Table 1. Specific activities of the enzymes of the $F_{420}H_2$:heterodisulfide oxidoreductase and H_2:heterodisulfide oxidoreductase systems.

Enzyme	Electron donor	Electron acceptor	Spec. activity[a] [U mg protein^{-1}]
$F_{420}H_2$ dehydrogenase	$F_{420}H_2$	**12**	0.20
$F_{420}H_2$ dehydrogenase	$F_{420}H_2$	MP	0.15
membrane-bound hydrogenase	H_2	**12**	2.2
membrane-bound hydrogenase	H_2	MP	3.2
heterodisulfide reductase	dihydro-**12**	CoB-S-S-CoM	2.3
heterodisulfide reductase	dihydro-MP	CoB-S-S-CoM	2.6

[a] 1 U = 1 μmol substrate converted per minute.

reductase uses the reduced form of methanophenazine (dihydro MP) as an electron donor for the heterodisulfide reduction. Therefore methanophenazine is able to mediate the electron transport between the membrane-bound enzymes, so that the conversion by the proton-translocating electron transport systems[6] can be subdivided in two partial reactions each (Scheme 1). In this way methanophenazine **1** was characterized as the first phenazine derivative involved in the electron transport of biological systems. The experiments reported here suggest that its role in the energy metabolism of methanogens is similar to that of ubiquinone in mitochondria and bacteria.

Experimental Section

The growth of *Methanosarcina mazei* Gö1 and the preparation of cytoplasmic membranes was performed as previously described.[7] Photometrical analysis to determine enzymatic activities were carried out at room temperature in glass cuvettes (1.7 mL) that were gassed with N_2 or H_2 and closed with rubber stoppers. The optical-enzymatic determination of the $F_{420}H_2$-dependent reduction of MP and the dihydro-MP dependent heterodisulfide reduction was performed under a nitrogen atmosphere. The cuvette was flushed with hydrogen to determine the hydrogen-dependent reduction of MP. The reactions were initiated by adding the respective electron acceptors. Final concentrations of the reactants were: F_{420}: 25 μM; **12**: 25 μM; MP: 24 μM (stock solution in dimethylformamide), and CoB-S-S-CoM: 38 μM. Protein concentration was 7.5 μg membrane protein per mL assay. Extinction coefficients: F_{420}: $\varepsilon_{420} = 40\,mM^{-1}cm^{-1}$; MP: $\varepsilon_{414} = 3.17\,mM^{-1}cm^{-1}$; **12** $\varepsilon_{425} = 4.5\,mM^{-1}cm^{-1}$.

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[14] $R_f = 0.51$ (diethyl ether/hexane = 1/1); ^{1}H NMR (500 MHz, C_6D_6, TMS): $\delta = 0.83$ (d, $^3J = 6.6$ Hz, 3H; 3′-CH_3), 1.14 – 1.23 (m, 1H; 4′-H_A), 1.32 – 1.39 (m, 1H; 4′-H_B), 1.44 (dt, $^2J = 13.5$ Hz, $^3J = 6.4$ Hz, 1H; 2′-H_A), 1.56 (s, 3H; 19′-CH_3), 1.60 – 1.65 (m, 1H; 3′-H) superimposed by 1.61, 1.62, 1.64 (3s, 3H each; 7′-CH_3, 11′-CH_3, 15′-CH_3), 1.68 (d, $^4J = 0.8$ Hz, 3H; 20′-H_3), 1.72 (ddt, $^2J = 13.5$ Hz, $^3J = 5.4$ Hz, $^3J = 6.8$ Hz, 1H; 2′-H_B), 1.97 – 2.27 (m, 14H; 5′-H_2, 8′H_2, 9′H_2, 12′-H_2, 13′-H_2, 16′-H_2, 17′-H_2), 3.79 (dt, $^2J = 10.7$ Hz, $^3J = 6.8$ Hz, 1H; 1′-H_A), 3.81 (dt, $^2J = 10.7$ Hz, $^3J = 6.4$ Hz, 1H; 1′-H_B), 5.25 (tt, $^3J = 6.9$ Hz, $^4J = 1.4$ Hz, 1H; 18′-H), 5.28 – 5.38 (m, 3H; 6′-H, 10′-H, 14′-H), 7.29 (ddd, $^3J = 8.6$ Hz, $^3J = 6.8$ Hz, $^4J = 1.6$ Hz, 1H; 7-H or 8-H), 7.32 (dd, $^3J = 9.6$ Hz, $^4J = 2.8$ Hz, 1H; 3-H), 7.35 (ddd, $^3J = 8.6$ Hz, $^3J = 6.8$ Hz, $^4J = 1.6$ Hz, 1H; 8-H or 7-H), 7.53 (d, $^4J = 2.8$ Hz, 1H; 1-H), 8.12 (d, $^3J = 9.6$ Hz, 1H; 4-H), 8.30 (dd, $^3J = 8.6$ Hz, $^4J = 1.6$ Hz, 1H; 6-H or 9-H), 8.31 (dd, $^3J = 8.6$ Hz, $^4J = 1.6$ Hz, 1H; 6-H or 9-H); ^{13}C NMR (125 MHz, C_6D_6): $\delta = 16.12$, 16.13, 16.15 (7′-CH_3, 11′-CH_3, 15′-CH_3), 17.73 (19′-CH_3), 19.56 (3′-CH_3), 25.78 (C-20′), 25.83 (C-5′), 27.11, 27.12, 27.23 (C-9′, C-13′, C-17′), 29.80 (C-3′), 36.01 (C-2′), 37.45 (C-4′), 40.20, 40.23 (C-8′, C-12′, C-16′), 66.91 (C-1′), 105.80 (C-1), 124.73, 124.77, 124.93, (C-10′, C-14′, C-18′), 125.04 (C-6′), 126.29 (C-3), 128.29 (C-7 or C-8), 129.58 (C-8 or C-7), 130.15 (C-6 or C-9), 130.27 (C-9 or C-6), 131.08 (C-19′), 131.30 (C-4), 134.99, 135.04, 135.09 (C-7′, C-11′, C-15′), 141.36 (C-4a), 142.63 (C-5a or C-9a), 144.12 (C-9a or C-5a), 145.89 (C-10a), 160.78 (C-2); IR (film): $\tilde{\nu} = 3059\ cm^{-1}$ (CH, olefinic), 2954, 2924, 2853 (CH, aliphat.), 1632, 1605, 1560, 1518 (C=C), 1483, 1445 (CH_2, CH_3), 1380, 1360 (CH_3), 1196 (C-O-C), 828, 757 (C=C, arom.); UV(CH_3CN): λ_{max}(lg ε) = 388 (3.72), 355 (3.78), 256 nm (4.71); MS(70 eV): *m*/*z* (%): 538 (100) [M^+], 470 (6) [$M^+ - C_5H_8$], 402 (8) [$470 - C_5H_8$], 334 (20) [$402 - C_5H_8$], 265 (4) [$334 - C_5H_9$], 196 (82) [$C_{12}H_8N_2O^+$], 168 (7) [196 – CO]; HR-MS: calcd for $C_{37}H_{50}N_2O$: 538.3923; found: 538.3923.

First Artificial Receptor for Caffeine—A New Concept for the Complexation of Alkylated Oxopurines**

Siegfried R. Waldvogel,* Roland Fröhlich, and Christoph A. Schalley

Dedicated to Professor R. R. Schmidt on the occasion of his 65th birthday

Molecular recognition and reactions with signaling ability are of potential use for the development of novel sensors.[1] The detection of small, biorelevant molecules is of particular interest because of their omnipresence in everyday life. Alky-

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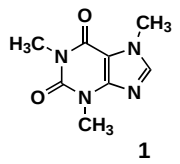

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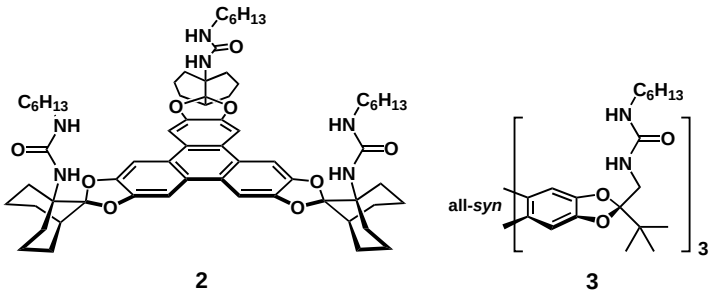
lated oxopurines such as caffeine (**1**), theophylline, or theobromine are among the most frequently consumed alkaloids.[2] Natural compounds like catechine[3] or cyclodextrins[4] are capable of binding caffeine or theobromine rather unspecifically through hydrophobic interactions. The tailor-made receptor by Kelly et al. for the recognition of structurally related uric acid employs only hydrogen bonds for substrate binding.[5] However, an extension of this two-dimensional recognition motif for the binding of caffeine is rendered impossible due to the presence of the methyl groups in **1**.

Here, we present a new concept for the binding of alkylated oxopurines. Our receptors **2** and **3** use the third dimension and surround the substrate as a C_3-symmetric cleft (Scheme 1).



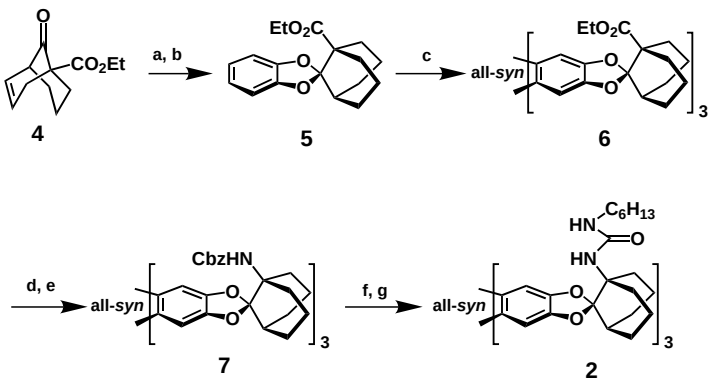
2 **3**

Scheme 1. Functionalized triphenylene ketals: rigid receptor **2** and flexible receptor **3**.

The novel receptor is based on a scaffold of trifunctionalized triphenylene ketals.[6] The combination of preorganized functional groups with a mutual distance of 11 Å and an electron-rich atomic surface in between allows C_3 or pseudo-C_3-symmetric guests to complex. Electron-deficient guest molecules are particularly suitable, because they offer the ability to interact with the host by donor–acceptor interactions in addition to the specific binding through hydrogen bonds. While the methyl groups of the caffeine block interaction with the Kelly-type receptors,[5] they fit perfectly into the free spaces between the urea anchors of our receptor.

The rigid receptor with its bicyclic spiroketal moieties has been prepared from the easily accessible precursor **4** (Scheme 2).[7] The products of the standard transformations can be separated by crystallization. Consequently, they can be synthesized by a rather simple procedure and are accessible on a large scale. The key step is the oxidative trimerization of the catechol ketals with molybdenum pentachloride.[6] Due to the rigid molecular structure, the separation of the isomers is nonproblematic, although a final chromatographic purification of **7** and **2** is recommended.[8, 9] The more flexible receptor **3** has been analogously prepared.

First, we studied the host–guest interaction of receptor and caffeine in dichloromethane solution. NMR titrations confirm a 1:1 stoichiometry of both components and show a complex formation constant of 35 600 M^{-1}. From this constant, a binding energy of approximately 6 kcal mol^{-1} can be estimated.[10] For fitting the titration data, dimerization of the receptor molecules has been taken into account with dimerization constants determined from dilution experiments.[11]



4 **5** **6** **7** **2**

Scheme 2. Synthesis of rigid receptor **2**: a) **4** (as a mixture of the double bond isomers), catechol, TsOH, Dean–Stark trap, toluene, 86%; b) H_2, Pd/C, 100%; c) $MoCl_5$, CH_2Cl_2, then separation of isomers, 18%; d) *t*BuOK, THF, H_2O; e) $(PhO)_2P(O)N_3$, NEt_3, DMF, then benzylalcohol, 49% from **6**; f) H_2, $Pd(OH)_2$, THF; g) hexyl isocyanate, CH_2Cl_2, 65% from **7**. Cbz = benzyloxycarbonyl, Ts = tosyl = toluene-4-sulfonyl.

During the ^{1}H NMR titration of **2** with caffeine, the signals for the proximal and distal (to the triphenylene plane) N–H protons shift downfield differently (Figure 1). While the signal

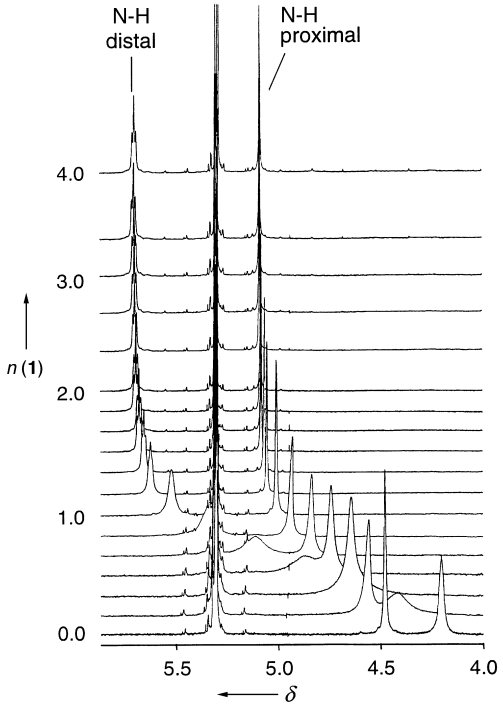


Figure 1. ^{1}H NMR titration of **2** with caffeine (N–H region). n(**1**) = number of equivalents of caffeine (**1**).

for the proximal urea protons experiences only a minor effect (+0.6 ppm), the distal counterpart shifts considerably more (+1.5 ppm). This points to stronger hydrogen bridges between the guest and the distal urea protons, while the proximal N–H atoms contribute less significantly to caffeine binding. After addition of one equivalent of caffeine, the titration curves bend rather sharply and the signals remain

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more or less at a constant position in the spectrum, if more caffeine is added. Consequently, receptor **2** forms a 1:1 complex with caffeine in which the guest molecule is located between the urea functions instead of binding to the open side through $\pi-\pi$ stacking, π-donor$-\pi$-acceptor, or hydrophobic interactions.[10]

The comparison of receptors **2**, **3**, and **7** clearly shows the rigid receptor **2** has a much better performance in caffeine binding (Table 1). Urea anchors, which are well preorganized for hydrogen bonding, increase the binding constant by a factor of more than 200 relative to the flexible molecule **3**. Host **7** hardly interacts with caffeine at all, which again points to a stronger substrate binding by the distal N–H protons than the proximal ones. This result is in agreement with the crossed titration curves for both urea protons discussed above. In addition to these NMR experiments, the mass spectrometric observation of the intact caffeine–receptor complex and IR spectroscopic evidence for hydrogen bonding support complex formation.

Table 1. Binding constants K.

Entry	Receptor	Substrate	K [M^{-1}]
1	**2**	**1**	$35\,600 \pm 2000$
2	**3**	**1**	170 ± 50
3	**7**	**1**	$< 10 \pm 5$
4	**2**	**8**	$9\,240 \pm 220$
5	**2**	**9**	–[a]
6	**2**	**10**	$1\,240 \pm 115$
7	**2**	**11**	420 ± 70
8	**2**	**12**	130 ± 50

[a] Not measurable due to the insolubility of **9** in CD_2Cl_2.

Variation of the substrates for receptor **2** allows a study of the geometric and electronic fit of the substrate. The binding constant of 8-methoxycaffeine (**8**)[12] is already smaller, because the methoxy group disturbes hydrogen bonding to the urea arms of the receptor. 1,3,7-trimethyl uric acid (**9**)[12] binds strongly to **2**; unfortunately, the quantification of the binding constant is impossible due to the insolubility of free **9** in CD_2Cl_2. Addition of approximately one equivalent of **2** to a suspension of **9** in dichloromethane leads spontaneously to a clear solution, which indicates substrate binding to the receptor. *N*,*N*′,*N*″-triallylcyanuric acid (**10**) is less strongly bound due to its localized amide bonds and decreased planar systems offering $\pi-\pi$ interactions. The binding constant further decreases, if one of the nitrogen atoms is replaced by a methylene group (as in **11**) which interferes with the coplanar orientation of substrate and receptor. Finally, *N*,*N*′-dimethyl uracil (**12**) bears only two acceptor groups. This substrate is incongruent with the symmetry of the receptor—the affinity to the host decreases.

Variable-temperature ^{1}H NMR experiments give a more profound insight into the nature of caffeine binding in solution. Upon cooling to 196 K, the ^{1}H NMR spectrum of a mixture of receptor **2** and two equivalents of caffeine contains separate sets of signals for free and bound caffeine. Complexation of the guest breaks the receptor's threefold symmetry and leads to different signals for all six urea protons. The aromatic protons of the triphenylene scaffold also split into a complex pattern.

From a solution of caffeine and receptor **2** in methanol, crystals were obtained, which were appropriate for a single-crystal X-ray structure analysis (Figure 2).[13] The crystal structure exhibits a binding pattern analogous to that observed by spectroscopic methods in solution. The three distal urea protons form hydrogen bonds to the caffeine guest. The crystal structure further demonstrates caffeine to be slightly too small for the receptor and, therefore, the spiro ketals are

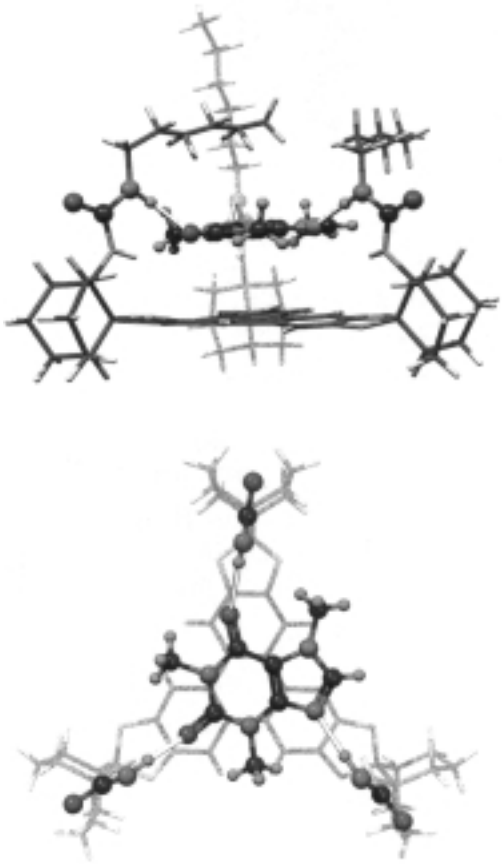
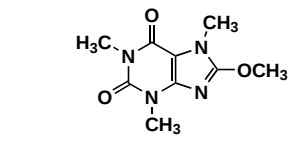


Figure 2. X-ray crystal structure of the host–guest complex of **2** with caffeine. Side and top views (above and below, respectively); caffeine and anchoring groups are emphasized as ball and stick models.



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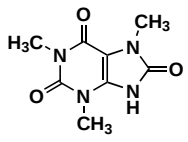

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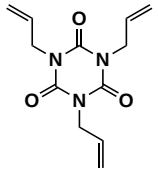

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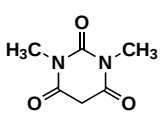

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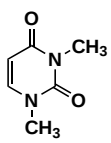

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bent towards the triphenylene by approximately 11 – 15°. As a consequence, the proximal NH protons are directed towards the aromatic plane rather than the caffeine molecule and interact only weakly. The distance between the coplanar aromatic surfaces is 3.42 Å which is optimal for a donor–acceptor interaction. It turned out to be impossible to accomplish the crystallization of this receptor with sidechains shorter than *n*-hexyl. The hexyl groups must be packed in the crystal and, indeed, two of them save space by folding in, while the third alkyl chain breaks the symmetry and produces a preferred directionality. Disordered caffeine was not observed. We were even able to localize the hydrogen atoms involved in hydrogen bonding.[14] The values found are in the typical ranges.

In conclusion, rigid functionalized triketals of hexahydroxytriphenylene open up the opportunity to generate novel receptors for the selective recognition of alkylated oxopurines. For caffeine, the bonding interaction can be observed directly. Together with the results from X-ray crystallography, a consistent picture of the receptor's guest binding features evolves.

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[8] All new compounds were obtained pure (elemental analysis (C, H, N) within ±0.4 %).

[9] Compound **2**: mp 198 °C; ^{1}H NMR (600 MHz, CD_2Cl_2, 25 °C, TMS): $\delta = 0.78$ (t, $^3J_{H,H} = 7$ Hz, 9H, CH_3), 1.06 – 1.18 (m, 24H), 1.64 – 1.73 (m, 12H), 2.12 – 2.31 (m, 21H), 2.78 – 2.88 (m, 12H), 4.51 (br., 3H, N–H distal), 4.71 (s, 3H, N–H proximal), 7.82 (s, 6H, triphenylene); ^{13}C NMR (150.8 MHz, CD_2Cl_2, 25 °C, TMS): $\delta = 14.15$, 21.45, 22.91, 26.94, 28.68, 30.44, 31.89, 34.77, 38.51, 40.51, 57.77, 101.94, 122.37, 124.97, 147.97, 157.85.

[10] The binding constants were obtained by fitting the titration curves with the Specfit program package: Specfit v.2.12, Spectrum Software Associates, Chapel Hill, NC, USA; H. Gampp, M. Maeder, C. J. Meyer, A. D. Zuberbühler, *Talanta* **1986**, *33*, 943, and references therein. The given error is systematical; multiple determination demonstrated an excellent reproducibility of the binding constants. A low mean variation is observed in the determined values.

[11] The receptors exhibit a slight tendency to self-aggregate. The Specfit program was used to determine dimerization constants from dilution experiments. These constants have been taken into account for the fit of the binding constants. For simplicity, higher aggregates have not been included. A model including receptor trimers was tested, but including these species did not change the good agreement of measured and fitted titration curve. The constants obtained from both models are the same within the error of the experiment.

[12] Syntheses of substrates: **8**: R. C. Huston, W. F. Allen, *J. Am. Chem. Soc.* **1934**, *56*, 1356 – 1358; **9**: E. Fischer, *Ann.* **1882**, *215*, 253 – 320.

[13] X-ray crystal structure analysis of **2** with caffeine: $C_{74}H_{100}N_{10}O_{11} \cdot 3.5\,CH_3OH$, $M_r = 1417.79$, light yellow crystal, $0.50 \times 0.35 \times 0.25$ mm^3, $a = 13.596(1)$, $b = 13.794(1)$, $c = 22.979(1)$ Å, $\alpha = 80.09(1)$, $\beta = 82.40(1)$, $\gamma = 67.41(1)°$, $Z = 2$, $V = 3909.2(4)$ Å^3, $\rho_{calcd} = 1.204$ g cm^{-3}, $\mu = 0.83$ cm^{-1}, absorption correction with SORTAV ($0.971 \le T \le 0.992$), triclinic, space group $P\bar{1}$ (No. 2), $\lambda = 0.71073$ Å, $T = 198$ K, ω and φ scans, 22410 reflections collected ($\pm h$, $\pm k$, $\pm l$), $[(\sin\theta)/\lambda] = 0.59$ Å^{-1}, 13700 independent ($R_{int} = 0.033$) and 8862 observed reflections [$I \ge 2\sigma(I)$], 911 refined parameters, $R = 0.094$, $wR^2 = 0.267$, max. (min.) residual electron density was 1.09(–0.69) e Å^{-3} close to the disordered solvate molecules, disorder refined with constraints, hydrogens calculated at the nitrogen atoms from difference fourier calculations, others calculated and refined as riding atoms. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-139021. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

Calcium-Catalyzed Selective and Quantitative Transformation of CH_4 and CO into Acetic Acid**

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Methane and ethane have exerted a profound economic and sociologic influence on the world at large because of their enormous reserves.[1] However, the use of methane in the direct synthesis of functionalized products is limited by the low reactivity of methane and poor product selectivity.[2] The search for new routes of methane transformation constituted an important field of research over the last two decades.[3] Carboxylation of methane with CO to afford acetic acid is an important functionalization process that is not industrially feasible at present. In 1992 we reported the Pd-catalyzed carboxylation of methane with CO in the presence of $K_2S_2O_8$ and CF_3COOH (TFA).[4] Recently we found that systems using a $Yb(OAc)_3/Mn(OAc)_2/NaClO/H_2O$ catalyst[5] and $Mg/K_2S_2O_8$/TFA promoter[6] cause the carboxylation of methane to give acetic acid. Magic-acid-induced[7] and $RhCl_3$-catalyzed[8] reactions of methane with CO were also developed. However, these processes have several practical drawbacks, such as low yield, cost of catalyst, and product selectivity. Herein we report almost quantitative carboxylation of methane with CO to afford acetic acid (**1**) with one of the cheapest chemicals, namely, $CaCl_2$, as catalyst.

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