191. Catalytic Cyclophanes

Part IX [1]

A Thiazolio-cyclophane as Model for Pyruvate Oxidase and One-Pot Synthesis of Aromatic Esters by Electrochemical Oxidation of Aldehydes Mediated by Bis(coenzyme) Catalysis

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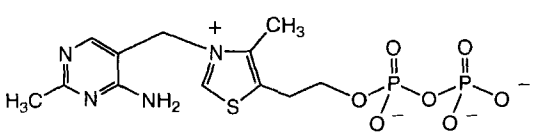
Macrocycle **3** with a hydrophobic cavity and an appended thiazolium ring is prepared following a novel synthetic sequence to monofunctionalized cyclophanes. Although the thiazolium ring of **3** prefers to be located in the cyclophane cavity, it could be displaced with low energetic costs by benzene and naphthalene guests which form stable 1:1 inclusion complexes with **3** in protic solvents. Initial rate studies show that **3** is a pyruvate-oxidase mimic and catalyzes the oxidation of aromatic aldehydes to carboxylic acids in aqueous solution. Cyclophane **3** also catalyzes the conversion of aromatic aldehydes to the corresponding esters in alcoholic solvents. The supramolecular catalyst **3** exhibits enzyme-like saturation kinetics, large turnover numbers, as well as high reaction and substrate selectivity, and it is far superior to the non-macrocyclic catalysts **4** and **5** which lack a substrate binding site. Following cyclic voltammetric investigations of the redox behavior and stability of thiazolium ions, a new one-pot electrochemical synthesis of aromatic esters is developed: Aromatic esters are prepared efficiently by indirect electrochemical oxidation of the corresponding aldehydes in alcoholic solvents, mediated by two coenzymes, the thiazolium ions **3** or **5** and flavin **21**. At the extraordinarily low working electrode potential of −300 mV (*vs.* Ag/AgCl), high yields of the esters are obtained with high current efficiencies and high turnovers of the catalysts which are stable under the reaction conditions. The origin of the substrate and reaction selectivity, which is particularly pronounced in the supramolecular reactions catalyzed by **3**, is analyzed.

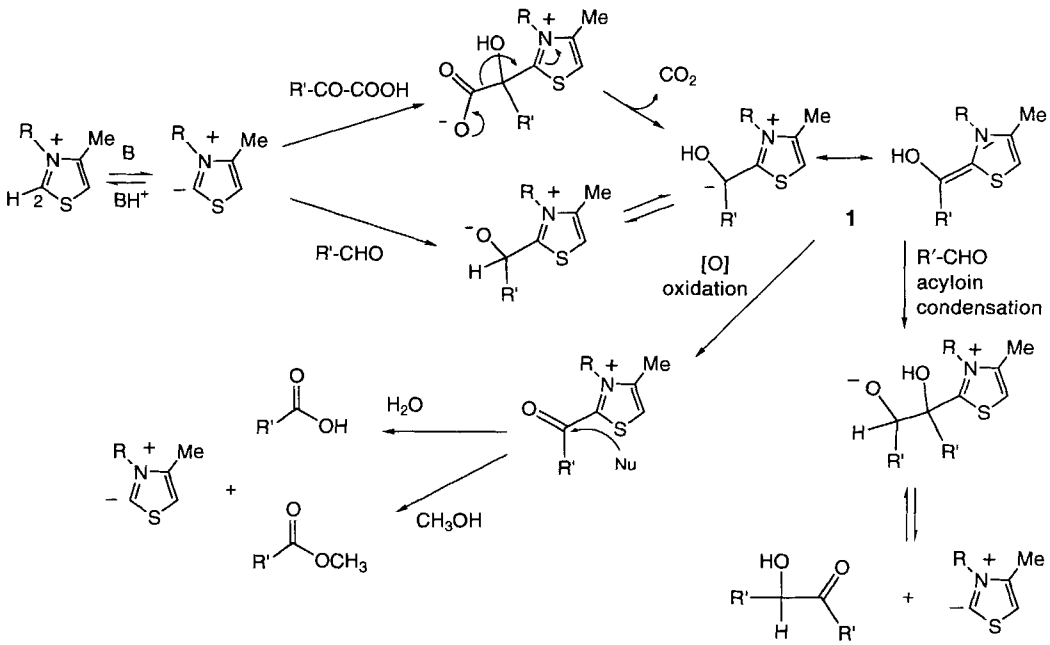
1. Introduction. – Thiamine pyrophosphate (TPP), the coenzyme form of vitamin B_1, is involved in a number of biochemical reactions in carbohydrate metabolism [2–4]. TPP-Dependent enzymes catalyze *i*) non-oxidative decarboxylations of α-keto acids (*e.g.* pyruvate decarboxylase), *ii*) oxidative decarboxylations of α-keto acids (*e.g.* pyruvate oxidase, pyruvate dehydrogenase), and *iii*) α-keto transfers (*e.g.* transketolase). The thiazolium ring accounts for most of the catalytic activity of TPP, and simple thiazolium salts effect these transformations even in the absence of enzyme [5].



TPP

The flavin-dependent enzyme pyruvate oxidase transforms pyruvate into acetate (*Scheme 1*) [6]. Decarboxylation of pyruvate [7] generates the 'active aldehyde' **1**, which is believed to be the reactive intermediate in TPP- and thiazolium-ion catalyzed reactions, although it was never directly observed [8]. The 'active aldehyde' is oxidized by the flavin to give the 2-acylthiazolium intermediate which is rapidly solvolyzed, producing acetate and regenerating the thiazolium ylide.

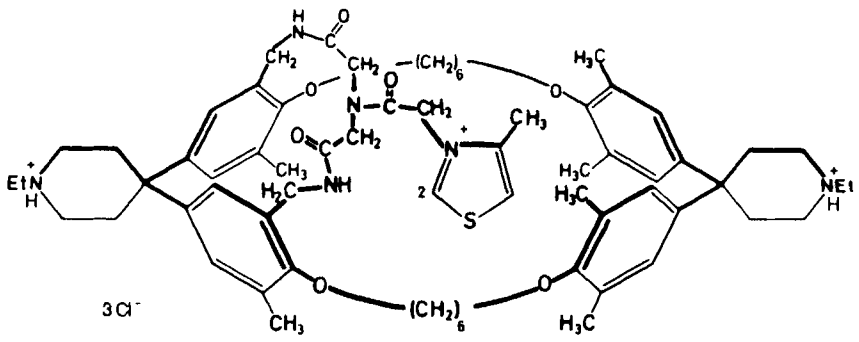
Scheme 1. *Oxidative Decarboxylation of Pyruvate, Oxidation of Aldehydes to Carboxyl Derivatives, and Acyloin Condensation, Catalyzed by Thiamine Pyrophosphate or Thiazolium Ions and Involving 'Active Aldehyde'* **1** *as a Common Intermediate*

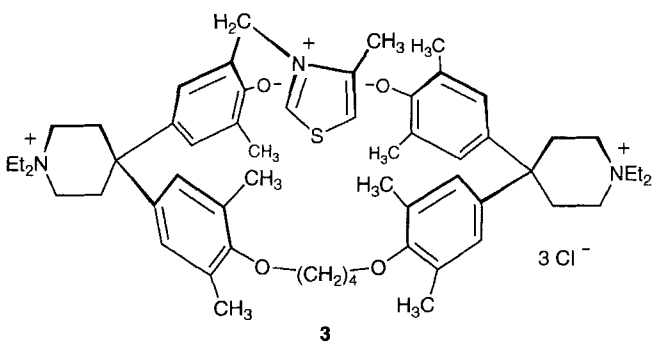


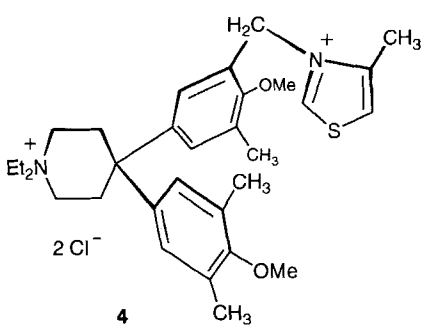
In a similar mechanistic sequence (*Scheme 1*), aldehydes are oxidized to carboxylic acids (in H_2O) and esters (in alcohols). These conversions were catalyzed by simple thiazolium ions [9], thiazolium micelles [10], and thiazolium-cyclodextrin derivatives [11] in the presence of stoichiometric amounts of oxidizing agents like nitrobenzene [9b, e], potassium ferricyanide [11a], and flavins [9a] [10b, c]. The synthetic utility of these reactions so far has been limited. The use of stoichiometric quantities of the oxidizing agent causes solubility problems and complicates product isolation. Also, the thiazolium catalysts are destroyed oxidatively in basic solution by ferricyanide [11a] [12], I_2 [13], and air [12] [14]. At higher substrate concentrations, the acyloin condensation, which involves reaction of the 'active aldehyde' with a second aldehyde molecule, becomes a competitive side reaction (*Scheme 1*) [10c] [15]. A new approach was necessary to improve the synthetic utility of this biomimetic oxidation.

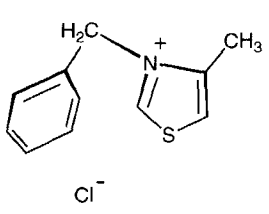
In earlier work, we prepared the thiazolio-cyclophane **2** with a cavity large enough to accommodate two benzaldehyde molecules and observed efficient supramolecular catalysis of the benzoin condensation in protic solvents [16]. Here, we describe the synthesis of

thiazolio-cyclophane **3** with a binding cavity complementary in size to only one benzene or naphthalene molecule. In comparative kinetic studies with **3**–**5** under initial rate conditions, we show that **3** acts as an artificial enzyme and efficiently catalyzes the oxidation of aromatic aldehydes to carboxylic acids and esters. Subsequently, we describe a preparative-scale, one-pot synthesis of aromatic methyl and ethyl esters [17] by electrochemical oxidation of aldehydes, mediated by two coenzyme catalysts, the thiazolium derivatives **3** or **5** and a flavin derivative. This study shows that combining the principles of electrocatalysis [18] with supramolecular catalysis not only leads to high reaction rates but also to enhanced yields of the desired products as a result of high reaction selectivity [19].



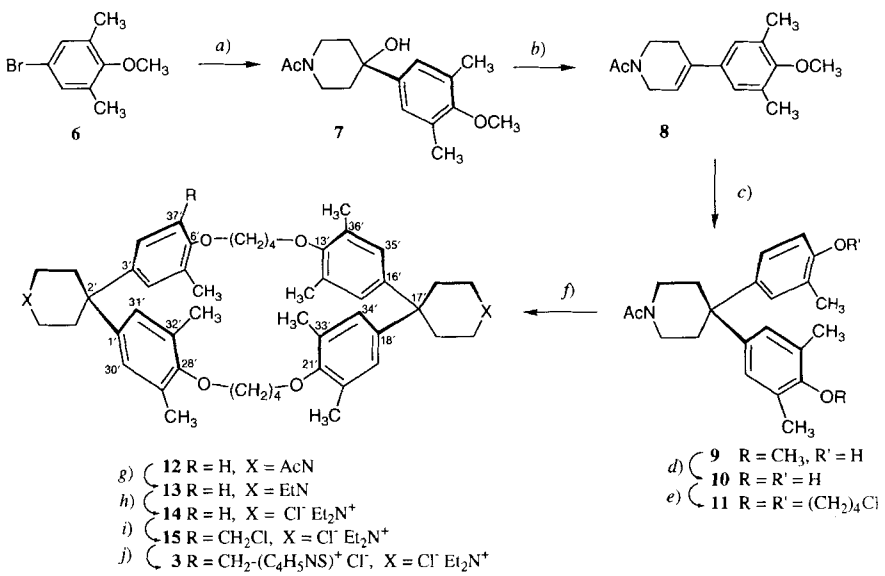






2. Results and Discussion. – 2.1. *Synthesis of the Thiazolium Catalysts* **3** *and* **4**. In the synthesis of the monofunctionalized cyclophane **3** (see *Scheme 2*), the *Grignard* reagent of 5-bromo-2-methoxy-1,3-dimethylbenzene (**6**) was reacted with 1-acetylpiperidin-4-one to form alcohol **7** which, upon dehydration, yielded olefin **8**. Treatment of **8** with $BF_3 \cdot Et_2O$ and 2-methylphenol afforded **9** which was demethylated with BBr_3 to give bisphenol **10**. Alkylation of **10** with $Cl(CH_2)_4Cl$ produced the dichloride **11** which was cyclized with 4,4′-(1-acetylpiperidine-4,4-diyl)-2,2′,6,6′-tetramethylbis(phenol) to cyclophane **12**. Reduction with $BH_3 \cdot THF$ afforded the bis(tertiary amine) **13** which was quaternized to give, after ion exchange (Cl^-), macrocycle **14**. Chloromethylation of **14** with HCl/CH_2O in AcOH led to the benzyl chloride **15** which, upon reflux in MeCN with an excess of 4-methylthiazole, was transformed into the H_2O-soluble thiazolio-cyclophane **3**.

Scheme 2. *Synthesis of Thiazolio-cyclophane* **3**

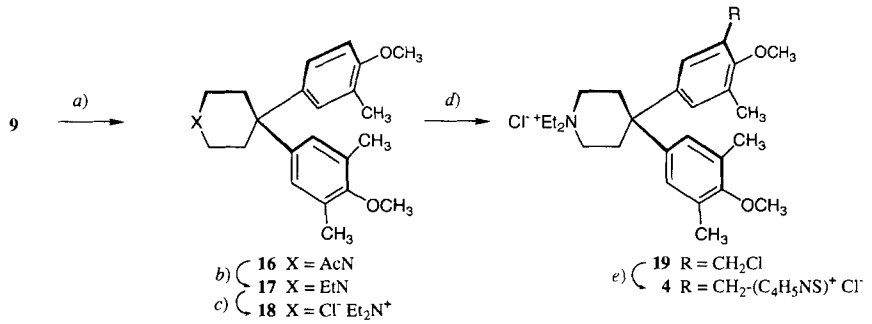


a) Mg, THF; then 1-acetylpiperidin-4-one, 65%. *b*) TsOH, toluene, reflux, 87%. *c*) $BF_3 \cdot OEt_2$, 2-methylphenol, 85°, 84%. *d*) BBr_3, $CHCl_3$, −78°, 94%. *e*) $Cl(CH_2)_4Cl$, Cs_2CO_3, DMF, 90°, 94%. *f*) 4,4′-(1-Acetylpiperidine-4,4-diyl)-2,2′,6,6′-tetramethylbis(phenol), Cs_2CO_3, MeCN, reflux, 22%. *g*) $BH_3 \cdot THF$, 91%. *h*) EtI, $CHCl_3$, then ion exchange (Cl^-), 82%. *i*) CH_2O, HCl, AcOH, 91%. *j*) 4-Methylthiazole, MeCN, 60°, 79%.

The non-macrocyclic comparison compound **4** was obtained by a similar sequence from **9** *via* **16**–**19** (see *Scheme 3*), which represents a novel general route to monosubstituted cyclophanes and diphenylmethane clefts.

2.2. *^{1}H-NMR Binding Studies.* The ^{1}H-NMR spectrum of cyclophane **3** in D_2O shows considerable upfield shifts (ppm) of the thiazolium resonances as compared to the same resonances in **5** (+ 0.70 for H–C(2), + 0.39 for H–C(5), + 0.27 for Me–C(4)), indicating that the thiazolium ring in **3** prefers to be located within the shielding cavity. Therefore, we performed 500-MHz ^{1}H-NMR binding titrations in D_2O/CD_3OD 3:2 at 293 K to determine how this self-complexation behavior [20] would affect the binding of aromatic substrates (*Table 1*). The comparison of binding free energies shows that the

Scheme 3. *Synthesis of the Thiazolio-cleft* **4**



a) KOH, Me_2SO_4, 91%. *b*) $LiAlH_4$, THF, 83%. *c*) EtI, CH_2Cl_2, then ion exchange (Cl^-), 70%. *d*) CH_2O, HCl, AcOH, 90%. *e*) 4-Methylthiazole, 85–95°, 76%.

complexes of thiazolio-cyclophane **3** are 0.4–0.7 kcal/mol less stable than those formed by cyclophane **14** without the thiazolium ring. A large part of this energy is presumably needed to displace the heterocycle from the cavity by an incoming guest.

Binding strength decreases from D_2O/CD_3OD 3:2, to $D_2O/(CD_3)_2SO$ 2:3, to pure CD_3OD (*Table 1*); these solvent-dependent data facilitated the choice of solvent and concentration ranges for the catalytic studies.

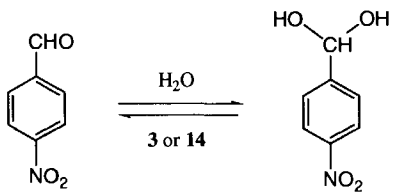
Table 1. *Association Constants* K_a *and Binding Free Energies* $-\Delta G^0$ *for 1:1 Complexes of* **3** *and* **4**[a])

Guest	K_a [l mol^{-1}]	ΔG^0 [kcal mol^{-1}]
Complexes of **14** *in* D_2O/CD_3OD *3:2 at 293 K*		
Benzaldehyde	$2.4 \cdot 10^2$	3.19
Benzene-1,4-dicarbonitrile	$1.1 \cdot 10^3$	4.10
Naphthalene-2-carbaldehyde	$6.3 \cdot 10^3$	5.10
6-Methoxynaphthalene-2-carbonitrile	$1.5 \cdot 10^4$	5.60
Complexes of **3** *in* D_2O/CD_3OD *3:2 at 293 K*		
Benzaldehyde	$1.2 \cdot 10^2$	2.79
Benzene-1,4-dicarbonitrile	$3.5 \cdot 10^2$	3.41
Naphthalene-2-carbaldehyde	$2.0 \cdot 10^3$	4.42
6-Methoxynaphthalene-2-carbonitrile	$4.8 \cdot 10^3$	4.94
Complexes of **3** *in* $D_2O/(CD_3)_2SO$ *2:3 at 303 K*		
Naphthalene-2-carbaldehyde	$1.2 \cdot 10^2$	2.86
Complexes of **3** *in* CD_3OD *at 293 K*		
Benzaldehyde	7	1.1
4-Cyanobenzaldehyde methyl hemiacetal	15	1.6
4-Cyanobenzaldehyde	27	1.9
Naphthalene-1-carbaldehyde	15	1.6
Naphthalene-2-carbaldehyde	40	2.1

[a]) Accuracy in ΔG^0: ± 0.1 kcal mol^{-1}.

In D_2O/CD_3OD 3:2, 4-nitrobenzaldehyde exists in equilibrium with the corresponding hydrate (*Eqn. 1*). Based on integration of the aldehydic (C*H*O) and hydrate (C*H*$(OH)_2$) resonances in the ^{1}H-NMR spectrum, an aldehyde/hydrate ratio of 0.65 is

calculated. In the presence of **3** or **14** ([receptor] = 4 mM, [aldehyde] = 0.5 mM), this ratio shifts to a value of *ca.* 1.6 in favor of the aldehyde. For the complex of **14** with the aldehyde, an association constant of $K_a = 330\ l \cdot mol^{-1}$ is estimated from the titration data, and for the complex with the hydrate, $K_a = 210\ l \cdot mol^{-1}$. The electron-rich cyclophane binds the electron-accepting aldehyde more strongly than the hydrate; in addition, inclusion complexation could interfere more with the stronger solvation of the $CH(OH)_2$ group than with the weaker solvation of the CHO function [21].



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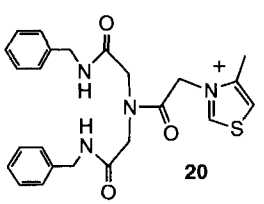
2.3. *Micropolarity Effect on the Kinetic Acidity of the Thiazolium Proton at C(2).* Recently, the pK_a of the acidic proton at C(2) of the thiazolium ring [22] was determined for thiamine and several thiazolium ions to be in the range of 17 to 19 [23] [24]. Since the ylide formed on deprotonation is less polar than the starting positively charged thiazolium ion, the pK_a decreases markedly in solvents of low dielectric constant which stabilize the ylide [25]. In TPP-dependent enzymatic reactions, it may indeed be one of the important roles of the apoenzyme to bind the thiazolium ring in a region less polar than H_2O so as to substantially decrease the pK_a of H–C(2) and favor the formation of the ylide, which subsequently undergoes nucleophilic attack of the substractes (*Scheme 1*) [2] [23] [26].

In studies with **2**, a pronounced micropolarity effect of the cyclophane cavity on the kinetic acidity of H–C(2) was observed [16]. In a KCl/DCl buffer at pD 1.8 and 303 K, the H/D-exchange rate of the thiazolio-cyclophane **2** was increased 66-fold over that of the simple thiazolium ion **20**. In deuterated citric-acid buffer (pD 3.4)/CD_3OD, the rate of H/D exchange observed for **2** was 3.8 times faster than the rate observed for **20**.



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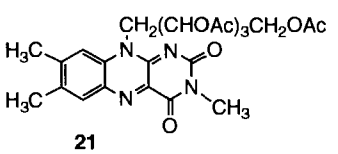

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To explore micropolarity effects in the series **3**–**5**, we used 360-MHz ^{1}H-NMR spectroscopy to determine the rate of H/D exchange at C(2) of the thiazolium ring in aqueous acetate buffer at pH 4.3 (pD 4.7) [27]. At this pD, the reaction could be conveniently monitored [28] and the H/D-exchange rate in cyclophane **3** was found to be 2.7 times faster than in **5** and 1.2 times faster than in **4** (*Table 2*). The apolar cavity of **3** seems to change the micropolarity around the thiazolium ion only weakly as compared to the non-macrocyclic derivatives **4** and **5**. The phenyl rings in **4** and **5** partially desolvate the region containing the thiazolium ion and its conjugate base, the ylide. The difference in environmental polarity for the thiazolium ions in **3**–**5** is, therefore, not as large. In

contrast, the thiazolium ion in **20** is fully exposed to the aqueous solution, and only the thiazolium ion in cyclophane **2** encounters a less polar environment. Support for this explanation was provided by the observation that in aqueous buffer at 298 K and pH 5.37, the H/D-exchange rate at C(2) of 3-benzyl-4-methylthiazolium bromide was 3 times faster than that of 3,4-dimethylthiazolium bromide [8a].

Table 2. *Observed First-Order Rate Constants for H/D Exchange at C(2) of Thiazolium Ions Determined by 360-MHz ^{1}H-NMR in Deuterated Acetate Buffer* (pD 4.7) *at 303 K*

Thiazolium catalyst	**3**	**4**	**5**
k_{obs} [s^{-1}]	$(6.1 \pm 0.1) \cdot 10^{-4}$	$(5.0 \pm 0.1) \cdot 10^{-4}$	$(2.3 \pm 0.1) \cdot 10^{-4}$

2.4. *Initial-Rate Studies of the Supramolecular Catalysis of the Oxidation of Naphthalene-2-carbaldehyde to Naphthalene-2-carboxylic Acid and Methyl Naphthalene-2-carboxylate.* The thiazolium-catalyzed oxidation of naphthalene-2-carbaldehyde to naphthalene-2-carboxylic acid according to the mechanism in *Scheme 1* was studied following the detailed optimized procedures of *Hilvert* and *Breslow* [11a]. Oxidations were run at 303 K with potassium ferricyanide as oxidizing agent in Me_2SO/aqueous phosphate buffer (0.025 M, pH 7.5) 3:2 in a 0.2-cm UV cuvette. The reaction was initiated by addition of a solution of the catalysts **3**–**5** in Me_2SO to premixed stock solutions of the aldehyde in Me_2SO and potassium ferricyanide in aqueous buffer, yielding homogeneous mixtures with [catalyst] = 0.5 mM, $[K_3(Fe(CN)_6)]$ = 5.0 mM and [aldehyde] = 2.0–36.0 mM. The course of the reaction was followed by monitoring the decrease in absorbance of the Fe^{III} chromophore at 420 nm (ε_{420} = 1040 M^{-1} cm^{-1}). The reaction is zero-order in ferricyanide, and initial velocities were determined by standard linear regression analysis of the initial linear portion of absorbance *vs.* time plots.

The thiazolium catalysts were themselves slowly oxidized under the experimental conditions, since the redox potential of ferricyanide ($E° \approx +0.690$ V *vs.* standard hydrogen electrode) apparently was too high. Therefore, the rates determined in the presence of an aldehyde substrate were corrected by subtracting independently measured background rates for slow thiazolium-catalyst oxidation [11a]. The background rate for oxidation of **3** was 5–15% of the total rate measured in the presence of naphthalene-2-carbaldehyde. Since the oxidation of the aldehyde by **4** and **5** was considerably slower (*Table 3*), the background oxidation rate of these catalysts was 25–95% of the total rate. No reduction of ferricyanide was observed in the absence of a thiazolium catalyst.

Table 3. *Oxidation of Naphthalene-2-carbaldehyde to Naphthalene-2-carboxylic Acid in the Presence of $K_3[Fe(CN)_6]$* (5.0 mM) *in Me_2SO/Aqueous Phosphate Buffer* (pH 7.5) *3:2 at 303 K*

Catalyst	Initial velocity [M s^{-1}][a])	Second-order rate constant [M^{-1} s^{-1}]
3	$4.18 \cdot 10^{-6}$	$k_{cat}/K_M = 2.8$
4	$1.17 \cdot 10^{-7}$	$k_2 = 0.037$
5	$3.90 \cdot 10^{-8}$	$k_2 = 0.0061$

[a]) At [aldehyde] = 6.0 mM, [catalyst] = 0.5 mM; corrected for background rate of catalyst oxidation.

Saturation kinetics were observed with cyclophane **3** (*Fig. 1*). A *Lineweaver-Burke* plot ($1/v$ *vs.* $1/[S]$) gave K_M = 5.4 mM and $v_{max} = 7.5 \cdot 10^{-6}$ M s^{-1}. The K_M value is in good agreement with the association constant for the complex of **3** with naphthalene-2-carb-

aldehyde (*Table 1*). The turnover number $k_{cat} = v_{max}/[3]$ was calculated to be 0.015 $s^{-1} = 0.90\ min^{-1}$. In contrast, rates in the presence of **4** and **5** increased in a linear fashion with increasing substrate concentration. A comparison of the apparent bimolecular rate constant k_{cat}/K_M for the reaction catalyzed by **3** with the calculated second-order rate constants for the reactions catalyzed by the simple thiazolium ions **4** and **5** revealed that the rate acceleration was 75-fold between **3** and **4** and 460-fold between **3** and **5** (*Table 3*). Comparison of initial velocities showed a catalytic advantage of similar magnitude for **3**. The formation of naphthalene-2-carboxylic acid in these reactions was confirmed by ^{1}H-NMR spectroscopy. Comparison with authentic samples of naphthalene-2-carbaldehyde and naphthalene-2-carboxylic acid showed that no by-products were formed, which demonstrates high reaction selectivity. In independent runs, the naphthoin condensation was studied by 500-MHz ^{1}H-NMR spectroscopy at 323 K under Ar in $(CD_3)_2SO/D_2O$ 3:2 (initial concentrations: [**3**] = 0.5 mM, [naphthalene-2-carbaldehyde] = 26 mM, [Et_3N] = 40 mM). Even after 4 h, no naphthoin could be detected. Since cyclophane **3** can accommodate only one aldehyde in its binding site, it was not capable of catalyzing a reaction requiring a bulky, π-π-stacking transition state involving two naphthalenecarbaldehydes.

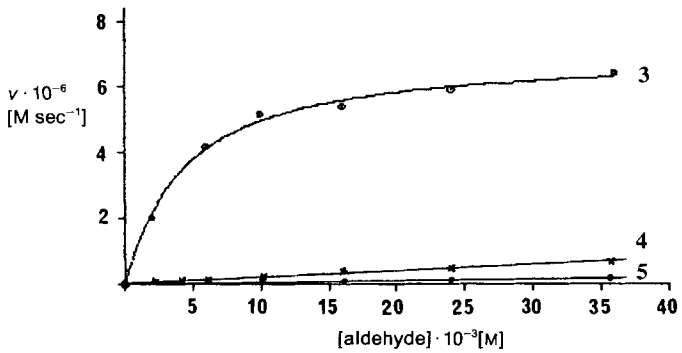


Fig. 1. Plot of initial rates vs. *substrate concentration for the oxidation of naphthalene-2-carbaldehyde catalyzed by the thiazolium derivatives* **3**–**5** (303 K, [catalyst] = 0.5 mM)

The increased rates of the supramolecular reaction catalyzed by **3**, compared to the bimolecular processes catalyzed by **4** and **5** can be explained by *i*) entropically favorable orientation and proximity effects in the complex and *ii*) by microenvironmental effects in the apolar cyclophane cavity of **3** [2] [16] [28]. Rates of thiazolium-catalyzed reactions increased with reduced environmental polarity, since the relevant reaction transition states are less polar than the ground states [26].

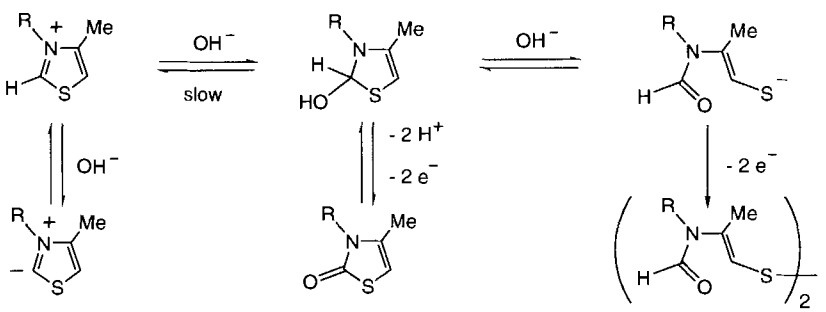
In contrast to $K_3[Fe(CN)_6]$, the redox potential of flavins such as tetra-*O*-acetyl-3-methylriboflavin **21** ($E_{1/2} \approx -500$ mV *vs.* Ag/AgCl in basic MeOH solution) was too low to cause undesired background oxidation of the thiazolium catalysts. Since ^{1}H-NMR binding assays in $(CD_3)_2SO/D_2O$ 3:2 at 303 K showed that this flavin derivative was too bulky to be included in the cavity of **3**, it seemed an ideal oxidizing agent for our studies. We first used **21** under the conditions described above for the oxidations by ferricyanide. At [**3**] = 0.5 mM, [**21**] = 2.0 mM, and [naphthalene-2-carbaldehyde] = 10 mM under Ar, an initial velocity of $7.1 \cdot 10^{-6}$ M s^{-1} was measured by monitoring the disappearance of the electronic absorption band of **21** at λ 420 nm upon reduction to the colorless dihy-

droflavin. This value was in good agreement with the initial velocity of $5.2 \cdot 10^{-6}$ M s^{-1} measured with $K_3[Fe(CN)_6]$ as the electron acceptor. The independence of the rates on the nature of the oxidizing agent supported the conclusion that the reactions are truly zero-order. The rate-determining step in both conversions is the formation of the 'active aldehyde' **1**.

The oxidation of naphthalene-2-carbaldehyde to methyl naphthalene-2-carboxylate was subsequently studied in MeOH under Ar at 303 K and at initial concentrations of [**3**] = 0.5 mM, [**21**] = 1.0 mM, [Et_3N] = 10.0 mM, and [naphthalene-2-carbaldehyde] = 2, 6, 13.3, 21, 33.3, and 66.7 mM. A *Lineweaver-Burke* plot ($1/v$ *vs.* 1/[S]) gave K_M = 150 mM and $v_{max} = 2.4 \cdot 10^{-5}$ M s^{-1}, from which a favorable turnover number k_{cat} = 0.048 s^{-1} = (2.9 min^{-1}) was calculated.

Although these initial-rate experiments looked very promising at first, limits of the utility of the chosen reaction conditions soon became apparent. The limited solubility of flavins in MeOH prevented their use as stoichiometric oxidizing agents in preparative reactions. When we attempted to work with catalytic amounts of flavin in the presence of O_2 to regenerate the oxidized flavin, poor conversions and yields of methyl naphthalene-2-carboxylate were obtained. As a competitive reaction to the oxidative regeneration of the flavin, the thiazolio moieties in **3**–**5** were readily oxidized by O_2 in the presence of base. *Scheme 4* shows the most important of the known oxidative degradation pathways of thiazolium ions [12] [29] [30]. Weakly basic solutions of thiazolium ions are stable only if all traces of O_2 are rigorously excluded. Since we were unable to work out conditions for preparative-scale oxidations of aldehydes by chemical oxidizing agents, we turned to electrochemical oxidations at the anode.

Scheme 4. *Mechanisms for Oxidative Degradation of Thiazolium Ions in Basic Solutions*



2.5. *Preparative-Scale Electrochemical Oxidation of Aldehydes Mediated by Bis(coenzyme) Catalysis.* 2.5.1. *Cyclic Voltammetric Investigation of the Redox Behavior and Stability of Thiazolium Ions in Alkaline Media.* The electrochemical behavior of the thiazolium ions **3**–**5** at platinum (Pt), gold (Au), and glassy carbon electrodes in various media was investigated by cyclic voltammetry under strict exclusion of air. The solvent systems in these studies included *a*) Me_2SO/aqueous phosphate buffer (pH 7.5) 3:2, *b*) methanolic borate buffer (pH 9.5), and *c*) MeOH/Et_3N. The following results were relevant for the development of the preparative-scale oxidation process described below [31]:

1) For each of the thiazolium catalysts **3**–**5**, a single anodic peak was observed in the potential range of 0 to +400 mV (*vs.* Ag/AgCl) (*Fig. 2*). No reduction peak was observed

on the reverse scans at all scan rates attempted between 20 and 1000 mV s^{-1}. The anodic peak remained on repeated scans showing that no passivation of electrodes occurred. The absence of a cathodic peak on the reverse scan may be due to irreversible electron transfer at the electrode or to a chemical follow-up reaction which removed the oxidized form from the electrode surface. Due to the absence of a reduction peak, the thermodynamic redox potential of the thiazolium catalysts could not be determined. However, from the anodic peak potential, it can be deduced that the redox potential should be less than +400 mV which is consistent with the fact that the thiazolium ions were readily oxidized by ferricyanide (+690 mV *vs.* standard hydrogen electrode) and air.

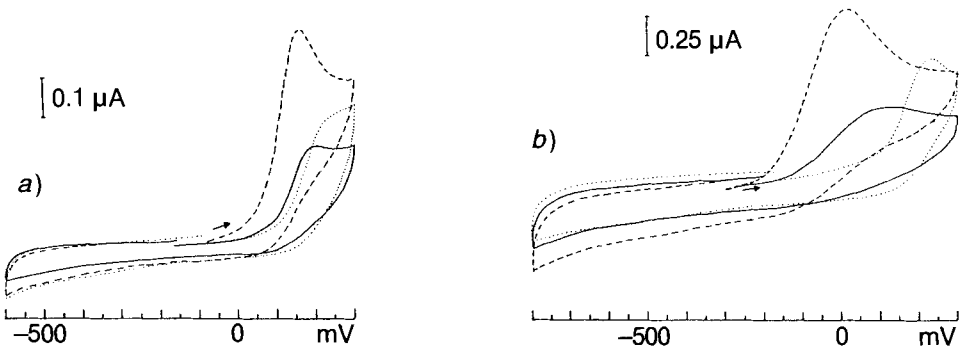


Fig. 2. *Cyclic voltammograms of* **3** (0.485 mM; · · · · ·), **4** (0.486 mM; —), *and* **5** (0.494 mM; – – – –) *in 100 mM solution of Et_4NBr in Me_2SO/aqueous phosphate buffer* (pH 7.5) 3:2 *at* a) *Pt and* b) *glassy carbon working electrodes.* Scan rate 20 mV s^{-1}, 298 K.

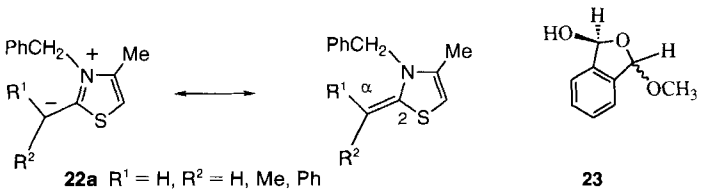
2) A base was required for the oxidation of the thiazolium catalysts. No oxidation peak was observed in pure MeOH in the absence of base.

3) In all solvent systems and at all three electrodes, cyclophane **3** had a more positive anodic peak than the non-macrocyclic thiazolium catalysts **4** and **5** and, hence, oxidative destruction of **3** at the electrode could be avoided more readily.

4) The electrochemical behavior of **3** was similar at all three electrodes, whereas, at the glassy carbon electrode, the anodic peak potentials of **4** and **5** were shifted in the cathodic direction by *ca.* 100 and 150 mV, respectively (*Fig. 2*). This showed that the overpotential for the oxidation of these thiazolium catalysts at the Pt or Au electrode was higher than at the glassy carbon electrode. Therefore, the Pt electrode was used for subsequent preparative runs.

The presence of substrates such as naphthalene-2-carbaldehyde did not significantly influence the cyclovoltammetric behavior of the thiazolium catalysts. No additional peak due to the formation of the 'active-aldehyde' intermediate (*Scheme 1*) in basic methanolic or $(CD_3)_2SO$ solutions was observed. There are several possible reasons for the absence of an anodic peak for the 'active-aldehyde' intermediate: *i*) the overpotential for the oxidation of the 'active aldehyde' at the electrode is very high, *ii*) the electron-transfer step is fast, while the preceding chemical steps are slow; therefore, the concentration of 'active aldehyde' in solution will be very low, and no peak due to its formation will be observed, and *iii*) no anodic peak for the 'active aldehyde' would be observed if the competing acyloin condensation side reaction which consumes this intermediate is fast.

Although the oxidation potential of the 'active-aldehyde' intermediate could not be determined directly by cyclic voltammetry, the potentials of related enamines **22a–c**, obtained from 2-alkylthiazolium ions in the presence of base, were measured by *Jordan* and coworkers [32]. The oxidation peak potentials at the Pt electrode of these derivatives were in the range of −169 to +144 mV *vs.* the standard calomel electrode (SCE). The MeO substituent at the C(α) position lowered the peak potential by *ca.* 25 mV compared to the H-substituent, and by *ca.* 120 mV compared to the Me substituent.



22a R^1 = H, R^2 = H, Me, Ph
b R^1 = R^2 = Me
c R^1 = MeO, R^2 = Me, Ph

23

Since there was no anodic peak observed in the cyclic voltammogram for the 'active-aldehyde' intermediate, it was difficult to determine the optimal working-electrode potential for the electrochemical oxidation of aldehydes to esters. The CV studies clearly suggested the use of Pt or Au electrodes with working-electrode potentials equal to or more negative than −200 mV (*vs.* Ag/AgCl). At potentials below −200 mV, the thiazolium catalysts are indeed very stable; however, more positive potentials may destroy them. After electrolysis for 21 h at −400 to −300 mV in Me_2SO/aqueous phosphate buffer (pH 7.5) 3:2 or in basic MeOH solution in a gas-tight electrochemical cell, there was no significant change in the cyclic voltammograms and the anodic peak currents of the two thiazolium derivatives **3** and **5** (*Fig. 3*).

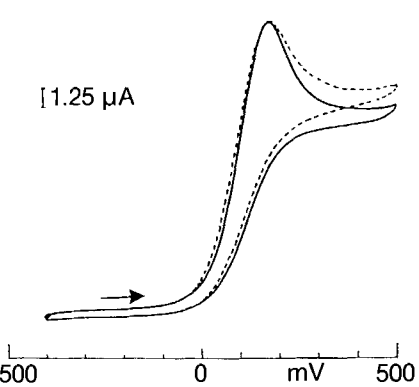


Fig. 3. *Cyclic voltammograms of* **5** (4.97 mM) *before* (—) *and after* (-----) *electrolysis in a 50 mM solution of* Et_4NBr *in methanolic borate buffer* (50 mM, pH 9.5) *at the glassy carbon electrode at −300 mV* (*vs.* Ag/AgCl) *for 21 h.* Scan rate 20 mV s^{-1}, 308 K.

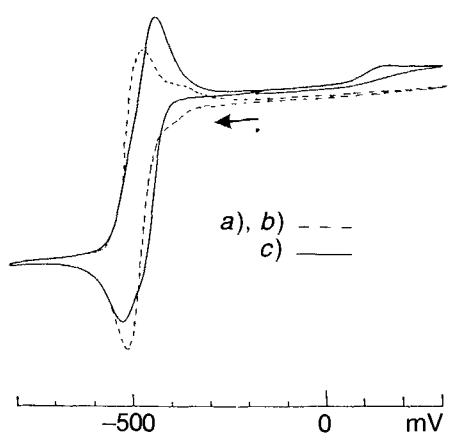


Fig. 4. *Cyclic voltammograms of* **21** (2.04 mM) *in 50 mM solution of* Et_4NBr *in MeOH* a) *before addition of* **5**, b) *after addition of* **5** (5.94 mM), *and* c) *after the addition of* **5** (5.95 mM) and *10 μl of* Et_3N *at glassy carbon working electrode.* Scan rate 20 mV s^{-1}, 308 K.

2.5.2. *High Overpotential in the Direct Electrooxidation: The Need for a Redox Mediator and Indirect Electrooxidation.* Attempts to oxidize naphthalene-2-carbaldehyde or 4-cyanobenzaldehyde in basic MeOH solutions in the presence of **5** directly at the various electrodes with working-electrode potentials of −250 to −400 mV (*vs.* Ag/AgCl) yielded disappointing results: only modest amounts of esters were obtained after several h of electrolysis. Clearly, there existed a high overpotential for the direct heterogeneous electron transfer from the dissolved 'active aldehyde' to the electrode. This slow electron transfer at the electrode surface may also account for the absence of an anodic peak for the 'active aldehyde' in the cyclic-voltammetry experiments.

Electrochemical oxidation processes are potentially very attractive as environmentally clean technology. Most of the known methods to oxidize organic compounds require stoichiometric amounts of oxidizing agents which often are heavy-metal salts [17a]. The use of stoichiometric amounts of oxidizing agents complicates product isolation, and the recycling of the redox-active oxidation state of heavy-metal salts, if successful, adds considerable cost to the industrial process. From an environmental point of view, it is important to develop convenient and inexpensive oxidation methods which do not employ stoichiometric amounts of oxidizing agent. Electrochemical oxidation processes constitute an attractive alternative to current methodology, however, due to the high overpotentials of many substrates, direct electrochemical oxidation is often unsuccessful.

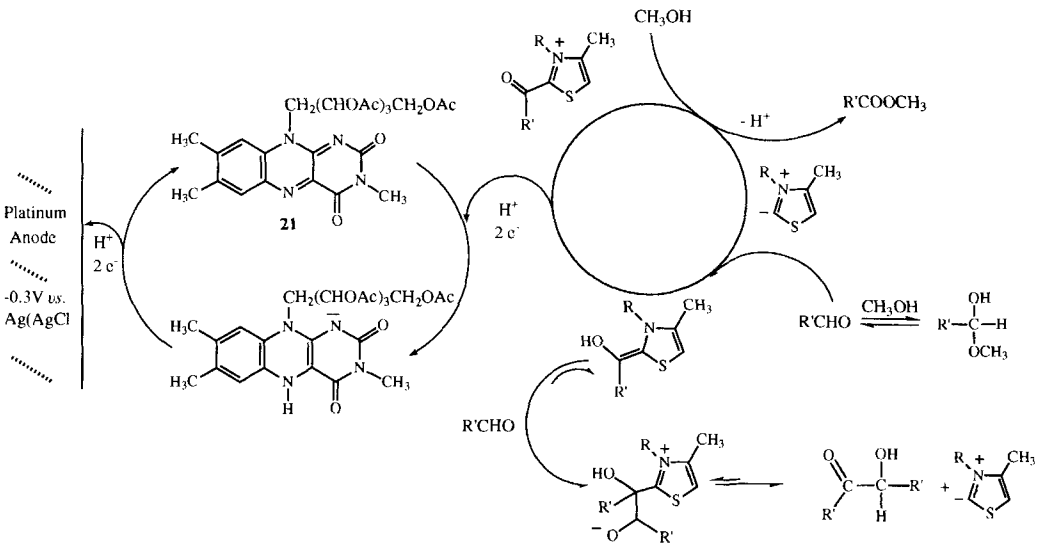
For the oxidation of benzaldehyde in $LiClO_4$/MeCN solution, *Chiba* and coworkers reported working-electrode potentials of +2.3 V (*vs.* SCE) and +1.7 V in NaCN/MeOH solution at the Pt electrode [33]. To overcome these high overpotentials, indirect electrooxidations using KI as a redox mediator [18] [34] were developed [35]. In the presence of KI, aldehydes could be oxidized to methyl esters at milder conditions, although a working-electrode potential of +0.6 to +0.8 V (*vs.* SCE), corresponding to the redox potential of I_2, was still required. At these still relatively high anodic potentials, primary and secondary alcohols were also oxidized [36]. A major advantage of indirect electrooxidation processes that occur at low overpotential is a high reaction selectivity. As an additional benefit, electrode corrosion, which frequently occurs at high potential, and passivation or fouling due to deposition and surface processes, can be avoided [18] [34].

With the example of the TPP- and flavin-dependent enzyme pyruvate oxidase, nature clearly showed us the way to overcome the problem of overpotentials and to develop an electrochemical method for selective oxidation of aldehydes at unprecedentedly low electrode potentials. Upon addition of flavin **21** as redox mediator, we observed that the electrochemical oxidation of aromatic substrates became an efficient method at working-electrode potentials in the range of −300 to −500 mV. Since the half-wave potential ($E_{1/2}$) of **21** (*Fig. 4*) in basic MeOH solution is *ca.* −500 mV (*vs.* Ag/AgCl), the redox potential of the 'active aldehydes' must be $\leqslant -500$ mV.

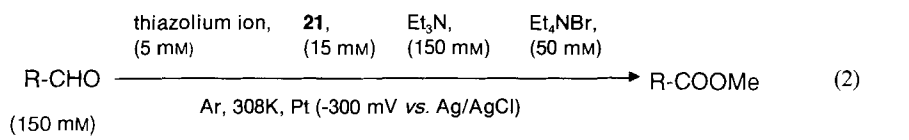
Under Ar atmosphere, **21** could be regenerated electrochemically at −300 mV without oxidative destruction of the thiazolium catalysts. Since the transfers of electrons from the substrate to **21** and from **21** to the electrode were fast, the use of **21** as a redox mediator avoided the high kinetic barriers for heterogeneous electron transfer and hence reduced the overpotential. The unprecedented electrochemical regeneration of two coenzymes in a preparative-scale process is shown in *Scheme 5*.

2.5.3. *Reaction Selectivity: Optimized Reaction Conditions Favor the Electrooxidation over the Acyloin Condensation.* A careful optimization of the reaction parameters in the

Scheme 5. *Electrochemical Regeneration of Thiazolium Ion and Flavin in the One-Pot Oxidation of Aldehydes to Carboxylic Esters*



multistep and multicomponent process was necessary not only to generate high rates and catalytic turnover but, in particular, to favor the electrochemical oxidation process over the competing acyloin condensation (*Scheme 5*). Following comprehensive experimentation [31], the reaction conditions shown in *Eqn. 2* were ultimately applied to the electrochemical oxidation of aldehydes to esters. Although the thiazolio-cyclophane **3** was superior in nearly all runs, reaction parameters were mainly optimized for conversions in the presence of the simple thiazolium catalyst **5** which, compared to **3**, is inexpensive and, therefore, of much greater use in preparative-scale reactions. The results obtained with a variety of aldehydic substrates under optimized conditions (*Eqn. 2*) in an undivided electrolysis cell are shown in *Table 4*. Reaction yields were either determined by gas-liquid chromatography (GLC) or by isolation of the products.



(2)

MeOH solutions of pH ≥ 9.5 gave the fastest rates of ester formation. The use of Et_3N (150 mM) to maintain a relatively constant weakly basic pH throughout the electrolysis led to faster rates than the use of borate buffers. A low concentration (50 mM) of Et_4NBr as supporting electrolyte was chosen, since higher concentrations (> 0.1M) decreased reaction rates and caused solubility problems. Generally, high ionic strength led to deceleration of thiazolium-catalyzed processes since the polar ground states of the multi-step reactions become stabilized over the less polar transition states [16] [37]. According to the reaction mechanism (*Scheme 5*), protons are released during the oxida-

tion process, however, despite the absence of buffer, the pH did not significantly change during the runs. Since the experiments were performed in an undivided cell, a constant pH of 11–12 was maintained by reduction of the protons at the cathode.

Table 4. *Electrochemical Oxidation of Aldehydes in 0.05* M *Solution of Et_4NBr in MeOH at the Pt Electrode.* 308 K, mol ratio of aldehyde (150 mM)/thiazolium ion **21**/Et_3N = 30:1:3:30.

Entry	Aldehyde	Ratio aldehyde/ hemiacetal[a])	Thiazolium ion	Time [h][b])	Yield of ester [%][c])	Turnover calculated for thiazolium **21**		Current efficiency [%][d])
1	Pentanal	1:16	**5**	26	17	5.1	1.7	77
2			**3**	26	20	6.0	2.0	83
3	Cyclohexane-carbaldehyde	1:6.4	**5**	24	7[e])	2.1	0.7	23
4	Naphthalene-1-carbaldehyde	1:0.09	**5**	24	25	7.5	2.5	n.d.
5			**3**	24	35	10.5	3.5	n.d.
6	Naphthalene-2-carbaldehyde	1:0.08	**5**	21	55	16.5	5.5	72
7			**3**	10	74 (76)	22.2	7.4	88
8	Benzaldehyde	1:0.10	**5**	21	54	16.2	5.4	60
9			**3**	10	48	14.4	4.8	n.d.
10	4-Chloro-benzaldehyde	1:0.22	**5**	18	78 (81)	23.4	7.8	84
11	4-Cyano-benzaldehyde	1:2.3	**5**	18	72 (69)	21.6	7.2	70
12			**3**	6	95 (88)	28.5	9.5	90
13	4-(Trifluoro-methyl)benz-aldehyde	1:1.4	**5**	16	64	19.2	6.4	n.d.
14			**3**	8	83	24.9	8.3	n.d.
15	2-(Trifluoro-methyl)benz-aldehyde	1:1.12	**5**	24	26	7.8	2.6	n.d.
16			**3**	24	21	6.3	2.1	n.d.
17	Methyl 4-formyl-benzoate	1:0.85	**5**	13	85 (83)	25.5	8.5	80
18			**3**	7.5	91	27.3	9.1	n.d.
19	Benzene-1,4-dicarbaldehyde	1:1.78:0.08[f])	**5**	18	6 + 87[g])	52.2	17.4	n.d.
20			**3**	12.5	5 + 89[g])	53.4	17.8	n.d.
21	Benzene-1,2-dicarbaldehyde	1:81[h])	**5**	22	28 + 1[g])	8.4	2.8	n.d.
22			**5**[i])	22	52 + 7[g])	1.7	5.2	n.d.

[a]) Determined by 200-MHz ^{1}H-NMR of 150 mM solutions of aldehydes in 150 mM Et_3N in CD_3OD.
[b]) The reactions were stopped when the current dropped to < 10% of the initial intensity.
[c]) Determined by GLC. Numbers in parentheses are isolated yields.
[d]) n.d. = not determined.
[e]) *Ca.* 80% of aldehyde remained unreacted.
[f]) Ratio dicarbaldehyde/mono-hemiacetal/bis-hemiacetal.
[g]) Yield of monoester (first number) and diester.
[h]) Ratio of dicarbaldehyde/**23** (see above).
[i]) Concentration of catalyst is increased by 9-fold.

The ratio of substrate (30 equiv.) to thiazolium ion (1 equiv.) to flavin (3 equiv.) was chosen to ensure that the oxidation process was preferred over the acyloin-condensation side reaction [10d]. To achieve this desirable reaction selectivity, the rate-determining step must occur during formation of the 'active aldehyde'. If the oxidation process becomes rate-determining, the 'active aldehyde' will not be efficiently trapped by the flavin and the amount of acyloin-condensation side products will increase [38].

The acyloin side reaction was particularly prominent with the non-macrocyclic thiazolium ion **5** which, in contrast to **3**, did not specifically favor the oxidation process by supramolecular catalysis (*Sect. 2.4*). When the relative amount of **21** in the mixture was decreased, the benzoin condensation became dominant. Whereas under the conditions of *Eqn. 2*, benzaldehyde gave a 48% yield of methyl benzoate (*Table 4*), reaction of benzaldehyde (1M), **5** (0.1M), and **21** (5 mM) gave only 8% of the ester together with 57% of benzoin. Under these conditions, the formation of the 'active aldehyde' was fast due to high substrate concentration, and the amount of **21** was too small to trap and efficiently oxidize the intermediate. In preparative reactions with high substrate concentrations ($\geq$ 1M), higher yields of ester could be obtained upon slow addition of the aldehyde over several h (*Table 5*). Slow substrate addition slowed down the formation of the 'active aldehyde' which, as a result, was more efficiently trapped and oxidized by the flavin.

Table 5. *Electrochemical Oxidation of Benzaldehyde, Catalyzed by* **5** *and* **21**, *in the Presence of* Et_3N *in 0.05*M *Solutions of* Et_4NBr *in EtOH/MeCN 7:3 at a Pt Working Electrode.* 333 K, −300 mV.

PhCHO [M]	Time of aldehyde addition	**5** [M]	**21** [M]	Et_3N [M]	Yield of ester after 24 h [%]
1	15 s	0.1	0.05	0.8	20
1	15 h	0.1	0.05	0.8	52
0.5	15 s	0.05	0.05	0.4	31
0.5	5 h	0.05	0.05	0.4	51

2.5.4. *Scope of the Bis(coenzyme)-Mediated Electrooxidation of Aromatic Aldehydes to Methyl Esters.* The data in *Table 4* show a strong dependency of the yield of ester on the nature of the substrate. Aromatic aldehydes with electron-withdrawing substituents in the *para*-position gave the highest yields (64–85%) with high current efficiencies (*Entries 10–18*), while benzaldehyde and naphthalene-2-carbaldehyde gave somewhat lower yields (48–76%, *Entries 6–9*). The electron-withdrawing substituent in the *para*-position activated the aldehyde for attack by the thiazolium ylide in the rate-determining formation of the 'active aldehyde'. Poor conversions were obtained with aliphatic aldehydes: pentanal and cyclohexanecarbaldehyde gave less than 20% yield (*Entries 1–3*). Product analysis by gas chromatography showed that *ca.* 80% of cyclohexanecarbaldehyde remained unreacted, showing that the low yield was not due to the acyloin-condensation side reaction.

^{1}H-NMR studies revealed a possible explanation for the observed selectivity for aromatic aldehydes. Under the reaction conditions, aliphatic aldehydes existed mainly in the hemiacetal form which was in a slow equilibrium with the aldehyde on the NMR time scale (*Table 4*). The low yield of aliphatic esters was presumably due to the competing formation of hemiacetals which significantly lowered the equilibrium concentration of aldehydes and hence the rate of formation of the 'active-aldehyde' intermediate. The

4-cyanobenzaldehyde also preferred the hemiacetal form (*Entry 11*), however, the strong activating effect of the CN group increased the rate significantly and compensated for the decrease in equilibrium concentration of the aldehyde due to hemiacetal formation.

The low yields of esters obtained from naphthalene-1-carbaldehyde and 2-(trifluoromethyl)benzaldehyde (*Entries 4*, *5*, *15*, and *16*) were probably due to steric effects. GLC Analysis showed the disappearance of the aldehydes after electrolysis, and TLC of the reaction mixture confirmed the presence of more than one side product. Since the aldehyde groups were hindered from nucleophilic attack by the thiazolium ion, the bis(coenzyme)-catalyzed oxidation could not compete efficiently with unidentified side reactions, and low yields of ester were obtained.

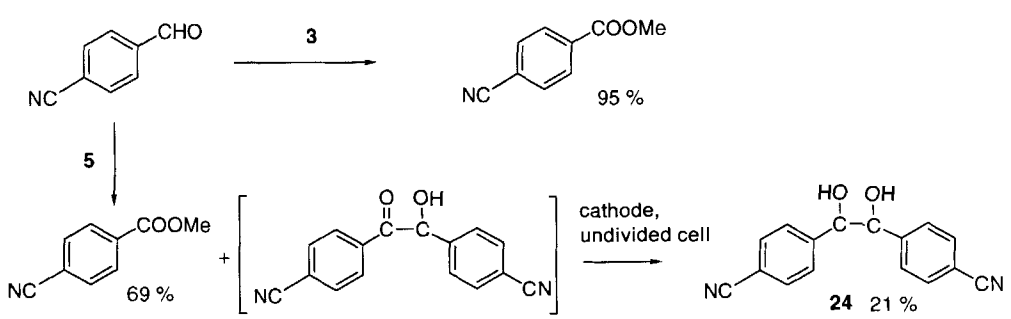
Benzene-1,4-dicarbaldehyde was readily oxidized to the corresponding diester (*Entries 19* and *20*). In contrast, benzene-1,2-dicarbaldehyde reacted rather slowly and yielded mainly the monoester (*Entries 21* and *22*). The preference for the monoester could be due to the fact that methyl 2-formylbenzoate existed mainly in the hemiacetal form **23** (aldehyde/hemiacetal 1:17.9) and to steric hindrance to further thiazolium-ylide attack by the presence of the ester group.

The selectivity for aromatic substrates was nicely demonstrated in an experiment in which a 1:1 mixture of naphthalene-2-carbaldehyde and cyclohexanecarbaldehyde was reacted in the presence of **3** under the conditions shown in *Eqn. 2*. Product analysis after 10 h of electrolysis showed the formation of methyl naphthalene-2-carboxylate (70%) as main product together with methyl cyclohexanecarboxylate (14%) and unreacted cyclohexanecarbaldehyde (82%).

Although the reaction conditions were optimized for the readily available, inexpensive catalyst **5**, supramolecular catalysis by **3** provided significant advantages in the reactions of those aromatic substrates that bound in the cyclophane cavity (*Table 1*). The reaction times in the presence of **3** were much shorter, and current efficiencies were higher. Besides catalytic advantages such as proximity and orientation, as well as micropolarity effects (*Sect. 2.4*), the electron-rich cyclophane bound the electron-accepting aldehyde more strongly than the hemiacetal (*Sect. 2.2*) which increased the equilibrium concentration of aldehyde and, therefore, the rate of 'active-aldehyde' formation.

Supramolecular catalysis not only accelerated the reactions but also enhanced their yields. Yields of aromatic esters in most entries were 10–20% higher in the presence of **3** than in the presence of **5** (*Table 4*, *Scheme 6*). The higher yields were a result of enhanced

Scheme 6. *Enhanced Reaction Selectivity in the Supramolecular Electrooxidation Process*



reaction selectivity in the supramolecular process! Workup of the electrochemical oxidation of 4-cyanobenzaldehyde catalyzed by **3** afforded exclusively methyl 4-cyanobenzoate in 95% yield. In contrast, isolation of the products from the reaction in the presence of **5** yielded 69% of methyl 4-cyanobenzoate and 21% of a white solid which was identified by MS and NMR to be a 1:1 mixture of the *meso*- and (±)-forms of 4,4′-(1,2-dihydroxyethane-1,2-diyl)bis(benzonitrile) (**24**; *Scheme 6*) [39] [40]. This pinacol side product was probably formed by the reduction of the initial acyloin-condensation product at the counter electrode in the undivided electrochemical cell. Since the binding site of **3** is complementary in size to only one benzene or naphthalene guest, competitive condensation side reactions were entirely suppressed.

A series of control experiments illustrates in an impressive way the advantages of the indirect electrooxidation process mediated by the two coenzymes (*Table 6*). No product was formed in the absence of thiazolium catalyst (*Entries h* and *i*). The high product yields obtained in *Entries a* and *b* were clearly due to the efficient regeneration of **21** at the anode. The amount of oxidation due to residual air present in the cell was insignificant, as shown by *Entries d* and *e*. *Entry c* shows that the 'active-aldehyde' intermediate formed from 4-cyanobenzaldehyde could be oxidized directly at the anode at −300 mV (*vs.* Ag/AgCl); however, direct oxidation was not sufficiently efficient to trap all of the 'active-aldehyde' intermediate. The poor yields in *Entries f* and *g* proved that regeneration of **21** or direct oxidation of the intermediate by air were unsatisfactory due to the destructive oxidation of the thiazolium catalyst.

Table 6. *Control Experiments Performed with 4-Cyanobenzaldehyde* (150 mM) *under the Conditions Described in* Eqn. 2

Entry	Thiazolium ion [mM]		**21** [mM]	Atmosphere	Working electrode potential[a])	Time [h]	Yield [%][b])
a	**5**	5	15	Ar	−0.3 V	18	72
b	**3**	5	15	Ar	−0.3 V	6	95
c	**5**	5	–	Ar	−0.3 V	20	19
d	**5**	5	15	Ar	–	20	12[c])
e	**5**	5	–	Ar	–	20	4
f	**5**	5	15	air	–	20	35
g	**5**	5	–	air	–	20	15
h	–	–	15	air	–	20	0
i	–	–	–	air	–	20	0

[a]) Potential with respect to Ag/AgCl reference electrode.
[b]) Determined by GLC.
[c]) Theoretical yield from **21** present is 10%.

3. Conclusion. – Thiazolio-cyclophane **3** is an excellent supramolecular catalyst for the oxidation of aromatic aldehydes to carboxylic acids and esters. In initial-rate studies, **3** exhibits saturation kinetics, large rate accelerations, and high catalytic turnovers as compared to simple thiazolium salts. Supramolecular catalysis by **3** is characterized by high reaction selectivity. Whereas the acyloin condensation is an important side reaction in the oxidation of aldehydes catalyzed by simple thiazolium ions, this side reaction is entirely suppressed in the presence of **3**. The binding site of **3** is complementary in size to

only one benzene or naphthalene guest, and the oxidation of a bound aromatic aldehyde is accelerated by entropically favorable proximity and orientation and by micropolarity effects in the supramolecular complex. In contrast, the benzoin condensation is decelerated, since the small cavity of **3** cannot bind and stabilize the π-π-stacking transition state involved in the attack of the 'active aldehyde' at a second aldehyde molecule in the benzoin condensation.

Aromatic esters can be prepared efficiently in the one-pot electrochemical oxidation of aldehydes, mediated by two coenzyme catalysts, thiazolium ion **3** or **5** and flavin **21**. This process occurs at the extraordinarily low electrode potential of −300 mV (*vs.* Ag/AgCl). High yields of aromatic esters are obtained with high current efficiency and high turnover numbers, if reaction conditions are chosen to make the formation of the 'active-aldehyde' intermediate the rate-determining step. Under such conditions, the intermediate is efficiently trapped by the redox mediator **21** which, in return, is readily re-oxidized at the anode. The high efficiency as well as the high substrate and reaction selectivity of **3** suggests that the development of synthetic transformations, which take advantage of the principles of electrocatalysis combined with molecular recognition, represents a worthwhile direction in research aimed at increasing the use of electrochemistry for environmentally clean oxidation technologies. In an expansion of this work, we now are developing conditions for the bis(coenzyme)-mediated electrochemical oxidation of aldehydes to carboxamides with amines added as nucleophiles in non-nucleophilic dipolar-aprotic solvents.

Experimental Part

General. All chemicals were reagent grade and used as received unless stated otherwise. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl under Ar. MeCN was freshly distilled from CaH_2. Dimethylformamide (DMF) was dried over basic alumina (*E. Merck*, act. I) for 1 h followed by filtration. Iodoethane was freshly distilled in an apparatus wrapped with aluminium foil. $BF_3 \cdot Et_2O$ was distilled from CaH_2 *in vacuo*. MeOH and Me_2SO used for electrochemical experiments were spectroanal. grade. Millipored H_2O was used for the preparation of aq. buffer solns. and for ion-exchange chromatography. Spectroanal. grade MeOH and MeCN were exclusively used for all operations with ionic compounds. Et_4NBr was purchased from *Eastman Kodak* and recrystallized from $CHCl_3/Et_2O$, then $MeOH/Et_2O$, and dried for 8 h at 120°/10^{-1} Torr [41]. Benzaldehyde was distilled at 2 Torr. Catalyst **5** was prepared according to [42]. Protective Ar for electrochemical experiments was purified by passing through *BTS* catalyst (*Fluka/BASF R3-11*) at 100°. Evaporations were carried out at H_2O aspirator pressure. If not otherwise stated, workup included washing the org. soln. with H_2O, drying ($MgSO_4$), and evaporation. Alkylammonium iodides were converted to the chlorides by passing a $MeCN/H_2O$ soln. through strongly basic anion-exchange resin (*Dowex 1 × 8–400*), prepared by rinsing sequentially with H_2O, 1N NaOH, and H_2O until neutral, 1N HCl, and then H_2O again until neutral. Reaction mixtures for the thiazolium-catalyzed oxidation of aldehydes were analyzed by HPLC, GLC, or by isolating the products as described below. Authentic samples used for the calibration of HPLC or GLC were purchased from *Aldrich* or synthesized as described below. Anal. TLC: *E. Merck* silica gel *60*, *F-254* precoated plates. Column chromatography: *E. Merck* silica gel *60* (70–230 mesh). HPLC: reversed-phase column, *Econosphere C18* (cart. 250 mm × 4.6 mm, 5 μ; *Alltech Associate Inc.*); *Perkin-Elmer-400* liquid chromatogram and *LC 90* UV-spectrophotometric detector. GLC: *Perkin-Elmer PE-17* (methyl 50% phenyl silicone) bonded-phase fused-silica capillary column (25 m, 0.25 mm i.d., film thickness 0.25 μm); *Perkin-Elmer 9000* autosystem gas chromatograph equipped with flame-ionization detector. HPLC and GLC data were processed with the *Perkin-Elmer-LCI-100* laboratory computing integrator. Cyclic voltammetry and controlled potential electrolysis experiments: *BAS-CV-27* voltammograph and *XY* recorder *MF-8050*; all potential values *vs.* Ag/AgCl reference electrodes *BAS MF-2020* or *MF-2021* (*ca.*−45 mV *vs.* SCE). M.P.: electrothermal apparatus; uncorrected. UV/VIS Spectra: *Varian-Cary-2300* spectrophotometer. IR Spectra (cm^{-1}): *Perkin-Elmer-PE-580* or *Perkin-Elmer-1600* FT-IR instruments. NMR Spectra: *Bruker-AF-200*, *-AM-360*,

and -*AM-500* instruments; chemical shift values δ (ppm) rel. to internal Me_4Si or rel. to the solvent peaks. MS (*m/z*, %): *AEI-MS902* high-resolution (HR) mass spectrometer at 70 eV; FAB spectra in 3-nitrobenzyl-alcohol matrix on *VG-7070-EHF* instrument. Elemental analyses were done at *Spang Microanalytical Laboratory*, Eagle Harbor, MI, and *Galbraith Laboratories, Inc.*, Knoxville, TN. *CAS Registry Service* provided the name for **3**, and names of other macrocycles were derived from it.

Complexation Studies. Samples were weighed using a *Sartorius-4503* microbalance, and all solns. were prepared with *Eppendorf* micropipettes. ^{1}H-NMR Titrations were performed on a *Bruker-AM-500* spectrometer, thermostated at 293.0 K. Samples were prepared by transferring 0.5-ml volumes of a stock soln. of the guest to preweighed samples of the host in half-dram vials. The samples were directly transferred to 5-mm-diameter NMR tubes. In a typical titration in D_2O/CD_3OD 3:2, the guest concentration was held constant at 0.5 mM, while the host concentration was varied stepwise from 0.5 to 5 mM. In CD_3OD, the guest concentration was held constant at *ca.* 5 mM, while the host concentration was varied from 5–60 mM. The complexation-induced change in chemical shift values of the guest resonances ($\Delta\delta = \delta_{free} - \delta_{obs}$) was plotted against the host concentration, and quantitative binding numbers (K_a, $-\Delta G°$, and $\Delta\delta_{sat}$) were obtained with a nonlinear least-squares curve-fitting program. The reported K_a and $-\Delta G°$ values are averages of those calculated from all protons of the guest that could be monitored during the titrations.

^{1}H-HMR Spectroscopic Analysis of H/D-Exchange Rates. The detailed procedures for these experiments were worked out by *Haake et al.* [42]. To analyze the rates of H/D exchange, the decrease in integrated intensity of the ^{1}H-NMR signal of H–C(2) of the thiazolium ring was followed as a function of time relative to the intensity of the signal of H–C(5) which was chosen as the internal standard. The CD_3COONa/CD_3COOD buffer of pD 4.7 was prepared by adding 45.9 mg (0.54 mmol) of CD_3COONa and 84.5 µl (1.5 mmol) of CD_3COOD to a dry 10-ml volumetric flask and filling up with D_2O. Solns. of the thiazolium salts **3**–**5** were prepared by adding 750 µl of the acetate buffer to a vial containing 7.5 µmol of thiazolium salt and transferring the resulting soln. into a NMR tube *via Fisher* pipet. The NMR tube was then placed into the spectrometer held at 303 K. The lock signal had been previously shimmed with a sample of pure D_2O, so that the first set of scans could be started within 1.5–3.5 min. Time zero was taken to be the moment the NMR tube was dropped into the probehead. For evaluation of the signal-intensity changes, the width of the integral window for H–C(2) from 9.019 to 8.974 ppm and for H–C(5) from 7.450–7.393 ppm was held constant during the entire run. All measurements were continued for up to 4 h until at least 95% H/D exchange had taken place. In a representative experiment, 25 spectra were recorded within 110 min during which time the relative intensity of H–C(2) of **3** had decreased in a first-order process from 100 to 2%. The pseudo-first-order rate constants k_{obs} were obtained by least-squares analysis using the equation ln[area H–C(5)/area H–C(2)] = $k_{obs}t$ + const. Correlation coefficients in triplicate runs were 0.99 or higher.

Initial Rate Studies of the Oxidation of Naphthalene-2-carbaldehyde by $K_3[Fe(CN)_6]$-Catalyzed by **3**–**5**. Stock solns. (5–90 mM) of naphthalene-2-carbaldehyde were made up by weighing the corresponding amount of aldehyde into a 10 ml-volumetric flask, filling up with Me_2SO, and inverting the stoppered flask several times. The aldehyde stock solns. were 2.5 times more concentrated than the mixtures that were ultimately measured after incubation. The 2.5 mM stock solns. of the thiazolium salts **3**–**5** were made up by weighing 0.0025 mmol of the thiazolium salt into a 0.5-dram vial and then dissolving it in a small amount of Me_2SO. This soln. was transferred to a 5-ml volumetric flask *via* a *Fisher* pipet and the 0.5-dram vial rinsed with small amounts of Me_2SO (3 or 4×). The flask was then filled up with Me_2SO, inverted several times, and transferred to a wide-mouthed vial. For the preparation of the pH 7.5 phosphate buffer [43], 5 ml of 0.5M KH_2PO_4 and 4.11 ml of 0.5M NaOH were mixed. H_2O was then added to fill the volume up to 100 ml. A 12.5 mM stock soln. of $K_3[Fe(CN)_6]$ was prepared by weighing 82.3 mg (0.025 mmol) into a 0.5-dram vial and dissolving in a small amount of phosphate buffer. This soln. was transferred to a 20-ml volumetric flask *via* a *Fisher* pipet and the 0.5-dram vial rinsed with small amounts of phosphate buffer (4×). The flask was then filled up with phosphate buffer, inverted several times, and transferred to a wide-mouthed vial.

Experiments were performed by observing the decrease in absorbance of the Fe^{III} chromophore at 420 nm (ε_{420} = 1040 M^{-1} cm^{-1}) [11a]. At this wavelength, the produced $K_2[Fe(CN)_6]$ does not absorb. The temp. of the 0.2-cm optical cuvettes was kept at 303 K. The reaction was initiated by addition of 120 µl of the 2.5 mM catalyst soln. in Me_2SO to a premixed soln. of 240 µl of a 5.0–90.0 mM stock soln. of the aldehyde in Me_2SO and 240 ml of the 12.5 mM stock soln. of $K_3[Fe(CN)_6]$ in the aqueous buffer. The cuvette was inverted 6–7 times before the run was started. Time zero was chosen when the cuvette was stoppered and inverted the first time. Absorbance measurement times were 1 s, and readouts were taken in intervals of 12 s. Measurements were usually completed within 5 min and initial velocities were calculated using the data during the first 1–2 min when the absorbance *vs.* time plots were linear. In the presence of **3**, the reactions were 7–15% completed during this time period. In

measurements of the background oxidation rate of the catalyst, 240 µl of pure Me_2SO was used in place of the aldehyde stock soln.

Initial velocities were calculated by standard linear-regression analysis using the initial linear portions of absorbance *vs.* time plots. A *Lineweaver-Burke* plot ($1/v$ *vs.* 1/[S]) was used to calculate the maximal velocity and the *Michaelis-Menten* constant for the reaction catalyzed by **3**. The turnover number k_{cat} was calculated by dividing the maximal velocity v_{max} by the concentration of catalyst. The second-order rate constants for the reactions catalyzed by **4** and **5** were calculated by taking the slope of the line created by plotting v *vs.* [S] and dividing by the concentration of catalyst. All kinetic runs were done in triplicate.

For product analysis of the reactions catalyzed by **3**, the contents of all runs were collected. H_2O was added, the soln. extracted with Et_2O (2×), and the Et_2O layer washed with 1N HCl (1×) and H_2O (2×), dried ($MgSO_4$), and evaporated. The products were analyzed by ^{1}H-NMR.

Cyclic Voltammetry. The experiments were performed under Ar in a conventional three-electrode cell with a Pt-wire counter electrode, a Ag/AgCl/3M NaCl reference electrode (*BAS MF 2020* or *MF-2021*) assembled in a *Haber-Luggin* capillary, and a working electrode which was a glassy carbon (*BAS MF*-2012, 3.0-mm-diameter disk), Pt (*BAS MF-2013*, 1.6-mm-diameter disk), or Au (*BAS MF-2014*, 1.6-mm-diameter disk) electrode. The cell consisted of an outer H_2O jacket which was connected to a thermostat. The working electrodes were polished with 0.05 µm alumina (*BAS CF-1050*), washed with millipored H_2O, then MeOH, or EtOH, and dried before each cyclic voltammetric experiment.

For cyclic voltammetric experiments in Me_2SO/aq. phosphate buffer (pH 7.5) or methanolic borate buffer (pH 9.5), 10 ml solns. of the thiazolium derivatives (0.5 mM or 5 mM) were transferred quickly to the cell by syringe and purged with Ar for 15 min. The methanolic borate buffer was prepared by mixing 50 ml of methanolic 0.1M boric acid and 43.7 ml of methanolic 0.1M NaOH [44]. For experiments in MeOH/Et_3N, 10-ml solns. of the thiazolium catalysts in MeOH were transferred into the cell and purged with Ar for 30 min. Then Et_3N, which had already been deoxygenated with Ar, was introduced to the cell by gas-tight syringe.

Electrolysis Experiments. Electrochemical oxidations of aldehydes were performed under Ar in an undivided cell equipped with a glassy carbon rod counter electrode (grade *GC 20S* from *Tokai Carbon Americal*, 6-mm o.d., 12-mm depth in soln.) and a Ag/AgCl/3M NaCl reference electrode (*BAS MF-2020* or *MF-2021*). The working electrode was a Pt foil (*AESAR Puratonic* 99.998%, 0.1 × 12 × 15 mm). The cell consisted of an outer H_2O jacket which was connected to a thermostat. The working-electrode potential was −300 mV (*vs.* Ag/AgCl).

For the electrolysis performed in MeOH/Et_3N/Et_4NBr with 1M aldehyde, the thiazolium catalyst and **21** were dissolved in a 10 ml soln. of Et_4NBr in MeOH, transferred to the cell, and the soln. purged with Ar for 20 min at 20°. The mixture was then warmed to 60°. Et_3N which had been deoxygenated by purging with Ar was introduced into the cell by gas-tight syringe. The aldehyde (neat or as a suspension in the solvent) was deoxygenated by purging with Ar for 30 min and introduced to the cell by gas-tight syringe, and the electrolysis was started. For the electrolysis with 150 mM aldehyde, the aldehyde (1.65 mmol) and **21** (0.165 mmol) were dissolved in a 10 ml soln. of Et_4NBr and Et_3N in MeOH. The soln. was transferred to the cell and purged with Ar for 30 min. The soln. of thiazolium catalyst (0.055 mmol) in MeOH (1 ml), which had been deoxygenated with Ar, was introduced to the cell by gas-tight syringe, and electrolysis was started.

The number of mol of product formed or of remaining starting reagent was calculated from the final volume of the soln. after electrolysis and from the concentration determined by calibrated GLC or HPLC. Some of the reaction mixtures were worked up after electrolysis, and products were isolated. After solvent evaporation, the residue was chromatographed (SiO_2, CH_2Cl_2). Yields of isolated products agreed with yields determined by calibrated GLC of HPLC within 10%.

1-Acetyl-4-(4-methoxy-3,5-dimethylphenyl)piperidin-4-ol [45] (**7**). The formation of the *Grignard* reagent was initiated by addition of a crystal of I_2 to a mixture of 5-bromo-2-methoxy-1,3-dimethylbenzene (1.5 g) [46] and Mg turnings (3.8 g, 0.15 mol) in dry THF (15 ml) under N_2. At gentle reflux, the remaining of 31.3 g (0.15 mol) of 5-bromo-2-methoxy-1,3-dimethylbenzene in THF (350 ml) was added and the resulting mixture stirred for 1 h at 20°. Upon slow addition of *N*-acetylpiperidin-4-one (21.6 g, 0.15 mol) in THF (40 ml), a thick white precipitate formed. The resulting mixture was stirred for 2 h and, after addition of 300 ml of 9% aq. H_2SO_4 soln., stirring was continued for 1.5 h at 20°. The soln. was neutralized with sat. aq. Na_2CO_3 soln. and the solvent evaporated. Washing the residual gummy solids with Et_2O (2 ×) afforded 26.2 g (65%) of colorless **7**. M.p. 203–204°. ^{1}H-NMR (500 MHz, $CDCl_3$); 1.66 (br. *s*, 1 H); 1.75 (*ddd*, J = 13.0, 2.4, 2.4, 1 H); 1.81 (*ddd*, J = 13.0, 2.4, 2.4, 1 H); 1.9–2.0 (*m*, 2 H); 2.13 (*s*, 3 H); 2.29 (*s*, 6 H); 3.08 (*ddd*, J = 13.0, 13.0, 3.0, 1 H); 3.58 (*ddd*, J = 13.0, 13.0, 3.0, 1 H); 3.61 (*s*, 3 H); 3.65–3.75 (*m*, 1 H); 4.55 (*ddd*, J = 13.0, 2.4, 2.4, 1 H); 7.05 (*s*, 2 H). EI-MS: 277 (100, M^+). Anal. calc. for $C_{16}H_{23}NO_3$ (277.4): C 69.29, H 8.36, N 5.05; found: C 69.38, H 8.50, N 4.98.

1-Acetyl-4-(4-methoxy-3,5-dimethylphenyl)-1,2,3,6-tetrahydropyridine [45] (**8**). A soln. of **7** (29.5 g, 0.106 mol) and TsOH · H_2O (1.74 g, 9.12 mol) in 150 ml of toluene was refluxed under N_2 for 2 h. The mixture was then washed with 1N NaOH and sat. aq. NaCl soln. Workup afforded 23.77 g (87%) of **8**. Colorless oil. ^{1}H-NMR (500 MHz, $CDCl_3$): 2.14, 2.17 (2 *s*, 3 H); 2.29 (*s*, 6 H); 2.45–2.55 (*m*, 2 H); 3.64, 3.79 (2 *t*, *J* = 5.7, 2 H); 3.72 (*s*, 3 H); 4.10, 4.21 (2*dd*, *J* = 3.2, 2.8, 2 H); 5.92, 5.99 (2*dd*, *J* = 3.0, 2.8, 1 H); 7.01, 7.02 (2*s*, 2 H). EI-MS: 259 (M^+). HR-MS: 259.1577 (M^+, $C_{16}H_{21}NO_2$, calc. 259.1572).

4-[1-Acetyl-4-(4-methoxy-3,5-dimethylphenyl)piperidin-4-yl]-2-methylphenol [45] (**9**). $BF_3 \cdot Et_2O$ (6 ml, 48 mmol) was added to a mixture of **8** (19.1 g, 0.074 mol) and 2-methylphenol (23.8 g, 0.22 mol) and the resulting soln. heated to 85° for 2 h under N_2. After addition of H_2O, most of the excess of 2-methylphenol was distilled off *in vacuo* to leave a gummy residue. Upon addition of Et_2O, containing a small amount of MeOH, a colorless precipitate was obtained which was washed with hot Et_2O to give 22.85 g (84%) of **9**. M.p. 221–223°. ^{1}H-NMR (500 MHz, $CDCl_3$): 2.09 (*s*, 3 H); 2.20 (*s*, 3 H); 2.22 (*s*, 6 H); 2.25–2.35 (*m*, 4 H); 3.4–3.5 (*m*, 2 H); 3.55–3.6 (*m*, 1 H); 3.63 (*s*, 3 H); 3.65–3.75 (*m*, 1 H); 6.75 (*d*, *J* = 8.4, 1 H); 6.82 (*s*, 2 H); 6.86 (*dd*, *J* = 8.4, 2.3, 1 H); 6.93 (*d*, *J* = 2.3, 1 H); 7.73 (br. *s*, 1 H). EI-MS: 367 (100, M^+). Anal. calc. for $C_{23}H_{29}NO_3$ (367.5): C 75.17, H 7.95, N 3.81; found: C 74.51, H 8.00, N 3.98.

4,4'-(1-Acetylpiperidine-4,4-diyl)-2,2',6-trimethylbis(phenol) (**10**). A suspension of **9** (22.25 g, 0.06 mol) in $CHCl_3$ (250 ml) was heated until dissolved. The soln. was then cooled to −78° and BBr_3 (10 ml, 0.106 mol) added slowly under Ar. After the addition was complete, the cooling bath was removed and the soln. stirred overnight. The reaction was quenched slowly with MeOH and the solvent evaporated leaving a gummy residue which was dissolved in AcOEt. Workup afforded a gummy precipitate which crystallized upon addition of Et_2O: 19.6 g (94%) of **10**. Colorless crystals. M.p. 243–244°. ^{1}H-NMR (500 MHz, $(CD_3)_2SO$): 1.96 (*s*, 3 H); 2.05 (*s*, 3 H); 2.09 (*s*, 6 H); 2.1–2.25 (*m*, 4 H); 3.3–3.4 (*m*, 4 H); 6.65 (*d*, *J* = 8.3, 1 H); 6.80 (*s*, 2 H); 6.87 (*dd*, *J* = 8.3, 2.1, 1 H); 6.95 (*d*, *J* = 2.1, 1 H); 8.67 (br. *s*, 1 H); 9.06 (br. *s*, 1 H). EI-MS: 353 (100, M^+). Anal. calc. for $C_{22}H_{27}NO_3 \cdot 0.5\ H_2O$ (362.5): C 72.90, H 7.79, N 3.86; found: C 72.82, H 7.62, N 3.73.

1-Acetyl-4-[4-(4'-chlorobutoxy)-3,5-dimethylphenyl]-4-[4-(4'-chlorobutoxy)-3-methylphenyl]piperidine (**11**). A soln. of **10** (10.3 g, 0.0284 mol), Cs_2CO_3 (37 g, 0.113 mol), and freshly distilled 1,4-dichlorobutane (40 ml, 0.37 mol) in DMF (150 ml) was stirred under N_2 at 90° for 2 d. After cooling, the salts were removed by filtration and the solvent evaporated. Chromatography (SiO_2, CH_2Cl_2/MeOH 98:2) afforded 14.2 g (94%) of **11**. M.p. 97–99°. ^{1}H-NMR (500 MHz, $CDCl_3$): 1.85–2.05 (*m*, 8 H); 2.07 (*s*, 3 H); 2.17 (*s*, 3 H); 2.21 (*s*, 6 H); 2.25–2.35 (*m*, 4 H); 3.4–3.5 (*m*, 2 H); 3.55–3.7 (*m*, 2 H); 3.63 (*t*, *J* = 6.2, 2 H); 3.64 (*t*, *J* = 6.4, 2 H); 3.75 (*t*, *J* = 6.1, 2 H); 3.96 (*t*, *J* = 5.6, 2 H); 6.71 (*s*, *J* = 9.2, 1 H); 6.83 (*s*, 2 H); 6.95–7.0 (*m*, 2 H). EI-MS: 533 (100, M^+). HR-MS: 533.2491 (M^+, $C_{30}H_{41}Cl_2NO_3$, calc. 533.2466).

1,1''-Diacetyl-5',14',20',29',32',33',36'-heptamethyldispiro[piperidine-4,2'-[7,12,22,27]tetraoxapentacyclo-[26.2.2.2^{3,6}.2^{13,16}.2^{18,21}]octatriaconta[3,5,13,15,18,20,28,30,31,33,35,37]dodecaene-17',4''-piperidine] (**12**). A mixture of **11** (6.00 g, 0.011 mol), 4,4'-(1-acetylpiperidine-4-4-diyl)-2,2',6,6'-tetramethylbis(phenol) [47] (4.36 g, 0.012 mol), and Cs_2CO_3 (15.6 g, 0.048 mol) in MeCN (1.15 l) was refluxed for 2 d. K_2CO_3 (4.2 g, 0.03 mol) was added and refluxing continued for another day. The soln. was cooled to 20°, and the salts were removed by filtration. The solvent was evaporated, and column chromatography (2×; SiO_2, CH_2Cl_2/MeOH 97:3, then AcOEt/hexane 3:2) afforded 2.1 g (22%) of **12**. M.p. 271–272°. ^{1}H-NMR (500 MHz, $CDCl_3$): 1.9–2.0 (*m*, 8 H); 2.05 (*s*, 3 H); 2.06 (*s*, 3 H); 2.11 (*s*, 3 H); 2.14 (*s*, 6 H); 2.16 (*s*, 6 H); 2.17 (*s*, 6 H); 2.25–2.35 (*m*, 8 H); 3.5–3.7 (*m*, 8 H); 3.7–3.85 (*m*, 6 H); 3.98 (*t*, *J* = 5.8, 2 H); 6.64 (*d*, *J* = 8.6, 1 H); 6.76 (*s*, 2 H); 6.78 (*s*, 4 H); 6.85 (*dd*, *J* = 8.6, 2.2, 1 H); 6.94 (*d*, *J* = 2.2, 1 H). FAB-MS: 829 (100, M^+). HR-MS: 828.5057 (M^+, $C_{53}H_{68}N_2O_6$, 828.5080).

1,1''-Diethyl-5',14',20',29',32',33',36'-heptamethyldispiro[piperidine-4,2'-[7,12,22,27]tetraoxapentacyclo-[26.2.2.2^{3,6}.2^{13,16}.2^{18,21}]octatriaconta[3,5,13,15,18,20,28,30,31,33,35,37]dodecaene-17',4''-piperidine] (**13**). A 1M borane-THF soln. (60 ml, 0.06 mol) was added to a soln. of **12** (0.57 g, 0.688 mmol) in THF (50 ml) and the resulting mixture refluxed for 3 h. Careful addition of MeOH and evaporation of the solvents afforded a colorless solid which was refluxed overnight in 20 ml of EtOH/conc. H_2SO_4 97:3. After cooling, the mixture was neutralized with sat. aq. Na_2CO_3 soln., the solvent evaporated, and the residue partitioned between CH_2Cl_2 and H_2O. Drying (Na_2SO_4) and evaporation afforded 0.50 g (91%) of colorless **13**. M.p. 274–276°. ^{1}H-NMR (500 MHz, $CDCl_3$): 1.04 (*t*, *J* = 7.2, 6 H); 1.9–2.0 (*m*, 8 H); 2.10 (*s*, 3 H); 2.14 (*s*, 6 H); 2.15 (*s*, 6 H); 2.16 (*s*, 6 H); 2.25–2.55 (*m*, 16 H); 2.32 (*q*, *J* = 7.2, 4 H); 3.7–3.85 (*m*, 6 H); 3.98 (*t*, *J* = 5.7, 2 H); 6.62 (*d*, *J* = 8.6, 1 H); 6.76 (*s*, 2 H); 6.78 (*s*, 2 H); 6.79 (*s*, 2 H); 6.84 (*dd*, *J* = 8.6, 1.7, 1 H); 6.96 (*d*, *J* = 1.7, 1 H). FAB-MS: 801 (100, M^+). HR-MS: 800.5452 (M^+, $C_{53}H_{72}N_2O_4$, calc. 800.5496).

1,1,1'',1''-Tetraethyl-5',14',20',29',32',33',36'-heptamethyldispiro[piperidine-4,2'-[7,12,22,27]tetraoxapenta-cyclo[26.2.2.2^{3,6}.2^{13,16}.2^{18,21}]octatriaconta[3,5,13,15,18,20,28,30,31,33,35,37]dodecaene-17',4''-piperidinium] Dichloride (**14**). A soln. of **13** (0.47 g, 0.587 mol) in freshly distilled EtI (25 ml) containing a minimum amount of

CH_2Cl_2 to dissolve the starting material, was stirred in the dark overnight. Evaporation gave a colorless solid which was dissolved in a minimum amount of MeCN/H_2O 7:3 and chromatographed on a *Dowex* anion-exchange column (Cl^-) using MeCN/H_2O 1:1 as eluent. Recrystallization from MeOH/Et_2O afforded 0.51 g (82%) of colorless hygroscopic **14**. M.p. 274–275° (dec.). ^{1}H-NMR (500 MHz, $CDCl_3$): 1.37 (*t*, *J* = 7.2, 12 H); 1.9–2.0 (*m*, 8 H); 2.11 (*s*, 3 H); 2.15 (*s*, 6 H); 2.16 (*s*, 6 H); 2.17 (*s*, 6 H); 2.5–2.7 (*m*, 8 H); 3.5–3.7 (*m*, 16 H); 3.75–3.85 (*m*, 6 H); 3.98 (*t*, *J* = 5.7, 2 H); 6.66 (*d*, *J* = 8.5, 1 H); 6.75 (*s*, 2 H); 6.77 (*s*, 2 H); 6.78 (*s*, 2 H); 6.89 (br. *d*, *J* = 8.5, 1 H); 6.92 (br. *s*, 1 H). FAB-MS: 894 (84, $[M - Cl]^+$). 830 (100, $[M - Et - 2\ Cl]^+$).

37′-(Chloromethyl)-1,1,1″,1″-tetraethyl-5′,14′,20′,29′,32′,33′,36′-heptamethyldispiro[piperidine-4,2′-[7,12,22,27]tetraoxapentacyclo[26.2.2.2^{3,6}.2^{13,16}.2^{18,21}]octatriaconta[3,5,13,15,18,20,28,30,31,33,35,37]dodecaene-17′,4″-piperidinium] Dichloride (**15**). A slow stream of HCl gas was bubbled for 2 h through a soln. of **14** (0.47 g, 0.453 mmol), glacial AcOH (2.1 ml), 37% aq. HCl soln. (2.1 ml), and 37% aq. CH_2O soln. (1.6 ml, 21.3 mmol). The mixture was carefully neutralized with sat. aq. Na_2CO_3 soln. and extracted with CH_2Cl_2. Workup followed by recrystallization from MeOH/Et_2O afforded 0.42 g (91%) of **15**. M.p. 260–261° (dec.). ^{1}H-NMR (500 MHz, $CDCl_3$): 1.37 (*t*, *J* = 7.1, 12 H); 1.9–2.05 (*m*, 8 H); 2.17 (*s*, 12 H); 2.18 (*s*, 6 H); 2.19 (*s*, 3 H); 2.55–2.75 (*m*, 8 H); 3.45–3.65 (*m*, 16 H); 3.7–3.8 (*m*, 6 H); 3.90 (*t*, *J* = 6.4, 2 H); 4.55 (*s*, 2 H); 6.77 (*s*, 4 H); 6.79 (*s*, 2 H); 6.92 (*d*, *J* = 1.9, 1 H); 7.05 (*d*, *J* = 1.9, 1 H). FAB-MS: 942 (100, $[M - Cl]^+$), 878 (75, $[M - Et - 2\ Cl]^+$). Anal. calc. for $C_{58}H_{83}Cl_3N_2O_4 \cdot 2\ H_2O$ (1014.7): C 68.66, H 8.64, N 2.76, Cl 10.48; found: C 68.50, H 8.56, N 2.71, Cl 10.59.

1,1,1″,1″-Tetraethyl-5′,14′,20′,29′,32′,33′,36′-heptamethyl-37′-[(4-methylthiazolium-3-yl)methyl]dispiro[piperidine-4,2′-[7,12,22,27]tetraoxapentacyclo[26.2.2.2^{3,6}.2^{13,16}.2^{18,21}]octatriaconta[3,5,13,15,18,20,28,30,31,33,35,37]dodecaene-17′,4″-piperidinium] Trichloride (**3**). A soln. of **15** (0.40 g, 0.41 mmol) and 4-methylthiazole (10 ml) in MeCN (30 ml) was heated at 60° overnight under Ar. The solvent was evaporated and the residue dissolved in H_2O. The aq. soln. was washed with Et_2O (5×) to remove the remaining 4-methylthiazole and the H_2O subsequently removed as an azeotrope with MeCN. Recrystallization from Et_2O/Me_2CO/MeCN gave 350 mg (79%) of a pale-yellow solid that was dried at 20°/10^{-4} Torr for 3 d. M.p. 265–266° (dec.). ^{1}H-NMR (500 MHz, CD_3CN): 1.15–1.25 (*m*, 12 H); 1.75–1.9 (*m*, 8 H); 2.11 (*s*, 6 H); 2.13 (*s*, 6 H); 2.16 (*s*, 6 H); 2.19 (*s*, 3 H); 2.39 (*s*, 3 H); 2.45–2.8 (*m*, 8 H); 3.2–3.4 (*m*, 16 H); 3.66 (*t*, *J* = 6.6, 2 H); 3.73 (*t*, *J* = 6.6, 2 H); 3.75 (*t*, *J* = 6.6, 2 H); 3.82 (*t*, *J* = 6.6, 2 H); 5.58 (*s*, 2 H); 6.95 (*s*, 2 H); 6.97 (*s*, 2 H); 7.00 (*s*, 2 H); 7.22 (*s*, 1 H); 7.36 (br. *s*, 1 H); 7.66 (br. *s*, 1 H); 10.40 (br. *s*, 1 H). FAB-MS: 1006 ($[M - 2\ Cl]^+$), 941 ($[M - H - Et - 3\ Cl]^+$), 908 ($[M - C_4H_5NS - 2\ Cl]^+$), 843 ($[M - C_4H_5NS - Et - 3\ Cl]^+$).

1-Acetyl-4-(4-methoxy-3,5-dimethylphenyl)-4-(4-methoxy-3-methylphenyl)piperidine (**16**). To an ice-cold soln. of **9** (3.5 g, 9.5 mmol) in DMF (50 ml) was added a soln. of 85% KOH (1 g, 15 mmol) in H_2O (10 ml). The ice-bath was removed after 5 min and dimethyl sulfate (2.4 ml, 25 mmol) added. The addition of KOH and Me_2SO_4 was repeated five more times at *ca.* ½-h intervals. After refluxing for 1 h, the solvent was evaporated and the residue partitioned between CH_2Cl_2 and H_2O. The aq. phase was extracted once more, and workup of the combined org. phases gave 3.3 g (91%) of **16**. M.p. 167°. ^{1}H-NMR (500 MHz, $CDCl_3$): 2.08 (*s*, 3 H); 2.18 (*s*, 3 H); 2.23 (*s*, 6 H); 2.25–2.35 (*m*, 4 H); 3.4–3.7 (*m*, 4 H); 3.70 (*s*, 3 H); 3.80 (*s*, 3 H); 6.74 (*d*, *J* = 8.4, 1 H); 6.84 (*s*, 2 H); 6.99 (br. *s*, 1 H); 7.01 (*dd*, *J* = 8.4, 2.2, 1 H). EI-MS: 381 (100, M^+). Anal. calc. for $C_{24}H_{31}NO_3$ (381.5): C 75.56, H 8.19, N 3.67; found: C 75.33, H 8.12, N 3.60.

1-Ethyl-4-(4-methoxy-3,5-dimethylphenyl)-4-(4-methoxy-3-methylphenyl)piperidine (**17**). A soln. of **16** (3.0 g, 7.9 mmol) and $LiAlH_4$ (1.0 g, 26 mmol) in dry THF (150 ml) was stirred at 20° for 1 h under Ar. The mixture was filtered through a pad of *Celite*, the solvent evaporated, and the residue refluxed in 1N HCl (150 ml) for 1 h. After cooling, the pH was adjusted to > 10 by slow addition of sat. aq. Na_2CO_3 soln. The aq. soln. was exhaustively extracted with CH_2Cl_2, and workup followed by chromatography (SiO_2, CH_2Cl_2/MeOH 9:1) gave 2.4 g (83%) of **17**. Colorless oil. ^{1}H-NMR (500 MHz, $CDCl_3$): 1.06 (*t*, *J* = 7.2, 3 H); 2.17 (*s*, 3 H); 2.22 (*s*, 6 H); 2.33 (*q*, *J* = 7.2, 2 H); 2.35–2.6 (*m*, 8 H); 3.68 (*s*, 3 H); 3.79 (*s*, 3 H); 6.72 (*d*, *J* = 9.2, 1 H); 6.85 (*s*, 2 H); 6.95–7.05 (*m*, 2 H). EI-MS: 367 (77, M^+), 245 (100, $[M - C_8H_{10}O]^+$), 231 (79, $[M - C_9H_{12}O]^+$). HR-MS: 367.2496 (M^+, $C_{24}H_{33}NO_2$, calc. 367.2513).

1,1-Diethyl-4-(4-methoxy-3,5-dimethylphenyl)-4-(4-methoxy-3-methylphenyl)piperidinium Chloride (**18**). A soln. of **17** (1.7 g, 4.6 mmol) in CH_2Cl_2 (15 ml) and EtI (55 ml) was stirred at 20° for 2 d under Ar. The solvent was evaporated and the residual pale yellow oil chromatographed on a *Dowex* ion-exchange resin (Cl^-) with H_2O/MeCN 2:1. The solvent was removed as an azeotrope and the residue recrystallized from AcOEt/MeOH: 1.4 g (70%) of **18**. Hygroscopic white solid. M.p. 244–245°. ^{1}H-NMR (200 MHz, $CDCl_3$): 1.39 (*t*, *J* = 7.2, 6 H); 2.18 (*s*, 3 H); 2.24 (*s*, 6 H); 2.5–2.75 (*m*, 4 H); 3.45–3.8 (*m*, 8 H); 3.68 (*s*, 3 H); 3.80 (*s*, 3 H); 6.77 (*d*, *J* = 8.4, 1 H); 6.83 (*s*, 2 H); 6.96 (br. *s*, 1 H); 7.02 (br. *d*, *J* = 8.4, 1 H). FAB-MS: 396 (100, $[M - Cl]^+$). HR-MS: 396.2899 ($[M - Cl]^+$, $C_{26}H_{38}NO_2$, calc. 396.2904).

4-[3-(Chloromethyl)-4-methoxy-5-methylphenyl]-1,1-diethyl-4-(4-methoxy-3,5-dimethylphenyl)piperidinium Chloride (**19**). Gaseous HCl was bubbled for 105 min through a stirred mixture of **18** (1.3 g, 3.0 mmol), AcOH (5

ml), 37% aq. HCl soln. (7 ml), and 37% aq. CH_2O soln. (3.4 ml, 45 mmol). The soln. was carefully neutralized with sat. aq. Na_2CO_3 soln. and extracted with CH_2Cl_2 (3×). The combined org. phases were dried ($MgSO_4$) and evaporated: 1.3 g (90%) of **19**. Colorless hygroscopic foam. ^{1}H-NMR (360 MHz, $CDCl_3$): 1.40 (*t*, *J* = 7.2, 6 H); 2.26 (*s*, 6 H); 2.27 (*s*, 3 H); 2.6–2.75 (*m*, 4 H); 3.45–3.75 (*m*, 8 H); 3.70 (*s*, 3 H); 3.81 (*s*, 3 H); 4.51 (*s*, 2 H); 6.85 (*s*, 2 H); 6.99 (*d*, *J* = 2.2, 1 H); 7.11 (*d*, *J* = 2.2, 1 H). FAB-MS: 444 (100, $[M - Cl]^+$). HR-MS: 444.2672 ($[M - Cl]^+$, $C_{27}H_{39}ClNO_2$, calc. 444.2655).

1,1-Diethyl-4-(4-methoxy-3,5-dimethylphenyl)-4-{4-methoxy-3-methyl-5-[(4-methylthiazolium-3-yl)methyl]-phenyl}piperidinium Dichloride (**4**). A soln. of **19** (1.2 g, 2.5 mmol) in 40 ml of 4-methylthiazole was heated for 3 h to 89–95° under Ar and then stirred overnight at 20°. After addition of H_2O (150 ml), the soln. was exhaustively extracted with Et_2O (10×) to remove all traces of 4-methylthiazole. H_2O was removed as an azeotrope with MeCN and the resulting pale yellow solid (1.1 g, 76%) dried at 20°/10^{-4} Torr for 2 d. M.p. 146–148° (dec.). ^{1}H-NMR (500 MHz, $CDCl_3$): 1.33 (*t*, *J* = 7.1, 3 H); 1.39 (*t*, *J* = 7.0, 3 H); 2.22 (*s*, 3 H); 2.25 (*s*, 6 H); 2.45–2.6 (*m*, 2 H); 2.71 (*s*, 3 H); 2.95–3.05 (*m*, 2 H); 3.4–3.85 (*m*, 8 H); 3.68 (*s*, 3 H); 3.69 (*s*, 3 H); 5.86 (*s*, 2 H); 6.90 (*s*, 2 H); 6.95 (br. *s*, 1 H); 7.95 (br. *s*, 1 H); 8.23 (br. *s*, 1 H); 11.34 (br. *s*, 1 H). FAB-MS: 543 (16, $[M - Cl]^+$), 507 (100, $[M - H - 2\,Cl]^+$), 409 (51, $[M - C_4H_5NS - 2\,Cl]^+$), 380 (16, $[M - C_4H_5NS - Et - 2\,Cl]^+$). HR-MS: 507.3034 ($[M - H - 2\,Cl]^+$, $C_{31}H_{43}N_2O_2S$, calc. 507.3048).

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