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Dynamic Combinatorial Libraries of 2,5-Diformylfuran-Derived Macrocycles

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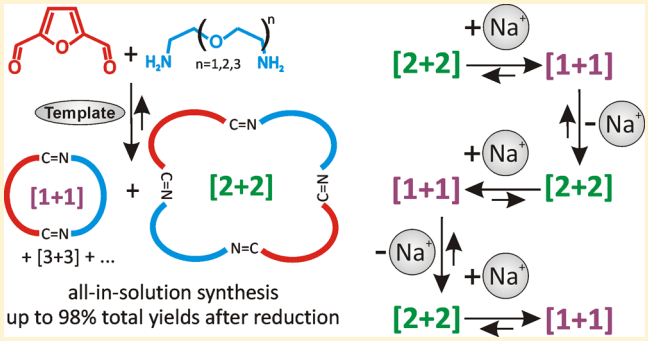
Supporting Information

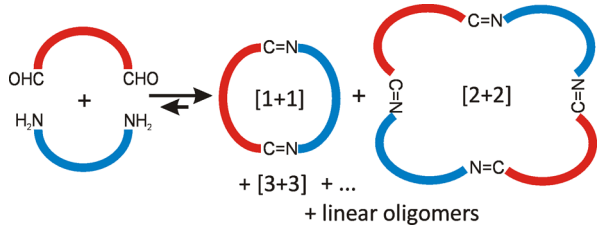
ABSTRACT: A series of polyazamacrocycles, containing a furan moiety, have been prepared using the all-in-solution approach of dynamic combinatorial chemistry. The methodology involves the use of a range of simple, fully soluble inorganic salts as templates and fast imine-to-amine reduction followed by high-performance liquid chromatography screening for the best reaction conditions. It offers an elegant and labor-efficient alternative to the classical methodology of imine trapping via crystallization of complexes. For all the presented 2,5-diformylfuran-derived libraries, the templates provided control over the libraries' behavior, which was reflected in increased isolated yields of the corresponding macrocyclic amines, compared to those of nontemplated libraries. The key parameters for achieving true thermodynamic control over the system, which are macrocyclization kinetics and imine reduction kinetics using $NaBH_4$ accompanied by various protic additives, have been discussed.



INTRODUCTION

The imination reaction was introduced early[1] to supramolecular chemistry as a promising way of synthesizing azamacrocycles, because it requires readily available substrates. The reaction proceeds under mild conditions and offers compatibility with a range of ionic templates. However, the rapid reversibility of this reaction was considered a serious drawback, because of the instability of the products. Control over imine-based systems was thus gained by suppressing the reversibility. Typically, this was achieved by trapping macrocyclic imine complexes in a solid form,[2,3] which always led to the least soluble species, but not necessarily to those intended. A new paradigm was introduced by dynamic combinatorial chemistry (DCC).[4−9] DCC treats the imine mixtures as a library of interconverting species (Scheme 1), the composition of which is governed by the thermodynamic stability of particular library members.[10]

Scheme 1. General Scheme of Macrocyclic Imine Library Formation from Dialdehydes and Diamines



However, only a few papers in which DCC principles are applied to azamacrocycle synthesis via the imination reaction have been published, focusing on the use of aromatic dialdehydes such as phthalic aldehydes,[11,12] 2,6-diformylpyridines,[13−16] diformylbipyrrole,[17] and 2,5-diformylfuran.[18] The ability to control the behavior of the dynamic combinatorial library (DCL) is obviously limited by the ability to reliably analyze the composition of the library at equilibrium.[19] The historically first and now routinely used approach involves "freezing" of imine libraries by reduction to amines using variety of reducing agents such us $NaBH_3CN$,[20] BH_3·2,6-lutidine,[21] BH_3·THF,[22] or $NaBH_4$.[11−16] Recently, we have found that careful $NaBH_4$ reduction can transform the whole primary library of imines into a resulting secondary library of amines in <1 min,[23] which is much faster than of any of the reequilibration processes that may take place.[24] The secondary library of amines can easily be analyzed using reversed phase HPLC.

In this contribution, we would like to present an application of this methodology to the study of the dynamics of the nontemplated and templated libraries derived from 2,5-diformylfuran (**1**) and diaminoethers (**2**−**5**) that vary in length (shown in Figure 1). We have chosen fully soluble alkali metal salts to act as templates that can amplify the formation of small- and medium-ring polyazamacrocycles.

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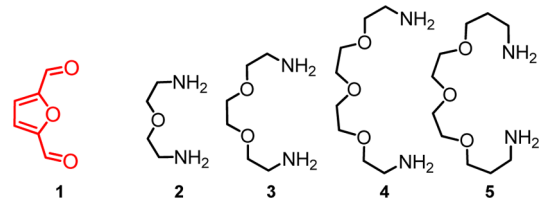

Figure 1. Imine library building blocks.

RESULTS AND DISCUSSION

In the case of imine libraries that are subsequently reduced to amines, the key parameters that need to be determined prior to the actual library experiments are the kinetics of macrocyclization and the kinetics of imine-to-amine reduction. This is to ensure that the protocols applied do not bias the libraries' responses to templates and that the concentrations measured reflect the situation at equilibrium. Kinetics of reduction can be easily monitored by UV spectroscopy because of the distinct absorption maxima of 2,5-diconjugated C═O and C═N derivatives (280−300 nm) and reduced species (~220 nm). In this project, the DCL created from dialdehyde **1** and diamine **2** [abbreviated (**1**+**2**)] was used as a model to examine the behavior of the system under the influence of various additives to satisfy the need for an external source of protons.[18,25] In particular, when methanol was used as a solvent, $NaBH_4$ reduction of either the (**1**+**2**) library (nontemplated or templated) or pure aldehyde **1** took <1 min (Figure 1a).

In acetonitrile, however, only dialdehyde **1** was reduced (in 10−15 min), while the (**1**+**2**) library stayed intact for at least 1 h (Figure 2b) if no external source of protons was provided.

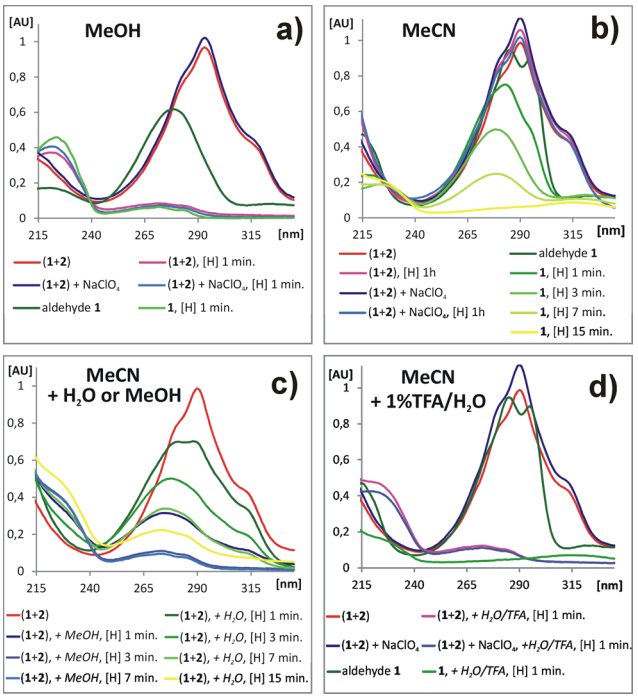

Figure 2. Kinetics of (**1**+**2**) imine library reduction with $NaBH_4$, measured by UV spectroscopy: (a) reactions in MeOH without additives, (b) reactions in MeCN without additives, (c) reactions in MeCN with water or MeOH added subsequent to $NaBH_4$, and (d) reactions in MeCN with 1% aqueous TFA added subsequent to $NaBH_4$. In the legends, protic additives are given in italics and [H] stands for $NaBH_4$ reduction.

The addition of methanol as a reduction cosolvent shortened the reduction time to ~3 min for the nontemplated (**1**+**2**) library (Figure 2c), which should be still considered too slow for some rapidly equilibrating libraries.[24−27] Water was also found to accelerate imine reduction (Figure 2c), but even less efficiently than MeOH. Finally, the best additive we found was 1% (v/v) TFA either in water (Figure 2d) or in MeOH (see Figure S1 of the Supporting Information). Both reduction systems were able to transform (**1**+**2**) libraries in MeCN into the corresponding amines in <1 min. In this project, we decided to use a H_2O/TFA solvent for reduction in MeCN-based libraries. UV-monitored reduction kinetic experiments, using MeOH or MeCN/H_2O/TFA protocols, were performed for all dialdehyde/diamine reagent pairs in both solvents. In all the cases, reduction took <1 min, which is consistent with previous observations made for phthalic[12] and bisfurylmethyl aldehydes[23,24] and practically ensures the freezing of the equilibrium imine composition into a resulting secondary library of amines.

Although direct measurements of the composition of imine DCLs by NMR[13−15,28] or mass spectrometry[14] were proposed for some substrate systems, we have found both techniques unsuitable for multimembered libraries such as those presented here. ^{1}H NMR spectra were complicated, and it was practically impossible to distinguish, assign, and integrate signals from particular library members. On the other hand, ESI mass spectrometry showed a tendency to oversimplify the libraries by presenting only macrocyclic species and also suggested false templation,[18] a problem we have previously encountered with phthalaldehyde-based libraries.[12] However, having in hand a fast reduction protocol, we applied it to the monitoring of DCL evolution with a nearly 1 min resolution on the time scale. Aliquots of the library mixtures were collected over the reaction time and reduced and subjected to HPLC analysis. Figure 3 presents the chromatograms obtained for nontemplated (**1**+**3**) libraries in methanol and acetonitrile. In the first case, the DCL reaches equilibrium in approximately 30 min, while in the second case, it takes ~6 h; however, the changes are already minor after 3 h.

HPLC analysis also revealed that library formation proceeded through many intermediate compounds that, after being initially formed, were then consumed as the DCL evolution progressed. In particular, initial ESI-MS studies, performed 15 min after mixing substrates **1** and **3** in MeCN, suggested a significant contribution from the [1+1] macrocycle, the analogue of diaza-15-crown-5, which could possibly be a kinetic product that was later unsupported at equilibrium. Indeed, HPLC monitoring of the reaction during the first minutes of library formation confirmed that there was a new substance that vanished over time. However, after the reaction mixture had been frozen at 15 min, instead of the [1+1] macrocycle we isolated a linear compound **6** (Figure 3) in 52% yield but could not identify and isolate the [1+1] macrocycle. The other isolated compound was diol **7**, the product of reduction of unreacted dialdehyde **1**.

Similar macrocyclization kinetic studies were performed for all reactant pairs, in both solvents, in the absence or presence of the inorganic salt (2 equiv of $NaClO_4 \cdot H_2O$), and these data are summarized in Table 1.

In methanol, as well as in acetonitrile, equilibrium kinetics varied by ~1 order of magnitude, depending on the amine used, despite the fact that their reactivity is supposed to be very similar. In all cases, the reaction in MeOH was significantly

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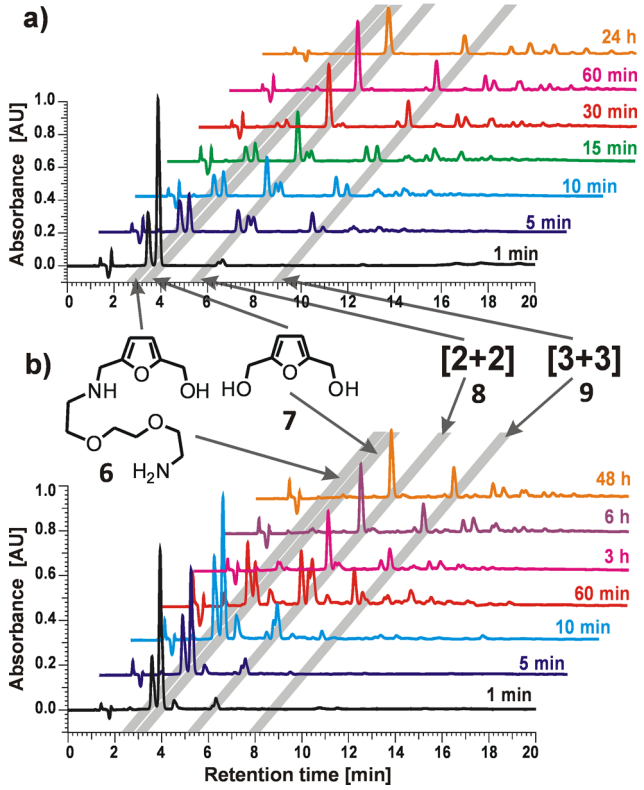


Figure 3. (**1**+**3**) imine library macrocyclization kinetics measured by HPLC of a secondary library of amines: (a) nontemplated library in MeOH and (b) nontemplated library in MeCN.

Table 1. Equilibration Times of the Libraries, Estimated by HPLC Analysis of Secondary Libraries of Amines

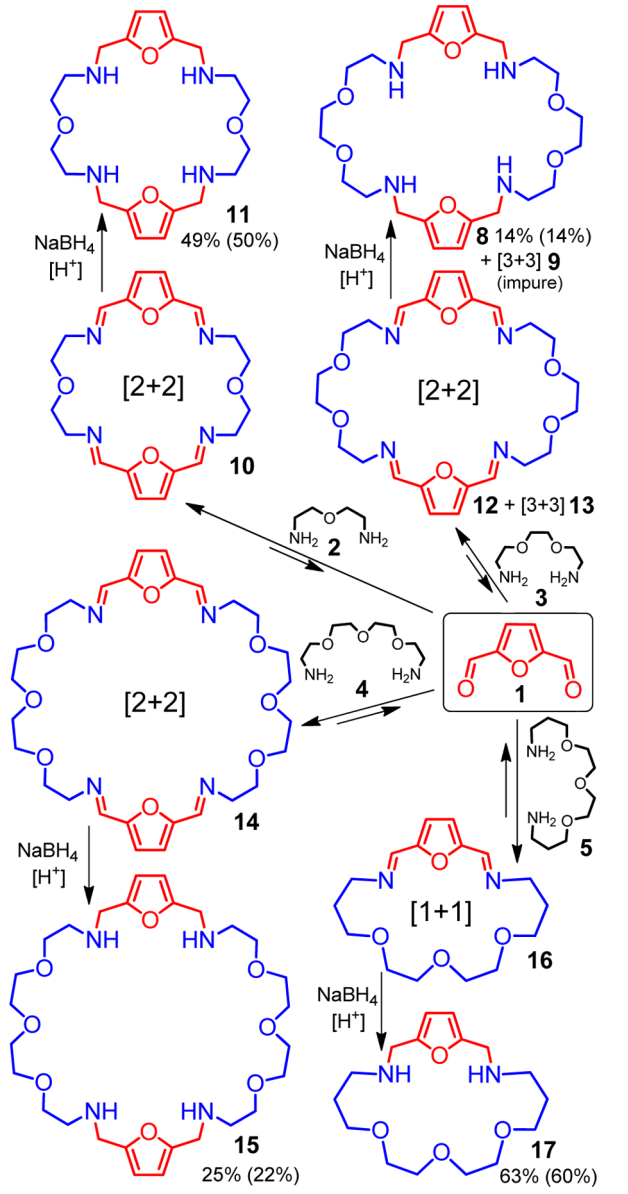
substrates	solvent	nontemplated	$NaClO_4$-templated	acceleration[a]
1 and **2**	MeOH	60 min	30 min	2-fold
	MeCN	180 min	120 min	1.5-fold
1 and **3**	MeOH	30 min	15 min	2-fold
	MeCN	360 min	60 min	6-fold
1 and **4**	MeOH	120 min	30 min	4-fold
	MeCN	480 min	120 min	4-fold
1 and **5**	MeOH	30 min	5 min	6-fold
	MeCN	360 min	120 min	3-fold

[a]The ratio of the equilibration time of the templated reaction to that of the nontemplated one.

faster than in MeCN. Further, for all the libraries, the presence of inorganic salt increased the reaction rate several-fold, even if the additive was later found not to be an active template promoting any of the DCL members. We can speculate that inorganic salts may act as weak Lewis acids activating aldehyde to nucleophilic attack. However, no particular acceleration by the inactive template was observed in the previously described imine system,[24] which altogether suggests that there is no simple mode of inorganic salt action. Taking into account the differences in macrocyclization kinetics, and also the slow dissolution of some of the templates, we conducted all the reactions for 16−24 h.

We started our studies of the library dynamics by analyzing nontemplated DCLs (Scheme 2) upon reduction to the corresponding secondary libraries of amines as described above. The most abundant products were isolated and characterized and served as a reference material for subsequent

Scheme 2. Macrocycles Isolated from the Nontemplated Libraries (upon $NaBH_4$ reduction)[a]



[a]For the yields, the first value corresponds to the reaction in MeOH while the value in parentheses to the reaction in MeCN.

studies. The isolated yields were calculated taking into account only the pure fractions collected upon single-column chromatography on silica gel and so reflect the combined chemical yield and purification efficiency.

In all the DCLs but one, (**1**+**5**), [2+2] macrocycles dominated and were the only ones isolated in pure form. Some other aspects are worth mentioning. First, the solvent used (MeOH or MeCN) seemed not to play any important role in the compositions of nontemplated libraries because the yields were virtually the same. Second, furan analogues of diaza-15-crown-5 [[1+1], in the (**1**+**3**) library] and diaza-18-crown-6 [[1+1], in the (**1**+**4**) library] were not detected. The (**1**+**4**) library also yielded a [3+3] macrocycle, although it was impure and present in only a small quantity. Third, and most strikingly, despite the small difference in amine partner length (13 vs 15 atoms), there was a qualitative difference in the reaction of

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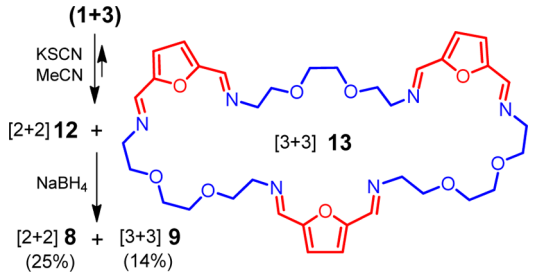
amines **4** and **5**. The latter was the only case in which nontemplated DCL produced a [1+1] macrocycle (60−63% for amine **17**), whereas the only compound we managed to isolate from the (**1**+**4**) library was a [2+2] macrocycle (22−25% for amine **15**) not previously described in the literature.

The structure of the library building blocks and thus the structure of the products made alkali metal cations the templates of choice. The following salts from this group were used: $LiClO_4·3H_2O$, $NaClO_4·H_2O$, KSCN, RbCl, and CsSCN, accompanied by $PbCl_2·2H_2O$, $SrCl_2·6H_2O$, and $CaCl_2$. The latter three cations proved to be effective in the crystallization approach described for the (**1**+**2**) and (**1**+**3**) reagent pairs by Nelson[29,30] and for the (**1**+**4**) pair by Fenton.[31,32] We use no common counterion. Instead, the particular metal salts were chosen for their best solubility in MeOH and MeCN, especially considering that all the experiments were conducted at relatively high concentrations (50 mM with respect to the substrates) in the presence of 2 molar equiv of inorganic salt. Our previous studies did not indicate any important role of the kind of anion in library equilibria, other than providing solubility.[12,23,24]

In the (**1**+**2**) DCLs, no qualitative change in the composition of the libraries in comparison to those of the nontemplated ones was observed using HPLC. However, several templates increased the isolated yield of [2+2] macrocycle **11**. The most effective were $NaClO_4·H_2O$ (75% of **11** in MeCN; in MeOH, the template was inactive) and $PbCl_2·2H_2O$ (67% of **11** in MeOH; in MeCN, the template was not soluble). The (**1**+**3**) library exhibited behavior toward the templates similar to that of (**1**+**2**) DCL. No new species were formed, but the yield and purity of the macrocycles observed previously in the nontemplated libraries increased. Templation by KSCN in acetonitrile was most effective and allowed isolation of [2+2] tetraamine **8** and [3+3] hexaamine **9** in 25 and 14% yields, respectively (Scheme 3). The latter 45-member macrocycle was not isolated in a pure form from the nontemplated DCLs.

Scheme 3. Templation by KSCN in the (1+3) Library in MeCN



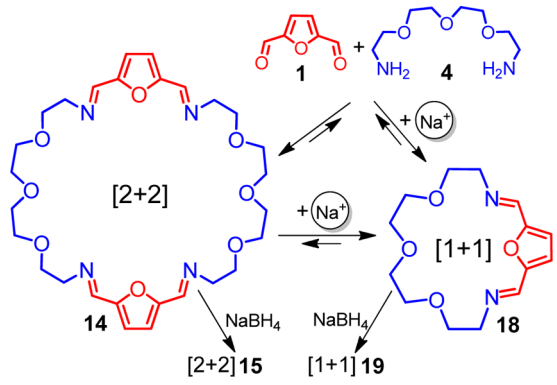
In the (**1**+**4**) library, alkali metal cations were able to strongly influence the equilibrium (Table 2), amplifying the formation of [1+1] macrocycle **18** (Scheme 4), which was not isolated from the nontemplated DCLs. The smallest cation, Li^+, was able to amplify formation of only the [1+1] macrocycle in acetonitrile (39% by HPLC, while that of the [2+2] macrocycle decreased to 30%) and was completely inactive in methanol. We have previously described a similar solvent dependence on Li^+ action.[24] In contrast, Na^+ was found to be the best template for the [1+1] macrocycle in MeOH, where the [2+2] macrocycle disappeared completely and the isolated yield of macrocyclic [1+1] diamine **19** (Scheme 4) was 80%, while in MeCN, some [2+2] macrocycle was still present. This is

Table 2. Template Effects in (1+4) Libraries[a]

	MeOH		MeCN	
template (2 equiv)	[1+1]	[2+2]	[1+1]	[2+2]
–	5	40 (25)	traces	50 (22)
$LiClO_4$[b]	traces	40	39	30
$NaClO_4$[c]	80 (80)	0	65 (70)	21 (10)
$NaClO_4$[c,e]	76	0	–	–
KSCN	49	24	61	22
RbCl[d]	42	22	16	41
CsSCN	34	25	47	24

[a]Data obtained by HPLC analysis of the corresponding secondary libraries of amines, presented as relative concentrations of key library members (percent of the corresponding HPLC peak with respect to the whole chromatogram at 222 nm) [isolated yields (percent) in parentheses]. [b]As $LiClO_4·3H_2O$. [c]As $NaClO_4·H_2O$. [d]Salt not fully soluble in MeCN. [e]One equivalent was used.

Scheme 4. [2+2] and [1+1] Macrocycle Selection in the Nontemplated and Na^+-Templated (1+4) Library



somewhat unexpected, because in the previously studied systems,[23,24] acetonitrile was always found to be a less demanding solvent in terms of templation. A stoichiometric amount of $NaClO_4$ in MeOH was already found to be efficient.

The possibility of "switching" the DCL response between [1+1] and [2+2] macrocycles by templation (Scheme 4) was used to demonstrate thermodynamic control over the library composition (Figure 4 and Table S2 of the Supporting Information). To a pre-equilibrated (**1**+**4**) DCL in methanol, which consisted of 40% [2+2] and 5% [1+1] as determined by HPLC (Figure 4a), was added 1 molar equiv of $NaClO_4·H_2O$. A stoichiometric amount of template already led to conversion of most of the library material into the [1+1] macrocycle [72% as determined by HPLC (Figure 4b)]. Then, sodium cations were "removed" by addition of a known effective Na^+ ligand, namely 15-crown-5, in 5 molar equiv, and the new equilibrium was established in which the [2+2] macrocycle dominated again [38% as determined by HPLC, accompanied by 11% [1+1] (Figure 4c)]. Then, an additional 5 equiv of $NaClO_4·H_2O$ was added, and because at least 1 equiv of Na^+ became accessible for the library, it produced the [1+1] macrocycle [73% as determined by HPLC (Figure 4d)]. As described above, an additional amount of template was "removed" by an excess of 15-crown-5 [35% [2+2] and 11% [1+1] as determined by HPLC (Figure 4e)]. In the sixth equilibration step, sodium salt was added again to the DCL and the library reequilibrated toward the [1+1] macrocycle [70% as determined by HPLC (Figure 4f)]. To the best of our knowledge, this is so far the longest sequence of multiple

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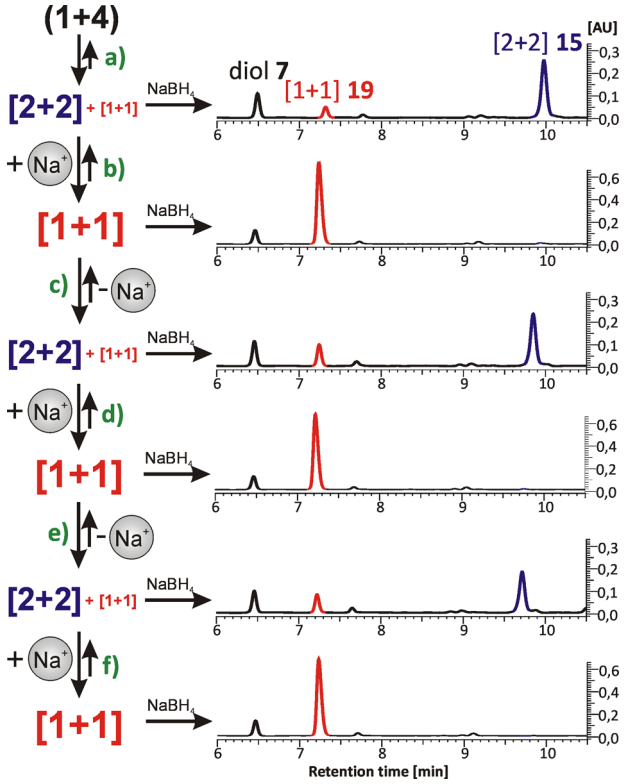

Figure 4. Multiple changes of the equilibrium in (**1**+**4**) DCL by addition and "removal" of Na^+ cations: (a) formation of nontemplated DCL in MeOH, to which was added in succession (b) 1 equiv of $NaClO_4$, (c) 5 equiv of 15-crown-5, (d) an additional 5 equiv of $NaClO_4 \cdot H_2O$, (e) an additional 25 equiv of 15-crown-5, and (f) an additional 27 equiv of $NaClO_4 \cdot H_2O$. Data are presented as chromatograms of the corresponding secondary libraries of amines.

templations in a single dynamic library. In this case, it was not possible to continue, because the amount of $NaClO_4$ and 15-crown-5 already exceeded 30% of the total mass of the mixture, yet the library responded as expected. Although the binding constant of [1+1] imine **18** with Na^+ was not established, experiments suggest it is at least comparable with that of 15-crown-5, because a large excess of crown ether was required. In the presence of 2 equiv of 15-crown-5, 27% of the [1+1] macrocycle remained [accompanied by 33% of the [2+2] macrocycle (Table S1 of the Supporting Information)]. As much as a 10-fold excess of 15-crown-5 reduced the content of the [1+1] macrocycle to 6% (accompanied by 38% of the [2+2] macrocycle), which is virtually the same as in the nontemplated DCL.

In light of these results, we reinvestigated the results of (**1**+**4**) macrocyclization kinetic experiments. Unlike in the (**1**+**2**) and (**1**+**3**) libraries, the [1+1] macrocycle was actually formed in the nontemplated (**1**+**4**) library as the kinetic product, which was later nearly completely consumed to build up the thermodynamically favorable [2+2] macrocycle.

The reaction of **1** with the longest amine **5** was the only case in which a 20-member [1+1] macrocycle dominated in the nontemplated library. Alkali metal templates did not give rise to any new species but increased the yield of the [1+1] macrocycle to nearly quantitative with KSCN as a template, which makes potassium-templated synthesis the method of choice for this compound (Table 3).

Table 3. Content of [1+1] Macrocycle 17 in the (1+5) DCLs[a]

template (2 equiv)	MeOH	MeCN
–	51 (63)	57 (60)
$LiClO_4$[b]	57	80
$NaClO_4$[c]	43	85 (60)
KSCN	98 (98)	92 (94)
RbCl[d]	90	58
CsSCN	92 (85)	63

[a]See footnotes [b,c,d] of Table 2.

The similar sizes of amines **4** and **5** used as DCL building blocks remain in contrast with their preference for the formation of variably sized macrocycles under template-free conditions. In addition, different cations, Na^+ and K^+, were found to be the most effective templates for (**1**+**4**) and (**1**+**5**) DCLs, respectively. This prompted us to conduct competition experiments in which 1 equiv of each diamine **4** and **5** was reacted with only 1 equiv of dialdehyde **1**. MeOH was chosen as a solvent. The HPLC traces of the corresponding secondary library of amines are shown in Figure 5.

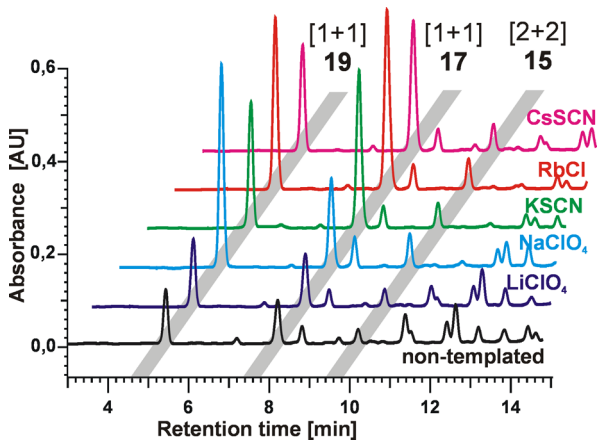

Figure 5. Competition experiments in the (**1**+**4**+**5**) DCL in MeOH measured by HPLC of the corresponding secondary library of amines.

The case with an insufficient amount of the carbonyl component altered the DCL responses. First, [1+1] macrocycle **18**, unsupported in a nontemplated (**1**+**4**) library (Table 2), now became one of the most abundant, even under template-free conditions, while the previously dominant [2+2] tetraimine **14** almost disappeared. This can be rationalized in light of the work by Roelens[33] and later Severin.[34] For a system governed by thermodynamics, in a situation in which there is an insufficient amount of a certain building block, those library members that "use" it in smaller amounts (one molecule of **1** is needed for the [1+1] macrocycle) gain additional stability over those that use it extensively (two molecules of **1** for the [2+2] macrocycle is needed). Stoichiometry is thus another important factor to take into account while working with imines. Second, the templation effects observed in the individual (**1**+**4**) and (**1**+**5**) DCLs were preserved. The amplification of [1+1] macrocycle **18** (amine **19** after reduction) was strongest when $NaClO_4$ was used as a template, whereas [1+1] **16** (amine **17** after reduction) derived from amine **5** dominated in the DCL templated with KSCN or CsSCN. Although in the (**1**+**4**) libraries K^+ and Cs^+ effectively templated formation of [1+1]

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imine **18**, in (**1**+**4**+**5**) DCL under competition conditions these cations preferred the larger [1+1] macrocycle **17**. Lithium stayed inactive, as in the simple (**1**+**4**) and (**1**+**5**) DCLs in MeOH. Third, despite the fact that aldehyde-to-amine stoichiometry is formally biased toward the formation of linear compounds, the macrocyclization reaction prevails, as no new significant peaks that may correspond to linear compounds were detected.

CONCLUSIONS

We have presented an application of the all-in-solution approach of dynamic combinatorial chemistry to the synthesis of azamacrocycles via an imination reaction. The methodology, validated in this project for furan-derived macrocycles, involves the use of a range of simple, fully soluble inorganic salts as templates and fast imine-to-amine reduction followed by HPLC screening for the best reaction conditions. It offers an elegant and labor-efficient alternative to the classical methodology of imine trapping via crystallization of complexes. For all the presented 2,5-diformylfuran-derived libraries, the templates provided control over the libraries' behavior, which was reflected in increased isolated yields of the corresponding macrocyclic amines, as compared to those of nontemplated libraries. Similarly, DCL dynamics can be controlled by the choice of reaction solvent or carbonyl-to-amine(s) stoichiometry. Small- and medium-ring azamacrocycles, containing a furan moiety, can further serve as versatile supramolecular scaffolds that could be easily modified using, independently, alkylation/acylation of secondary amines and/or furan chemistry, such as a Diels–Alder reaction, oxidative ring opening, or diastereocontrolled ring reduction that may quickly deliver advanced supramolecular structures.

EXPERIMENTAL SECTION

General Information. All of the reagents and solvents were purchased from commercial sources and used without further purification. All the libraries were prepared in HPLC-grade MeOH or MeCN. Chemical shifts in ^{1}H and ^{13}C NMR spectra were referenced to tetramethylsilane, used as an internal reference, or to the residual solvent peak. Column chromatography was performed with silica gel (100–200 mesh) as the stationary phase. For all HPLC measurements, an HPLC apparatus equipped with a DAD UV–vis detector and a low-pressure gradient pump was used. HPLC-grade MeCN, distilled and further deionized water (18.2 MΩ), and analytical-grade TFA were used as a mobile phase constituents. HPLC analyses were performed at room temperature (nonthermostated column).

General Procedure for the Formation of Imine Libraries and Their Transformation into Corresponding Secondary Amine Libraries on the "Analytical Scale". All the reaction mixtures used for initial screening of libraries' behavior were prepared on a 1 mL scale, typically in a series of several experiments. A mixture of dialdehyde **1** and the proper diamine (**2**–**5**) was prepared for the whole series by mixing solutions of dialdehyde **1** and diamine in a proper solvent (MeOH or MeCN) to obtain the final concentration of 50 mM with respect to each substrate. This solution was added (1 mL) to vials containing proper inorganic templates (typically 2 equiv) immediately upon mixing. The vials, protected from air by a stopper and parafilm, were then left for 1 day for equilibration. Then, stirring rods were placed in reaction vials; mixtures were cooled with an ice–water bath, and powdered $NaBH_4$ was added (5 equiv with respect to substrates, 0.25 mmol/mL of solution) while stirring was continued. In the case of MeCN-based libraries, this was followed by immediate addition of 1 mL of 1% (v/v) TFA in water. The vials (MeOH- or MeCN-based libraries) were corked with a needle-punctured stopper and left, while being stirred, in an ice/water bath until the evolution of hydrogen ceased (typically 30–60 min). Then, the resulting secondary libraries of amines were subjected to HPLC analysis.

(1+4) DCL Multiple-Templation Experiments. The procedure follows the "analytical scale" general procedure. The initial library was made on a 3.5 mL scale; after equilibration, a 0.5 mL aliquot was taken and reduced, and to the remaining imine DCL was added $NaClO_4 \cdot H_2O$. Then, after equilibration, a 0.5 mL aliquot was taken and reduced, and to the remaining imine was added 15-crown-5 and the mixture left to equilibrate. This sequence was repeated, and the collected amine samples were then analyzed by HPLC.

Competition Experiments in the (1+4+5) DCL. The procedure follows the "analytical scale" general procedure. Libraries were prepared in MeOH; the concentration of aldehyde **1** was 50 mM, and 1 equiv of amine **4** and **5** and 2 equiv (with respect to aldehyde **1**) of inorganic salts were used.

HPLC Conditions. The following settings were used: spectral range of 190–400 nm, detection at λ = 222 nm, flow rate of 2 mL/min, and injection volume of 20 μL. Crude reaction mixtures of amines were diluted 50-fold (to 1 mM with respect to the substrates) with the "A" mobile phase and injected directly without any sample pretreatment on the column and run in a gradient of solvent mixtures "A" and "B", where "A" was a 100:0.1 (v/v) H_2O/TFA mixture and "B" was a 90:10:0.1 (v/v/v) MeCN/H_2O/TFA mixture.

*(**1**+**3**) Library Macrocyclization Kinetic Studies (Figure 3).* A precolumn-guarded Discovery HS C18 column (250 mm × 4.6 mm, 5 μm) was used, with the following gradient program: 95% "A" and 5% "B" at 0 min to 90% "A" and 10% "B" at 5 min to 80% "A" and 20% "B" at 15 min to 80% "A" and 20% "B" at 18 min to 95% "A" and 5% "B" at 21 min.

*(**1**+**4**) Library (Figure 4).* A precolumn-guarded Polaris C-18A column (250 mm × 4.6 mm, 5 μm) was used, with the following gradient program: 100% "A" at 0 min to 80% "A" and 20% "B" at 15 min to 80% "A" and 20% "B" at 25 min to 100% "A" at 30 min.

*(**1**+**4**+**5**) Library (Figure 5).* A precolumn-guarded Polaris C-18A column (250 mm × 4.6 mm, 5 μm) was used, with the following gradient program: 95% "A" and 5% "B" at 0 min to 90% "A" and 10% "B" at 5 min to 80% "A" and 20% "B" at 15 min to 80% "A" and 20% "B" at 20 min to 95% "A" and 5% "B" at 25 min.

General Procedure for the Formation of Imine Libraries and Their Transformation into Corresponding Secondary Amine Libraries on the Preparative Scale. The synthesis follows the "analytical scale" general procedure. Reactions were conducted on a 1–2 mmol scale. Because of intense foaming in the reduction step, in the case of MeOH-based libraries, $NaBH_4$ was added in two or three portions, and in the case of MeCN-based libraries, a water/TFA solvent was added slowly. When the reduction was finished, the mixture was carefully concentrated on the rotavap (possible foaming!) to approximately $^{1}/_{4}$ of the volume (in the case of MeOH-based libraries water, 50% with respect to methanol volume, was added prior to concentration). Then the residue was acidified with 5% HCl to pH 2, then basified with 25% ammonia followed by 20% NaOH to pH 12, and extracted five times with $CHCl_3$. Extracts were washed with 2% NaOH and dried with Na_2SO_4. The drying agent and solvents were removed, and the crude was purified by silica gel column chromatography in a $CHCl_3$/MeOH/$NH_4OH_{(25\%\ aq)}$ gradient. Collected samples were evaporated several times with $CHCl_3$ to remove water and then dissolved in a small volume of MeOH, and CH_2Cl_2 was added and filtered via a small plug of Celite to remove dissolved silica gel. Finally, for tetra- and hexaamines, products were dissolved in $CHCl_3$ and dried with Na_2SO_4. All solvents were rotoevaporated, and traces of solvents were removed under high vacuum (<1 mmHg). Macrocyclic amines were stored in a freezer.

Yields and Analytical Data. *(**1**+**2**) Library.* Conditions and yields: nontemplated, in MeCN, 50% (98 mg) of **11**; nontemplated, in MeOH, 49% (96 mg) of **11**; $NaClO_4 \cdot H_2O$ templated (2 equiv), in MeOH, 75% (147 mg) of **11**; $PbCl_2 \cdot 2H_2O$ templated (2 equiv), in MeOH, 67% (131 mg) of **11**.

*[2+2] Tetraamine **11**.* Yellowish, slowly solidifying oil: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.16 (4H, brs), 2.75 (8H, t, J = 5.0 Hz), 3.52 (8H, t, J = 5.0 Hz), 3.73 (8H, s), 6.07 (4H, s); ^{13}C NMR (50 MHz,

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$CDCl_3$) δ 46.4, 48.5, 70.4, 107.8, 153.3; LR ESIMS m/z 393.3 $[M + H]^+$, 415.2 $[M + Na]^+$, 431.2 $[M + K]^+$; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{20}H_{32}N_4O_4Na$ 415.2321, found 415.2318.

(1+3) Library. Conditions and yields: nontemplated, in MeCN, 14% (34 mg) of **8** and traces of **9** (impure); nontemplated, in MeOH, 14% (34 mg) of **8** and traces of **9** (impure); $NaClO_4{\cdot}H_2O$ templated (2 equiv), in MeCN, 18% (42 mg) of **8** and traces of **9** (impure); $NaClO_4{\cdot}H_2O$ templated (2 equiv), in MeOH, 18% (43 mg) of **8** and traces of **9** (impure); KSCN templated (2 equiv), in MeCN, 25% (118 mg) of **8** and 14% (68 mg) of **9**; nontemplated in MeCN, reaction stopped after 15 min, 52% (70 mg) of **6**.

[2+2] Tetraamine ***8***. Yellowish oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.21 (4H, brs), 2.81 (8H, t, J = 5.1 Hz), 3.59−3.63 (16H, m), 3.77 (8H, s), 6.11 (4H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 46.2, 48.3, 70.2, 70.4, 107.6, 153.0; LR ESIMS m/z 481.4 $[M + H]^+$, 503.3 $[M + Na]^+$; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{24}H_{40}N_4O_6Na$ 503.2846, found 503.2836.

[3+3] Hexaamine ***9***. Yellow slowly solidifying oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.15 (4H, brs), 2.79 (12H, t, J = 5.2 Hz), 3.56−3.61 (24H, m), 3.75 (12H, s), 6.08 (6H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 46.4, 48.5, 70.4, 70.6, 107.6, 153.2; LR ESIMS m/z 721.4 $[M + H]^+$, 743.4 $[M + Na]^+$; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{36}H_{61}N_6O_9$ 721.4500, found 721.4471.

Compound ***6***. Yellow slowly solidifying oil: ^{1}H NMR (200 MHz, CD_3OD) δ 3.08−3.16 (4H, m), 3.69−3.77 (8H, m), 4.16 (2H, s), 4.52 (2H, s), 6.34 (1H, d, J = 3.2 Hz), 6.51 (1H, d, J = 3.2 Hz); ^{13}C NMR (50 MHz, CD_3OD) δ 40.1, 44.9, 47.9, 57.3, 67.9, 68.1, 71.3, 109.6, 113.1, 148.5, 157.2; LR ESIMS m/z 259.2 $[M + H]^+$, 281.2 $[M + Na]^+$; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{12}H_{23}N_2O_4$ $[M + H]^+$ 259.1658, found 259.1679.

(1+4) Library. Conditions and yields: nontemplated, in MeCN, 22% (62 mg) of **15**; nontemplated, in MeOH, 25% (72 mg) of **15**; $NaClO_4{\cdot}H_2O$ templated (2 equiv), in MeCN, 80% (114 mg) of **19**; $NaClO_4{\cdot}H_2O$ templated (2 equiv), in MeOH, 70% (200 mg) of **19** and 10% (29 mg) of **15**.

[1+1] Diamine ***19***. Yellow oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.66−2.70 (6H, m), 3.46−3.57 (12H, m), 3.67 (4H, s), 5.99 (2H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 46.1, 48.1, 69.8, 69.9, 70.1, 107.4, 152.5; LR ESIMS m/z 285.2 $[M + H]^+$, 307.2 $[M + Na]^+$; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{14}H_{25}N_2O_4$ 285.1814, found 285.1805.

[2+2] Tetraamine ***15***. Brownish, slowly solidifying oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.42 (4H, brs), 2.79 (8H, t, J = 5.1 Hz), 3.57−3.66 (24H, m), 3.76 (8H, s), 6.10 (4H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 46.4, 48.5, 70.47, 70.54, 70.7, 107.8, 153.29; LR ESIMS m/z 569.3 $[M + H]^+$, 591.3 $[M + Na]^+$; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{28}H_{49}N_4O_8$ 569.3550, found 569.3575.

(1+5) Library. Conditions and yields: nontemplated, in MeCN, 60% (188 mg) of **17**; nontemplated, in MeOH, 63% (197 mg) of **17**; $NaClO_4{\cdot}H_2O$ templated (2 equiv), in MeCN, 60% (187 mg) of **17**; KSCN templated (2 equiv), in MeCN, 94% (293 mg) of **17**; KSCN templated (2 equiv), in MeOH, 98% (307 mg) of **17**; CsSCN templated (2 equiv), in MeOH, 85% (264 mg) of **17**.

[1+1] Diamine ***17***. Dark yellow, slowly solidifying oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.74−1.82 (4H, m), 2.55 (2H, brs), 2.73 (4H, t, J = 6.4 Hz), 3.54−3.65 (12H, m), 3.77 (4H, s), 6.10 (2H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 29.4, 46.1, 46.8, 70.3, 70.4, 70.7, 107.7, 153.0; LR ESIMS m/z 313.2 $[M + H]^+$, 351.2 $[M + K]^+$; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{16}H_{29}N_2O_4$ 313.2127, found 313.2117.

Synthesis of 2,5-Dihydroxymethylfuran (7). To the solution of 62 mg (0.5 mmol) of dialdehyde **1** in 5 mL of methanol, cooled in an ice/water bath, was added 38 mg of $NaBH_4$ (2 equiv, 1 mmol) in three portions. When the evolution of hydrogen ceased (approximately 45 min), the ice bath was removed and 5% HCl was added dropwise until the pH reached 2. Then, the mixture was alkalized with 25% NH_{3aq} until the pH reached 12 and extracted seven times with DCM. Organic extracts were washed with brine and dried with $MgSO_4$. After removal of the drying agent and solvents, the crude product was filtered via silica with a DCM/2-propanol mixture (97:3) as the eluent and then crystallized form DCM to afford 60 mg (94%) of pure 2,5-dihydroxymethylfuran (**7**): off-white solid; mp 72−75 °C; ^{1}H NMR (300 MHz, MeCN-d_4) δ 3.25 (2H, brs), 4.47 (2H, s), 6.23 (2H, s); ^{13}C NMR (75 MHz, MeCN-d_4) δ 56.3, 107.9, 117.4; LR ESIMS m/z 151.2 $[M + Na]^+$, 167.0 $[M + K]^+$, 279.2 $[2M + Na]^+$; HRMS (EI-TOF) m/z $[M^{+\bullet}]$ calcd for $C_6H_8O_3$ 128.0473, found 128.0475.

Macrocyclization Kinetic Experiments. The protocols follow the general procedure. Reactions were conducted on a several milliliter scale to afford 250 μL of solution for every measuring point. Aliquots were added to precooled (4 °C) vials containing 5 equiv of $NaBH_4$ and a stirring bar, and reduction was further conducted in an ice/water bath. Then, the resulting secondary libraries of amines were subjected to HPLC analysis.

UV−Vis Determination of Imine-to-Amine Reduction Kinetics. All measurements were taken using the following settings of the UV spectrophotometer: optical path of 10 mm (quartz cuvette), spectral range of 200−335 nm, scan speed of 240 nm/min, bandwidth of 1 nm, data interval of 1 nm, and temperature of 20−22 °C. The libraries were reduced according to the common protocols. In particular, for MeCN-based libraries, protic additives (H_2O, MeOH, H_2O/1% TFA, and MeOH/1% TFA) were added immediately after $NaBH_4$. After a given period of reduction, 30 μL of the reaction mixture was added to 270 μL of pure solvent (MeOH or MeCN, the same that was used to generate the library). Then, 30 μL (MeOH libraries) or 60 μL (MeCN libraries) of the solution described above was injected into the UV cuvette filled with 3000 μL of the corresponding solvent (to a final concentration of ~5×10^{-5} M with respect to the substrates); the solution was mixed, and spectra were recorded. Two dilution steps were used to avoid working with very small volumes of the bubbling reaction mixture. The whole operation took 20−30 s, which was not included in the "reaction time".

■ ASSOCIATED CONTENT

Supporting Information

Additional UV−vis data, additional data for (**1+4**) multiple-templation experiments, and copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

This paper is dedicated to Prof. M. Mąkosza on the occasion of his 80th birthday.

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