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[16] SPE = Solid-phase extraction; for filtration columns with RP-18 material was used in conjunction with a "VacMaster SPE Processing Station" (Separtis IST); mobile phase: acetonitrile/water.

[17] Purification and mass detection were performed on an HPLC-MS (Waters) fitted with a LC/MS detector (Micromass ZMD; electrospray ionization (ESI) mode). Chromatography performed on Xterra RP-18 (analytic: 3.5 μm, 4.6 × 100 mm; semi-preparative: 7.0 μm, 19 × 150 mm) columns (Waters) with an acetonitrile–water gradient.

[18] The following references were utilized for the synthesis of bromocoumarins **2**–**4**, **7**, and **8**: **2**: F. Peters, H. Simonis, *Chem. Ber.* **1908**, *41*, 830–837; **3**: K. Takagi, M. Hubert-Habart, *Bull. Soc. Chim. Fr.* **1980**, *2*, 444–448; **4**: a) B. B. Dey, K. K. Row, *J. Chem. Soc.* **1923**, *123*, 3375–3384; b) B. B. Dey, T. R. Seshadri, *Chem. Zentralbl.* **1926**, *97*, 1648–1649; **7**, **8**: N. A. Gordeeva, M. A. Kirpichenok, N. S. Patalakha, I. I. Grandberg, *Chem. Hetreocycl. Compd. (Engl. Transl.)* **1990**, *26*, 1329–1337; Bromocoumarins **5** and **6** were available by selective nitration and subsequent reduction starting from coumarin **2** and **3**: KNO$_3$ (1.22 g, 12 mmol) was added to a solution of coumarin **2** or **3** (10 mmol) in 96% sulfuric acid (60 mL) at 0°C. After stirring at 0°C for 2.5 h, the solution was poured into crushed ice forming a precipitate. This precipitate was collected and washed successively with diluted Na$_2$CO$_3$ solution. The pure 6-nitrated derivatives were obtained by recrystallizing from ethanol/water (95/5). For the reduction, the nitro compounds (10 mmol) were dissolved at 100°C in 80% acetic acid (200 mL) and treated portionwise with iron powder (3.35 g, 60 mmol). After 10 min the solution was poured into ice and extracted several times with chloroform. The solvent was subsequently removed and the crude product purified by column chromatography on silica (hexane/ethylacetate 50/50; overall yields: 66% (**5**), 63% (**6**)).

[19] Representative example for a parallel Suzuki cross-coupling: synthesis of 7-amino-4-methyl-3-*p*-tolyl-chromen-2-one (**7 A 2**): Coumarin **7** (25.4 mg, 0.1 mmol), boronic ester **A 2** (35.2 mg, 0.2 mmol), CsF (121 mg, 0.8 mmol), and [Pd(PPh$_3$)$_4$] (5.78 mg, 5 mol%) were heated at 90°C under argon in dry dioxane for 16 h. The solvent was evaporated and the residue was dissolved in acetonitrile/water. This solution was then filtered through a SPE (RP-18) column and purified by automated HPLC-MS affording the pure product (21.2 mg, 80%). M.p. 260–262°C; ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25°C): $\delta = 7.44$ (d, $J = 8.7$ Hz, 1H), 7.20 (d, $J = 7.9$ Hz, 2H), 7.12 (d, $J = 7.9$ Hz, 2H), 6.60 (dd, $J = 8.7$, 1.9 Hz, 1H), 6.45 (d, $J = 1.9$ Hz, 1H), 6.07 (broad s, 2H), 2.33 (s, 3H), 2.13 (s, 3H); ^{13}C NMR (100 MHz, [D$_6$]DMSO, 25°C): $\delta = 160.8$, 154.6, 152.8, 148.6, 136.6, 132.5, 130.5 (2C), 128.7 (2C), 126.8, 119.8, 111.6, 109.4, 98.5, 21.0, 16.3; UV/Vis (ethanol): λ_{max} (ε [L mol^{-1} cm^{-1}]) = 360 nm (22500); EI-MS (70 eV): m/z (%) : 265 (88) [M^+], 237 (100) [$M^+ - CO$].

[20] For further structure validation 20% of the library members were characterized spectroscopically (^{1}H NMR).

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Single-Compound Libraries of Organic Materials: From the Combinatorial Synthesis of Conjugated Oligomers to Structure–Property Relationships[**]

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Eva M. Bonsen, Wolfgang Schuhmann, and
Peter Bäuerle*

The development process of novel materials is often encumbered by the time-consuming "one-at-a-time" process of material synthesis and evaluation. This situation is particularly true for π-conjugated oligomers which serve as model compounds for conducting polymers and are recognized as materials in their own right.[1] Accordingly, there is a need for novel methods that provide for both rapid compound generation and subsequent evaluation. Combinatorial methodologies that were developed for the high-speed synthesis and high-throughput screening of pharmaceuticals could help to overcome these bottlenecks in the materials development process.[2] Moreover, the rapid generation of data sets provided by combinatorial methods and their subsequent translation into structure–property relationships may enable the rational design of new materials.

While most of the combinatorial approaches in materials science concentrate on the development of inorganic solid-state materials, polymeric materials, and catalytic systems,[3] we report here and in the preceding correspondence[4] the development of combinatorial strategies for the generation of organic materials. The focus of this study is the combinatorial synthesis and subsequent screening of oligothiophenes which are one of the most examined classes of π-conjugated oligomers.[5] The strategy covers all stages of the combinatorial discovery process: design of the lead structure, elaboration of the synthetic route, generation of the library and purification, screening, and data analysis. We focused on a regioregular head-to-tail coupled quater(3-arylthiophene) as the lead structure (Scheme 1). Because of their defined structure these aryl substituted oligomers, together with the already intensively investigated oligo(3-alkylthiophene)s, are outstanding model compounds for the parent (polydisperse) poly(3-arylthiophene)s and poly(3-alkylthiophene)s.[6] The

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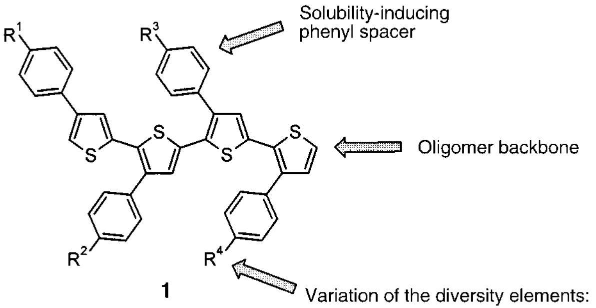
Supporting information for this article is available on the WWW under http://www.angewandte.com or from the author.



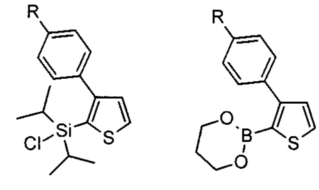
Scheme 1. Lead structure: quater(3-arylthiophene) **1**.

latter are already successfully employed as active components in electronic devices, such as organic field-effect transistors.[7] The oligothiophene **1** is substituted at the 3-position of each thiophene subunit with phenyl groups that are in turn substituted at their *para* positions with four diversity elements of different electronic nature ($R = CF_3$, H, CH_3, OCH_3).

The phenyl spacer should increase the solubility of the oligomers and ensure the electronic communication between the substituents and the oligomer backbone. These four backbone substituents should influence the electronic structure of the quaterthiophenes without greatly changing the overall geometry of the molecule (which is mainly determined by the phenyl groups). The lead structure **1** should therefore permit a systematic investigation of the substitutent influence on the energy levels of the molecular orbitals and the development of structure–property relationships.

As previously demonstrated by several research groups, the utilization of solid-phase synthesis offers substantial advantages for the synthesis of π-conjugated oligomers over solution-phase synthesis.[8] These advantages include quicker and more effective purification techniques and maximized overall yields. The synthesis of the quater(3-arylthiophene)s **1** is based on the recently published solid-phase synthesis of a regioregular head-to-tail coupled quater(3-*p*-tolyl)thiophene (Scheme 2).[8e]

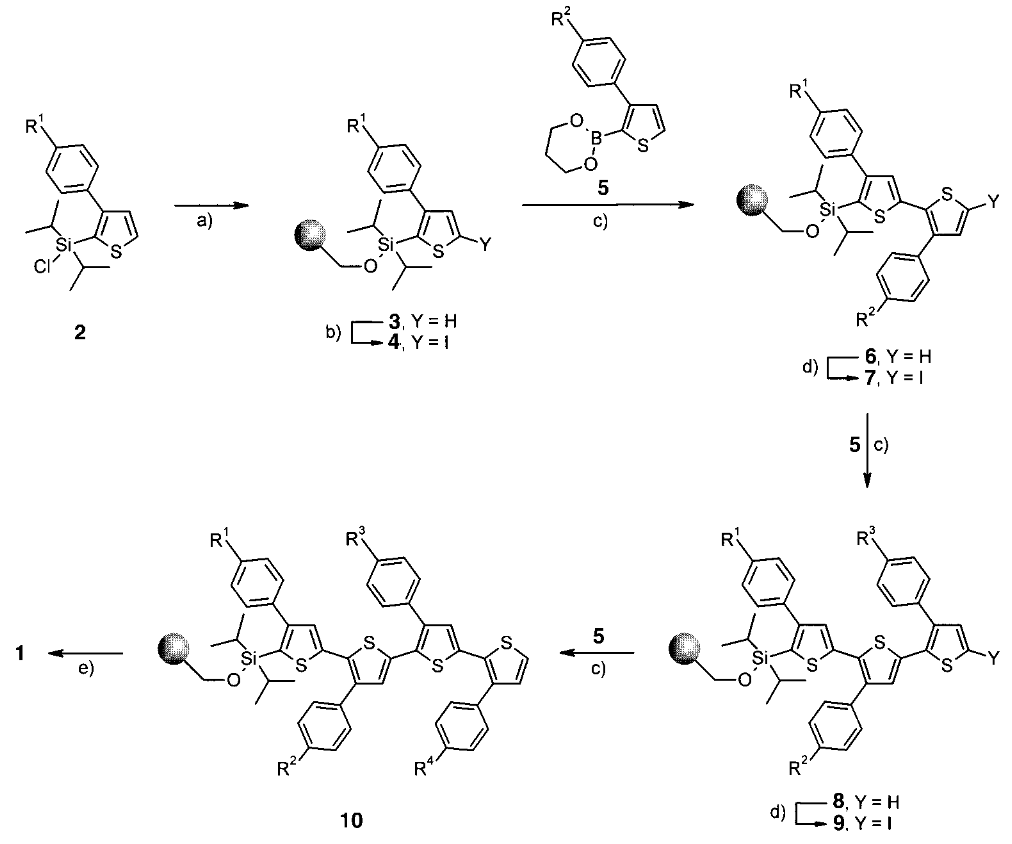
In a stepwise addition approach the first of the four arylthiophenes is anchored to the polymer matrix by a traceless silyl linker; this is realized by treating a (chlorosilyl)thiophene **2** with hydroxymethylated polystyrene. Oligomer growth is accomplished by an iterative sequence of iodination and Suzuki cross-coupling with the thiophene boronic ester **5**. Resin-bound thiophene **3** was halogenated to **4** by metalation with lithium diisopropylamide (LDA) and subsequent reaction with iodine. In contrast, a mercuration–ododemercuration reaction ($Hg(OCOC_5H_{11})_2$ instead of LDA) was required for the selective access to the iodinated bi- and terthiophenes **7** and **9**. The cross-couplings for the preparation of dimer **6**, trimer **8**, and tetramer **1** required a $[Pd(PPh_3)_4]$ catalyst. Finally, quaterthiophene **1** was liberated from the resin by treating the derivatized polymer support with 10% trifluoroacetic acid (TFA) in CH_2Cl_2.



2a, R = CF_3
2b, R = H
2c, R = CH_3
2d, R = OCH_3

5a, R = CF_3
5b, R = H
5c, R = CH_3
5d, R = OCH_3

The (chlorosilyl)thiophene **2a–d** and thiophene boronic ester **5a–d** building blocks are needed to introduce diversity in the final quaterthiophenes. These building blocks were synthesized in good yields following literature procedures starting from the corresponding 2-bromo-3-arylthiophenes.[8e, 9] In the optimization studies the electronic influence of these diversity elements on the reactivity of the building blocks and the resin-bound oligomers was readily apparent. For example, the markedly different reactivity between the boronic esters **5a–d** required a further optimization of the reaction conditions for the Suzuki cross-coupling. The C–C bond formation reaction between the



Scheme 2. Solid-phase synthesis of the quater(3-arylthiophene)s **1**: a) hydroxymethylated polystyrene, imidazole, DMF, 20 °C; b) 1. LDA, THF, −60 °C; 2. I_2; c) $[Pd(PPh_3)_4]$, THF/H_2O, $NaHCO_3$ or Na_2HPO_4/NaH_2PO_4; d) 1. $Hg(OCOC_5H_{11})_2$, CH_2Cl_2, 20 °C; 2. I_2, CH_2Cl_2; e) 10% TFA, CH_2Cl_2, 20 °C. Selected spectroscopic data can be found in the Supporting Information.

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resin-bound iodinated thiophenes and boronic esters **5b–d** with $NaHCO_3$ as the base gave nearly quantitative conversions. However, under these conditions the trifluoromethyl substituted building block **5a** furnished the coupling product in very low conversions. Therefore, a buffer system of NaH_2PO_4/Na_2HPO_4 was employed and proved to be highly efficient in cross-couplings with the boronic ester **5a**.

With the development and optimization of the synthetic method complete, the oligomer library was constructed by utilizing both the parallel and the "mix-and-split" synthesis. This library included all possible permutations of the four diversity elements (functional groups) resulting in a library of 256 tetramers. The synthesis of the iodobithiophenes **7** was performed in parallel, the subsequent oligomer growth to the quaterthiophenes **1** used the "mix-and-split" technique. In the latter technique, the individual compounds are synthesized in micro-reactors each labeled with a unique radiofrequency tag for identification.[10] Using this procedure a 256-membered quaterthiophene library was synthesized after successful generation of a 16-membered test library.

Since the purity of the compounds is a crucial prerequisite for a meaningful screening, all the oligomers were purified using automated preparative high-pressure liquid chromatography (HPLC).[11] 243 of the 256 library members could be isolated in milligram quantities with purities of greater than 98 %. In addition, the integrity and identity of the oligomers could be assessed by coupled mass spectrometry. The quaterthiophenes were available in isolated overall yields of 2–51 % which do not reflect the overall reaction conversions but rather display the separation difficulties during the HPLC purification. The ^1H NMR spectroscopic analysis of selected raw products revealed an overall conversion of 40–55 % (which appeared to be nearly independent of the building blocks employed) corresponding to an average conversion of 89–93 % per reaction step.

In view of the technological applications of π-conjugated oligomers and their corresponding polymers the investigation of optical and electrochemical properties is of interest. The screening of the purified oligomers by means of absorption and fluorescence spectroscopy and cyclic voltammetry should allow the development of detailed structure–property relationships which can be used to estimate the properties of similar oligomers and polymers. The screening of optical properties revealed only a marginal influence by the substituents on the absorption maxima ($\lambda_{abs} = 381–392$ nm) and emission maxima ($\lambda_{em} = 492–518$ nm). However, the optical gap which is associated with the energy difference of the frontier orbitals slightly increases with the electron-donating nature of the substituents ($\Delta E = 2.71–2.74$ eV).

The electronic consequences of the oligomer substitution on the relative energy levels of the frontier orbitals were further investigated by cyclic voltammetry. A significant increase of the probe throughput was obtained by using a fully automated screening device. The apparatus constructed for the electrochemical screening is shown in Figure 1. It comprises a 96-well plate (which was used as an array of electrochemical cells), a three-electrode setup (Pt working electrode, Pt counter electrode, and Ag/AgCl reference electrode), a solvent dispenser, a potentiostat, and a computer for data acquisition. To precisely position the electrode setup into the wells the microtiter plate was fixed to a holder which could be orientated in the *x*,*y* plane and the electrode setup was attached to a holder with *z*-direction mobility. Tailored software[12] allowed the positioning of the electrodes into the cavities of the well plate, the dosing of the electrolyte[13] under exclusion of oxygen using a serially controlled solvent dispenser, and after a predefined delay (which was necessary for solvating the compound) acquisition of the voltammetric data. Cyclic voltammograms for each measurement were stored in a separate file.

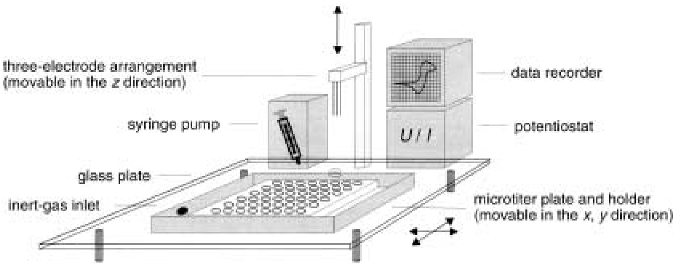

Figure 1. Apparatus for the automated cyclic voltammetry.

By extracting the relevant data from the voltammograms, information on the substituent effects on redox potentials was provided. The first oxidation potentials of the quaterthiophenes (E_1^0) covered a large range of 0.42–0.68 V.[14] A systematic shift to higher oxidation potentials occurred when the substituents had a more pronounced acceptor character. This general trend is illustrated in the color-coded diagram, Figure 2. A similar relationship was found for the second oxidation potentials of the quaterthiophenes (E_2^0), these covered a range of 0.78–0.90 V.

The correlation of the collected redox potentials with the substituent descriptor $\Sigma\sigma_p^+$ (which was defined as sum of the

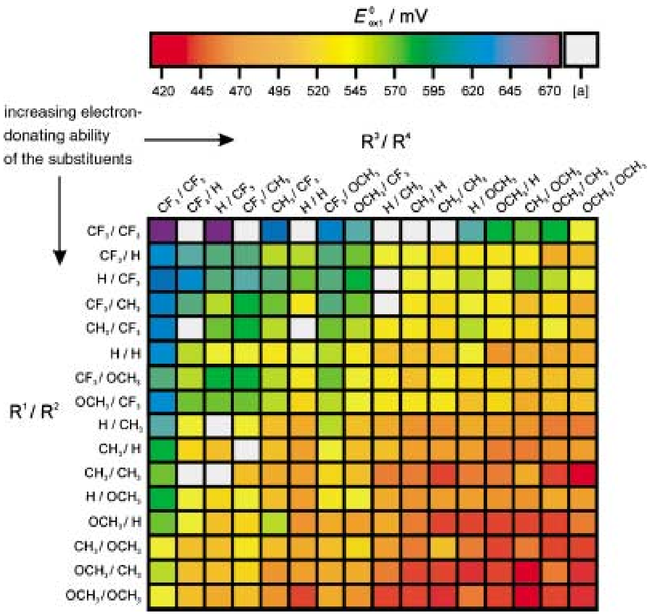

Figure 2. Color-coded matrix of the first oxidation potentials (E_1^0) of the quaterthiophenes **1**. The substituents R^1 and R^2 are arranged along the ordinate, the substituents R^3 and R^4 along the abscissa. [a] Not determined because of sample impurity.

Hammett constants σ_p^+ of the individual substituents[15]) facilitated a detailed analysis of the substituent effects. This descriptor, which numerically reflects the overall contributions of the individual substituents, is plotted in Figure 3 against the first and second oxidation potentials.[16] This plot displays, on first inspection, a linear correlation between $\Sigma\sigma_p^+$ and the redox potentials. While the potentials reflect the overall electron affinity of the four substituents, the slopes of the trend lines indicate the susceptibility of the oxidation potentials to the electronic influence of the substituents.[17] The first oxidation potential is therefore more influenced by the electronic nature of the substituents than the second. In addition, for some of the oligomers with the same substituent constitution (same $\Sigma\sigma_p^+$ value) a scattering of the oxidation potentials of up to 80 mV (E_1^0) is observed. This fact indicates that, beside their electronic nature, the sequence of the four substituents also influences the oxidation potential. Finally, the electrochemical energy gaps ($\Delta E = 2.84-2.91$ V, difference between the first oxidation potential E_1^0 and the reduction potential were determined for some representative quaterthiophenes,[18] these electrochemical energy gaps were found to be in good agreement with the data obtained by the optical analysis.

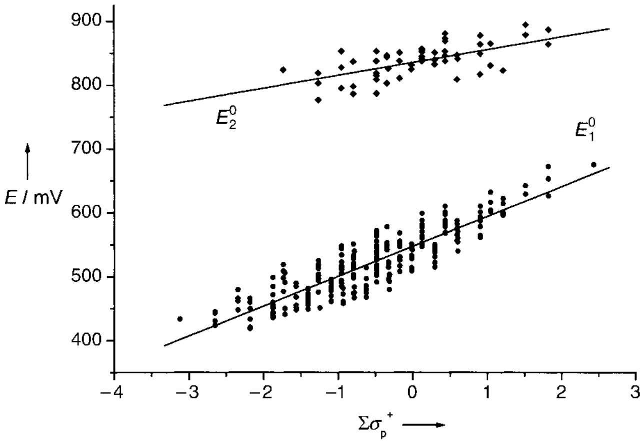

Figure 3. Correlation between the first and second oxidation potentials E_1^0 and E_2^0 of the quaterthiophenes **1** and the substituent descriptor $\Sigma\sigma_p^+$.

These results and those of the preceding study[4] clearly demonstrate that the principles of combinatorial chemistry can be utilized for the development of organic materials. The stepwise oligomer growth by solid-phase synthesis and the subsequent screening for optical and electrochemical properties enabled the collection of large data sets which could be used to deduce structure–property relationships. The substitution with the different electronically diverse elements opens the avenue to the effective control and fine-tuning of the optical and electrochemical properties of such π-conjugated oligomers.

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[9] **2a** (73%), **2d** (79%): 1) 2-bromo-3-arylthiophene (aryl = *p*-trifluormethylphenyl or *p*-anisyl), *n*BuLi, Et_2O, −70°C; 2) $Cl_2Si(i\text{Pr})_2$, −30°C. **5a** (71%): 1) 2-bromo-3-(*p*-trifluormethylphenyl)thiophene, *n*BuLi, THF, −70°C; 2) *O,O'*-bis(2,6-dioxaborinan-1-yl)propane-1,3-diol, −70°C; 3) BF_3, −30°C. **5d** (85%): 1) 2-Bromo-3-(*p*-anisyl)-thiophene, Mg, THF; 2) $B(Oi\text{Pr})_3$, −70°C; 3) H_2O; 4) 1,3-propandiol, molecular sieve (4 Å). Compounds **2b**, **c** and **5b**, **c** are reported in ref. [8e].

[10] The "AccuTag-System" from IRORI was used for the "mix-and-split" synthesis.

[11] The chromatography was performed on normal phase (nitrophenyl) using CH_2Cl_2/*n*-hexane as the eluant.

[12] The software for the cyclic voltammetry, the control of the stepper motors (for the positioning of the electrodes and samples) and the solvent dispenser was written in Visual Basic 3.0 (W. S.).

[13] 0.1M Bu_4NPF_6 in CH_2Cl_2 was used as electrolyte. Ferrocene was used as an internal standard.

[14] Potentials are referenced to the ferrocene/ferricinium ion (Fc/Fc$^+$) redox pair and were determined at a scan rate of $v = 100\ \text{mV}\,\text{s}^{-1}$.

[15] For review, see: C. Hansch, A. Leo, R. W. Taft, *Chem. Rev.* **1991**, *91*, 165–195; Hammett constants of diversity elements: $\sigma_p^+ = 0.61$ for R = CF_3, 0 for R = H, −0.31 for R = CH_3, −0.78 for R = OCH_3.

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[17] The trend lines were fitted using the method of least squares: for the first oxidation potential: E_1^0 [V] = $0.55 + 0.047\ \Sigma\sigma_p^+$ (correlation coefficient $R = 0.90$, standard deviation 0.02 V); for the second oxidation potential: E_2^0 [V] = $0.84 + 0.020\ \Sigma\sigma_p^+$ (correlation coefficient $R = 0.62$, standard deviation 0.02 V).

[18] For the determination of the electrochemical energy gaps cyclic voltammograms were recorded in acetonitrile (0.1M Bu_4NPF_6).

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