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[18] Analytical data for **2**: M.p. 1359 °C (hexene) [ref. [9]: m.p. 135.5–1369 °C (hexene)]; IR (KBr): $\tilde{\nu}$ = 3337, 1645, 1609, 1460, 1380, 1320, 1234, 1209, 1043 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.48 (br. s, 1H), 5.85 (s, 1H), 5.12 (br. s, 1H), 3.84 (s, 3H), 2.63 (d, 1H, J = 13.7 Hz), 2.49 (d, 1H, J = 13.7 Hz), 2.06–1.97 (m, 1H), 1.92–1.83 (m, 1H), 1.63 (dt, 1H, J = 12.7, 3.3 Hz), 1.54 (s, 3H), 1.47–1.04 (m, 6H), 1.00 (s, 3H), 0.97 (d, 3H, J = 6.1 Hz), 0.92–0.88 (m, 1H), 0.84 (s, 3H); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 182.4, 182.1, 161.8, 153.2, 144.0, 120.9, 117.6, 102.0, 56.8, 47.8, 43.1, 38.5, 37.8, 36.0, 32.3, 27.9, 27.0, 20.2, 19.8, 18.2, 17.7, 17.4; MS: (EI, 70 eV, 858 C): m/z: 358 [M^+], 281, 236, 191, 168; HRMS (EI) calcd for $C_{22}H_{30}O_4$ 358.2144, found 358.2131; $[\alpha]_D^{20}$ = +62.4 (c = 0.25, $CHCl_3$) [ref. [9] $[\alpha]_D^{20}$ = +64.8 (c = 1, $CHCl_3$)].

[19] Analytical data for **1c**: IR (KBr): $\tilde{\nu}$ = 3417, 1679, 1650, 1597, 1556, 1391, 1209 cm^{-1}; ^1H NMR (500 MHz, [D_6]DMSO): δ = 7.16 (d, 1H, J = 7.3 Hz), 5.34 (s, 1H), 5.06 (s, 1H), 4.21 (m, 1H), 3.82 (m, 1H), 3.78 (m, 1H), 2.43 (d, 1H, J = 13.5 Hz), 2.32 (d, 1H, J = 13.5 Hz), 2.01–1.89 (m, 3H), 1.54 (m, 1H), 1.47 (s, 3H), 1.39–1.15 (m, 4H), 1.03–0.98 (m, 2H), 0.93 (s, 3H), 0.89 (d, 3H, J = 7.3), 0.77 (s, 3H); MS: (–FAB, diethanolamine matrix): m/z: 432 [M+H], $[\alpha]_D^{20}$ = +62 (c = 0.13, EtOH) [ref. [8] ($[\alpha]_D^{20}$ = –73° (c = 0.03, EtOH)].

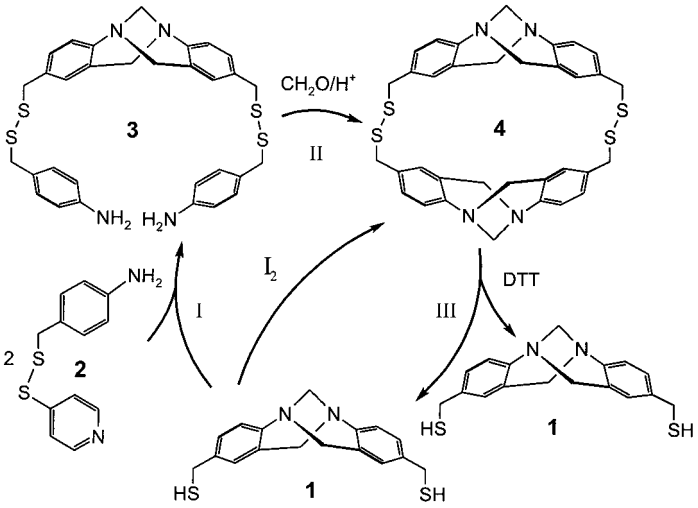
[20] The direction of the specific rotation reported for nakijiquinone C isolated from natural sources is indeed incorrect. Reexamination of the original sample yielded a value of $[\alpha]_D^{20}$ = +138° (c = 0.1, EtOH): Prof. Jun'ichi Kobayashi, Hokkaido University, Sapporo; personal communication.

Stepwise Replication of a Tröger's Base Analogue**

Braja G. Bag and Günter von Kiedrowski*

Molecular replication lies in the heart of biological systems. In its minimal representation, molecular replication is the ability of a molecule to form a copy of itself with transfer of constitutional information. In recent years, the phenomenon has been studied with various chemical model systems based on oligonucleotides,[1] peptides,[2] and other synthetic supramolecular systems,[3] aiming to gain an improved understanding of prebiotic replication.[4] A common problem of these template-mediated catalytic systems, regardless of whether they are autocatalytic or cross-catalytic, is product inhibition leading to parabolic amplification. Recently, an exponential amplification procedure based on oligonucleotides immobilized on a solid support was reported by Luther et. al.[5] Here we report a new scheme for stepwise replication that is based on a Tröger's base analogue and utilizes macrocyclization and covalent templating.

Tröger's base with its rigid V-shaped geometry has become attractive in recent years in the general area of supramolecular chemistry.[6] For the design of a novel replicating system based on a Tröger's base analogue, we realized that a thiol–disulfide exchange reaction[7] could be integrated with the formation of Tröger's base.[6b] Molecular modeling using the PCMODEL[8] program supported the geometric feasibility of the "dimeric" macrocyclic structure **4** (see Scheme 1). We chose compound **1**, which has two appended thiol groups at the 2- and 8-methyl groups of Tröger's base, as a template. It occurred to us that reaction of **1** with **2** will produce **3** by a thiol–disulfide exchange reaction (Scheme 1). Intramolecular condensation of the two aniline units of **3** will produce **4**. Reductive cleavage of the disulfide linkages of **4** will generate a replica of **1** along with the parent template.



Scheme 1. Stepwise replication of Tröger's base analogue **1** by macrocyclization and covalent templating.

We have previously reported the synthesis of compound **1**.[9] Indirect evidence for the practicability of the replication Scheme came from the fact that oxidation of **1** with iodine[10] under high dilution conditions in THF afforded **4** as the major product detectable by HPLC (Table 1). Treatment of a solution of **1** in chloroform with **2** in the presence of *p*-toluenesulfonic acid afforded **3** in quantitative yield. The insoluble byproduct 4-thiopyridone was separated by filtration and the bis-amine **3** was directly used for the macrocyclization. Condensation of **3** with formalin in chloroform/

[*] Prof. Dr. G. von Kiedrowski, Dr. B. G. Bag
Lehrstuhl für Organische Chemie I – Bioorganische Chemie
der Universität
Universitätsstrasse 150, D 44780 Bochum (Germany)
Fax: (+49) 234-32-14355
E-mail: kiedro@ernie.orch.ruhr-uni-bochum.de

[**] This work was supported by the Deutsche Forschungsgemeinschaft (SFB 452) and the Fonds der Chemischen Industrie. We thank Rolf Breuckmann, Beate Materue and Klaus Körner for their technical assistance.

Table 1. Selected data for compounds **2**–**4**.

2: M.p. 129–131 °C; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 8.40$ (d, $J = 6.3$ Hz, 2H), 7.32 (d, $J = 6.3$ Hz, 2H), 7.05 (d, $J = 8.4$ Hz, 2H), 6.57 (d, $J = 8.4$ Hz, 2H), 3.88 (s; CH_2), 3.67 (brs, 2H; NH_2); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta =$ 147.8, 145.3, 129.4, 124.3, 119.1, 114.0, 42.2; MS: *m/z* (%): 248 (M^+, 1.5), 138 (3), 106 (100); HR-MS: calcd for $C_{12}H_{12}N_2S_2$: 248.0442, found: 248.0432

3: ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 7.05$ (s, 4H), 6.96 (d, $J = 8.4$ Hz, 4H), 6.73 (s, 2H), 6.58 (d, $J = 8.4$ Hz, 2H), 4.66 (d, $J = 16.3$ Hz, 2H), 4.29 (s, 2H), 4.11 (d, $J = 16.3$ Hz, 2H), 3.49 (s, 4H), 3.47 (s, 4H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 146.7$, 144.3, 132.7, 130.0, 128.2, 127.4, 127.3, 124.6, 115.4, 66.6, 58.3, 42.5, 39.8; FAB-MS (positive ion): calcd for $C_{31}H_{33}N_4S_4$ (M^++H): 589.8, found: 589.2

4: ^{1}H NMR (400 MHz, $CDCl_3$, for the mixture of diastereomers): $\delta =$ 7.07–7.01 (m, 4H), 6.81–6.75(m, 4H), 6.49 (brs, 4H), 6.39 (brs, 4H; the integration ratio of the peaks at 6.49 and 6.39 is 1:1.8), 4.67 (d, $J = 16.1$ Hz, 4H), 4.64 (d, $J = 16.6$ Hz, 4H), 4.38 (s, 4H), 4.37, (s, 4H), 4.06 (d, $J =$ 16.6 Hz, 4H), 4.05 (d, $J = 16.1$ Hz, 4H), 2.91 (d, $J = 12.6$ Hz, 4H), 2.85 (d, $J = 12.3$ Hz, 4H), 2.75 (d, $J = 12.3$ Hz, 4H), 2.69 (d, $J = 12.6$ Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$, for the mixture of diastereomers): $\delta = 146.9$, 146.7, 133.4, 133.1, 129.1, 128.9, 127.8, 127.3, 124.5, 124.4, 67.7, 67.5, 59.9, 59.7, 42.8, 41.9; FAB-MS (positive ion): calcd for $C_{34}H_{33}N_4S_4$ (M^++H): 625.2, found: 625.2

ethanol (3/1) under high dilution conditions in the presence of hydrochloric acid produced **4** as a 1:1.8 mixture of diastereomers. The crude reaction mixture was directly used for the reduction step after neutralization with ammonia and equilibration with water. Reduction with dithiothreitol (DTT)[11] in the presence of triethylamine afforded compound **1**. The progress of the individual reaction steps was monitored by HPLC, and the yield of the final product was determined from the area of the HPLC peak. After a complete replication cycle the amount of compound **1** increased by 40%. A control experiment with the amine **2** at twice the initial concentration with respect to macrocyclization yielded only traces of the desired Tröger's base derivative, and most of the starting material was recovered. This supported the template-mediated pathway shown in Scheme 1.

The presence of an excess of the reducing agent DTT and traces of triethylamine gave anomalous results in recycling the material. However, the use of a controlled amount of DTT during reduction (Scheme 1, step III) followed by thorough removal of triethylamine under reduced pressure and the use of an acidic catalyst (*p*-toluenesulfonic acid) in the following step (step I) gave satisfactory results upto three generations with about 35–40% yield per cycle (Figure 1).[12]

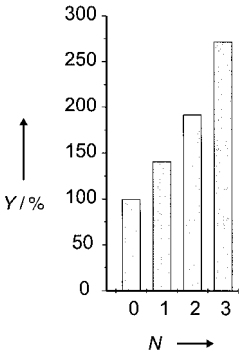


Figure 1. Plot of total yield *Y* of compound **1** versus the number of replication cycles *N*. When the reaction is initiated with 0.75 g of **1**, the total yields were 141, 192, and 272% for first, second, and third replication cycles, respectively, affording 2.04 g of **1** in the end.[12]

The stepwise replication procedure described here represents a new way for exponential amplification during chemical self-replication and can be further extended to other classes of coupling reactions. Current efforts in our laboratory address the question of chirality transfer during stepwise replication. Also, studies of similar coupling reactions to generate a chiral center[13] might prove useful for the design of new chiral amplification strategies.[14]

Received: June 21, 1999 [Z13589IE]
German version: *Angew. Chem.* **1999**, *111*, 3960–3962

Keywords: macrocycles · self-replication · template synthesis · Tröger's base

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[12] With an average yield of 39% per replication cycle, the total yield *Y* can be expressed by the equation $Y = 100(1 + x)^N$, where *N* is the number of replication cycles and *x* is 0.39 ± 0.03. It may be added that for a value of $x > 0$ the equation indicates an exponential increment of the template concentration.[5]

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