/10^{-3} Torr afforded 0.45 g (32%) of **10**: mp 127 °C; IR (KBr) ν 1660 (C=O) cm^{-1}; ^1H NMR (80 MHz, Me_2SO-d_6) δ 3.85–4.5 (m, 10 H, $ArCH_2NCOCH_2$, CH_2Br), 6.8–7.5 (m, 10 H, ArH), 8.6–8.85 (m, 1 H, NH), 9.0–9.25 (m, 1 H, NH); MS, *m/z* (relative intensity) 351 (10, M^+ – HBr), 91 (100, C_7H_7), 79 (100, Br). Anal. Calcd for $C_{20}H_{22}BrN_3O_3$ (432.1): C, 55.54; H, 5.13; Br, 18.49; N, 9.72. Found: C, 55.52; H, 5.19; Br, 18.39; N, 9.62.

3-[[N,N-Bis[(N-benzylcarbamoyl)methyl]carbamoyl]methyl]-4-methylthiazolium Chloride (3). A solution of 0.45 g (1.04 mmol) of **10** in 2 mL of 4-methylthiazole was stirred for 48 H at 20 °C under Ar. The crude product, which precipitated upon addition of ether, was collected by filtration and dried at 20 °C/10^{-3} Torr. For ion exchange, the product was chromatographed on Dowex ion-exchange resin (1 × 8, Cl^-) from doubly distilled water. Recrystallization from methanol/ether and drying for 3 days at 30 °C/10^{-3} Torr afforded 0.33 g (65 %) of **3** as a colorless solid: mp 102 °C dec; IR (KBr) ν 1660, (C=O) 1578 (thiazolium ring) cm^{-1};[34] ^1H NMR (80 MHz, Me_2SO-d_6) δ 2.36 (d, *J* = 1.0 Hz, 3 H, thiaz–CH_3), 3.95–4.5 (m, 8 H, $ArCH_2NCOCH_2$), 5.73 (s, 2 H, N^+CH_2), 7.25–7.3 (m, 10 H, ArH), 8.0–8.1 (m, 1 H, 5-H_{thiaz}), 8.45 (t, *J* = 5.7 Hz, 1 H, NH), 9.22 (t, *J* = 5.7 Hz, 1 H, NH), 10.19 (d, *J* = 2.8 Hz, 1 H, 2-H_{thiaz}); MS, *m/z* (relative intensity) 351 (11, M^+ – HCl – C_4H_5NS), 99 (18, C_4H_5NS), 91 (100, C_7H_7). Anal. Calcd for $C_{24}H_{27}ClN_4O_3S$ (486.1): C, 59.24; H, 5.59; Cl, 7.19; N, 11.52; S, 6.57. Found: C, 59.05; H, 5.75; Cl, 7.09; N, 11.41; S, 6.43.

1-Acetyl-4,4-bis(3-bromo-4-methoxy-5-methylphenyl)piperidine (14). A solution of 10 g (20 mmol) of 1-acetyl-4,4-bis(3-bromo-4-hydroxy-5-methylphenyl)piperidine[2b] in 40 mL of 5% NaOH was cooled in an ice bath to 0 °C. A total of 5.2 g (41 mmol) of dimethyl sulfate was added dropwise at a rate to keep the reaction temperature below 40 °C. After the addition was completed, the solution was stirred for 30 min below 40 °C and then heated to reflux for 1.5 h. A total of 200 mL of saturated NaCl was added, and the aqueous solution was exhaustively extracted with $CHCl_3$. The combined organic phases were dried over sodium sulfate, and the solvent was evaporated in vacuo. Chromatography on silica gel from ethyl acetate followed by recrystallization from ether afforded 7.2 g (68%) of colorless **14**: mp 184 °C; IR (KBr) ν 1640 (C=O) cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ 2.07 (s, 3 H, $NCOCH_3$), 2.1–2.3 (m, 10 H, $ArCH_3$, 3-H_{pip}), 3.25–3.55 (m, 4 H, 2-H_{pip}), 3.78 (s, 6 H, OCH_3), 6.94 and 7.24 (AB, *J* = 2.3 Hz, 4 H, 2-H_{arom}, 6-H_{arom}); MS, *m/z* (relative intensity) 523 (100, M^+). Anal. Calcd for $C_{23}H_{27}Br_2NO_3$ (525.3): C, 52.59; H, 5.18; Br, 30.43; N, 2.67. Found: C, 52.50; H, 5.13; Br, 30.20; N, 2.64.

1-Acetyl-4,4-bis(3-cyano-4-methoxy-5-methylphenyl)piperidine (15). A solution of 2.74 g (30.6 mmol) of CuCN and 6.98 g (13.3 mmol) of **14** in 30 mL of dry DMF was heated to reflux for 15 h. The mixture was cooled to 20 °C, and 200 mL of chloroform was added. The inorganic salts were removed by filtration, and the organic solution was stirred for 2 h at 20 °C with concentrated NH_4OH. The phases were separated, and the extraction with concentrated NH_4OH was repeated until the aqueous solution became colorless. The organic phase was dried over sodium sulfate, and the solvent was evaporated in vacuo. The residue was chromatographed on silica gel from ethyl acetate/ligroin (40–60 °C), and recrystallization from ether afforded 4 g (72%) of colorless **15**: mp 176 °C; IR (KBr) ν 2230, (CN) 1640 (C=O) cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ 2.08 (s, 3 H, $NCOCH_3$), 2.15–2.55 (m, 10 H, $ArCH_3$, 3-H_{pip}), 3.35–3.8 (m, 4 H, 2-H_{pip}), 4.01 (s, 6 H, OCH_3), 7.20 (s, br, 4 H, 2-H_{arom}, 6-H_{arom}); MS, *m/z* (relative intensity) 417 (100, M^+). Anal. Calcd for $C_{25}H_{27}N_3O_3$ (417.5): C, 71.92; H, 6.52; N, 10.07. Found: C, 72.14; H, 6.80; N, 10.12.

1-Ethyl-4,4-bis(3-(aminomethyl)-4-methoxy-5-methylphenyl)piperidine (16). A total of 208 mL (208 mmol) of a 1 M solution of borane in THF was added under Ar to a solution of 12.6 g (30.1 mmol) of **15** in 100 mL of THF. The mixture was heated under Ar to reflux for 24 h. The solution was cooled to 20 °C, and the excess of borane was hydrolyzed by adding carefully a mixture of water/THF (1:1). After the solvents were removed in vacuo, the residue was dissolved in 100 mL of ethanol and 3 mL of concentrated sulfuric acid, and the mixture was heated to reflux for 30 min. The solution was neutralized by addition of 2 N NaOH, and the solvent was evaporated under reduced pressure. The residue was partitioned between $CHCl_3$ and 2 N NaOH, and the aqueous solution was exhaustively extracted with $CHCl_3$. The combined organic phases were dried over sodium sulfate, and evaporation of the solvent in vacuo afforded 12.2 g (98%) of **16** as a colorless oil, which was used in the following cyclization reaction without further purification: IR (film) ν 3200 (NH) cm^{-1}; ^1H NMR (360 MHz, Me_2SO-d_6) δ 0.95 (t, *J* = 7.0 Hz, 3 H, NCH_2CH_3); 2.16 (s, 6 H, $ArCH_3$); 2.17 (q, *J* = 7.0 Hz, 2 H, NCH_2CH_3), 2.2–2.45 (m, 8 H, 2-H_{pip}, 3-H_{pip}), 3.63 (s, 4 H, $ArCH_2$), 3.69 (s, 6 H, OCH_3), 6.98 (s, 2 H, 6-H_{arom}), 7.28 (s, 2 H, 2-H_{arom}); MS, *m/z* (relative intensity) 411 (50, M^+), 260 (100).

11-[(Benzyloxy)carbonyl]-1′-ethyl-5,17-dimethoxy-4,18-dimethyl-8,11,14-triaza-2,6:16,20-dimethenospiro[cyclocosa-2,4,16,18-tetraene-1,4′-piperidine]-9,13-dione (17). A solution of 400 mg (0.97 mmol) of **16** in 60 mL of degassed, dry $CHCl_3$ and a solution of 580 mg (0.97 mmol) of the bis(pentafluorophenyl ester) **7**[2b] in 60 mL of the same solvent were added under Ar dropwise and synchronously to 100 mL of $CHCl_3$ stirred at 20 °C. A high-dilution apparatus described by Vögtle[33] was used in this procedure. After the addition, stirring was continued for 3 h. The solvent was removed in vacuo, and the crude product was separated from polymeric material by filtration over silica gel. Chromatography (MPLC) on silica gel from chloroform, saturated with NH_3/methanol (100:5), afforded 210 mg (33%) of colorless **17**: mp 149–151 °C (ether); IR (KBr) ν 1710, 1650 (C=O) cm^{-1}; ^1H NMR (360 MHz, Me_2SO-d_6) δ 0.93 (t, *J* = 7.1 Hz, 3 H, NCH_2CH_3), 2.17 (s, 6 H, $ArCH_3$), 2.25–2.45 (m, 10 H, NCH_2CH_3, 2-H_{pip}, 3-H_{pip}), 3.62 (s, 6 H, OCH_3), 4.09 (s, 2 H, $COCH_2N$), 4.13 (s, 2 H, $COCH_2N$), 4.24 and 4.27 (AB, *J* = 5.5 Hz, 4 H, $ArCH_2$), 5.07 (s, 2 H, OCH_2), 6.95–7.05 (m, 4 H, Ar-H), 7.25–7.45 (m, 5 H, Ar-H), 9.07 (m, 2 H, NH); MS, *m/z* (relative intensity) 535 (100, M^+ – C_7H_7O). Anal. Calcd for $C_{37}H_{46}N_4O_6$ (642.8): C, 69.14; H, 7.21; N, 8.72. Found: C, 69.12; H, 7.44; N, 8.45.

1′-Ethyl-5,17-dimethoxy-4,18-dimethyl-8,11,14-triaza-2,6:16,20-dimethenospiro[cyclocosa-2,4,16,18-tetraene-1,4′-piperidine]-9,13-dione (18). A solution of 100 mg (0.15 mmol) of **17** in 100 mL of ethanol containing 0.1 mL of 2 N HCl was stirred for 4 h at 20 °C in a hydrogen atmosphere (4 bar) in the presence of 80 mg of palladium (10%) on charcoal. The catalyst was removed by filtration. The residue was partitioned between $CHCl_3$ and 2 N NaOH. The organic phase was dried over sodium sulfate, and the solvent was evaporated in vacuo. Chromatography (MPLC) on silica gel from $CHCl_3$, saturated with NH_3/methanol (100:5), followed by recrystallization from ether/*n*-heptane afforded 73 mg (93%) of **18** as colorless microcrystals: mp 194 °C; IR (KBr) ν 1650 (C=O) cm^{-1}; ^1H NMR (360 MHz, Me_2SO-d_6) δ 0.94 (t, *J* = 7.1 Hz, 3 H, NCH_2CH_3), 2.1–2.25 (m, 8 H, $ArCH_3$, NCH_2CH_3), 2.25–2.5 (m, 8 H, 2-H_{pip}, 3-H_{pip}), 3.19 (s, 4 H, CH_2NCH_2), 3.62 (s, 6 H, OCH_3), 4.30–4.35 (m, 4 H, $ArCH_2$), 7.02 (s, 2 H, ArH), 7.13 (s, 2 H, ArH), 8.31 (m, 2 H, CONH); MS, *m/z* (relative intensity) 510 (30, M^+ + H), 84 (100). Anal. Calcd for $C_{29}H_{40}N_4O_4$ (508.6): C, 68.48; H, 7.93; N, 11.02. Found: C, 68.29 H, 7.99; N, 11.30.

11-(Bromoacetyl)-1′-ethyl-5,17-dimethoxy-4,18-dimethyl-8,11,14-triaza-2,6:16,20-dimethenospiro[cyclocosa-2,4,16,18-tetraene-1,4′-piperidine]-9,13-dione (19). A solution of 0.30 g (1.5 mmol) of α-bromoacetyl bromide in 5 mL of dry chloroform was added dropwise under Ar to a solution of 0.60 g (1.1 mmol) of **18** in 10 mL of $CHCl_3$. After the solution was stirred for 2 h at 20 °C, 20 mL of $CHCl_3$ was added. The organic solution was extracted with 2 N NaOH and dried over sodium sulfate, and the solvent was evaporated in vacuo. Chromatography (MPLC) on silica gel from chloroform, saturated with NH_3/methanol (100:15), afforded 0.27 g (37%) of **19**: mp 312 °C dec; IR (KBr) ν 1650 (C=O) cm^{-1}; ^1H NMR (360 MHz, Me_2SO-d_6) δ 0.95 (t, *J* = 6.5 Hz, 3 H, NCH_2CH_3), 2.18 (s, 6 H, $ArCH_3$), 2.25–2.45 (m, 10 H, NCH_2CH_3, 2-H_{pip}, 3-H_{pip}), 3.63 (s, 6 H, OCH_3), 4.10 and 4.12 (2 s, 4 H, CH_2NCH_2), 4.23 (d, *J* = 5.2 Hz, 2 H, $ArCH_2$), 4.32 (d, *J* = 5.2 Hz, 2 H, $ArCH_2$), 4.33 (s, 2 H, CH_2Br), 6.94 (s, 1 H, ArH), 6.96 (s, 1 H, ArH), 7.03 (d, *J* = 1.6 Hz, 2 H, ArH), 8.72 (t, *J* = 5.2 Hz, 1 H, CONH), 9.16 (t, *J* = 5.2 Hz, 1 H, NH); MS (FAB), *m/z* (relative intensity) 628 (100, M^+). Anal. Calcd for $C_{31}H_{41}BrN_4O_5$ (629.6): C, 59.14; H, 6.56; Br, 12.69; N, 8.90. Found: C, 59.39; H, 6.62; Br, 12.60; N, 9.10.

1′-Ethyl-5,17-dimethoxy-4,18-dimethyl-11-(4-methylthiazolium-3-ylacetyl)-8,11,14-triaza-2,6:16,20-dimethenospiro[cyclocosa-2,4,16,18-tetraene-1,4′-piperidinium]-9,13-dione Dibromide (2). A solution of 70 mg (0.14 mmol) of **18** and 30 mg of α-bromoacetyl bromide in 2 mL of $CHCl_3$ was stirred under Ar at 20 °C for 2 h. A total of 20 mL of ether was added, and the precipitated hydrobromide of **19** was collected by filtration and dried at 20 °C/10^{-3} Torr. In a 5-mL flask, the crude hydrobromide of **19** was reacted at 20 °C under Ar for 48 h with 1 mL of 4-methylthiazole. Upon addition of ether, the thiazolium salt pre-

(34) Stetter, H.; Kuhlmann, H. *Chem. Ber.* **1976**, *109*, 2890–2896.

cipitated and was recrystallized three times from ether/acetone/*n*-heptane to give 89 mg (75%) of hygroscopic colorless crystals of **2**, which were analyzed as dihydrate: mp > 310 °C dec; IR (KBr) ν 1660 (C=O) cm^{-1}; ^1H NMR (500 MHz, Me_2SO-d_6) δ 1.22 (m, 3 H, NCH_2CH_3), 2.15–2.3 (m, 8 H, $ArCH_3$, 3′-H_{ax}), 2.37 (d, J = 3.5 Hz, 3 H, thiaz–CH_3), 2.65–2.80 (m, 2 H, 3′-H_{eq}), 3.0–3.2 (m, 4 H, NCH_2CH_3, 2′-H_{ax}), 3.45–3.8 (m, 8 H, OCH_3, 2′-H_{eq}), 4.0–4.5 (m, 8 H, CH_2NCH_2, $ArCH_2$), 5.6–5.7 (m, 2 H, N^+CH_2), 6.8–7.2 (m, 4 H, ArH), 8.03 (m, 1 H, 5-H_{thiaz}), 8.7–8.8 (m, 1 H, CONH), 9.2–9.25 (m, 1 H, NH), 10.08 (d, J = 2.4 Hz, 1 H, 2-H_{thiaz}); MS (FAB), analyzed for the free amine $C_{35}H_{46}BrN_5O_5S$ (727.3), m/z (relative intensity) 728 (2.1, $M^+ + 1$), 648 (100, $M^+ - Br$). Anal. Calcd for $C_{35}H_{46}BrN_5O_2S \cdot HBr \cdot 2H_2O$ (863.7): C, 48.67; H, 6.19; Br, 18.50; N, 8.11; S, 3.71. Found: C, 48.37; H, 6.15; Br, 18.29; N, 8.18; S, 3.93.

Kinetic Investigations. ^1H NMR Spectroscopic Analysis of the Benzoin Condensations Catalyzed by 1–3. A total of 5–25 mg of catalysts **1–3** was introduced into a ^1H NMR tube. Using a syringe, a 60 mM solution of triethylamine in methanol-d_4 was added in an amount calculated to give a 20 mM solution of catalyst. Depending on the amount of catalyst, a total of 20–25 μL of benzaldehyde was added via syringe to give a 0.4 M solution of substrate. At 20 °C, Ar gas was bubbled through the solution for 3 min and the NMR tube was tightly sealed. The reaction mixture was incubated at 323 K in the magnet of the 360- or 500-MHz spectrometer, and the following measurements were controlled with a computer program. Spectra were recorded at hourly or smaller intervals, and each individual measurement involved the accumulation of 100 scans at an acquisition time of 1.2–1.5 s. At 360 MHz, a relatively small pulse Pw = 2 μs and a delay time of 3.6 s were chosen to allow for sufficient proton relaxation and to assure very reproducible integrations with small errors (±10%).

For evaluation of the progress of the reaction, the change in integrated intensity of the proton signals of substrate (decrease of the singlet for the aldehyde proton at δ = 9.97 ppm) and product (increase of the isolated doublet at δ = 7.93 for the aromatic protons ortho to the carbonyl group) was followed relative to the intensity of the methyl signal of triethylamine as internal standard. Figure 1 shows the progress of benzoin condensations as monitored by ^1H NMR. The rates of the reactions catalyzed by **1** and **2** were evaluated assuming a first-order dependency from the aldehyde concentration. The first-order rate constants were calculated with a nonlinear least-squares fitting computer program that fits the experimental data according to the equation $y = ae^{-k_{obsd}t} + b$. For the conversion in the presence of **1** (Figure 1), the parameters a = 14.3, k_{obsd} = 0.70 h^{-1}, and b = 0.80 are obtained. No significant b value is obtained, if only the four first data points (≥80% conversion) are fitted. For the conversion in the presence of **2** (Figure 1), the parameters are a = 82.1, k_{obsd} = 0.35 h^{-1}, and b = 8.25.

For initial rate measurements by ^1H NMR, accumulations of 25 scans were taken for 30 min (<15% conversion) at intervals of 4 min.

Medium-Pressure Liquid Chromatographic (MPLC) Analysis of Benzoin Condensations Catalyzed by 1–3. A thick glass column (V = 100 mL, d = 2.5 cm) was packed tightly and homogeneously with silica gel, 12–21 μm, using a newly developed dry packing apparatus.[30] The column was conditioned with chloroform/ligroin (40–80 °C) (1:1 v/v). At a pressure of 5 bar, the retention times of benzaldehyde and benzoin were 3.7–3.8 and 4.4–4.5 min, respectively, and base-line separations were obtained. Product detection occurred in a 0.2-mm quartz flow cell by monitoring the UV absorption at λ = 254 nm. For quantitative analysis, a computing integrator was used. The integrator was calibrated before kinetic runs by analyzing sample volumes of 10 μL with known content of benzaldehyde and benzoin. If initial rates were to be determined, the ratio of benzaldehyde to benzoin in the calibration samples was ≈10:1. By use of the corrected area normalization method, accuracies in measured concentrations of ±0.4% were obtained.

For the measurement of initial rates, the calculated amounts of catalyst and aldehyde were dissolved in 3 mL of methanol in a 5-mL reaction vessel. Argon gas was bubbled for 3 min through the solution which then was thermostated at 318 K in a water bath. The addition of the desired amount of base via syringe marked the start of the reaction (t = 0). Within t = 300–1200 s (5–10% conversion), 6–8 aliquots of 10 μL were taken from the reaction vessel and analyzed quantitatively via MPLC.

^1H NMR Spectroscopic Analysis of H/D-Exchange Rates. The detailed procedures for these NMR experiments were worked out by Breslow[7] and Haake et al.[24] To analyze the rates of H/D exchange, the decrease in integrated intensity of the ^1H NMR signal of the proton 2-H at the thiazolium ring was followed as a function of time relative to the intensity of the signal of 5-H at the thiazolium ring which was chosen as the internal standard. The experimental data (see Figures 4 and 5) are fitted to a first-order rate equation with a nonlinear least-squares fitting computer program. Measurements at 500 MHz included the recording of 8–15 spectra with 8–20 scans each at small pulse width and acquisition times of 1.2–1.8 s.

All ^1H NMR and MPLC kinetic data given are averages of duplicate or triplicate runs.

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