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Controlling and Measuring the Equilibration of Dynamic Combinatorial Libraries of Imines

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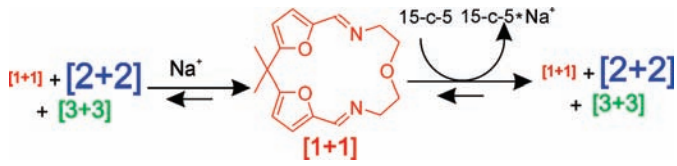
ABSTRACT



Imine formation is one of the most powerful methods for the construction of azamacrocycles, especially when combined with Dynamic Combinatorial Chemistry. Careful $NaBH_4$ reduction of the imine libraries opens the possibility of determination of their composition via HPLC analysis of the resulting amine mixture. Templates, reagent concentrations, as well as reaction conditions influence the library composition.

In the decade since its inception, Dynamic Combinatorial Chemistry (DCC)[1] has proven its usefulness in solving two major problems of synthetic supramolecular chemistry: the design of ligands suited to bind a specific guest molecule and their synthesis.[2] Among several reversible reactions fulfilling the requirements of DCC,[2b,3−5] the imine formation process seems to be attractive for the synthesis of macrocycles. However, the vast majority of successful applications utilize the poor solubility of some polyimines or their complexes,[6] so that only several examples of such syntheses via dynamic combinatorial libraries (DCLs) are described in the literature.[7] Therefore, we decided to further explore the DCC methodology with the aim of adopting it for the synthesis of azacoronands. This task requires that the following requirements be fulfilled: (1) the versatility of library composition control, (2) the availability of an analytic tool for the rapid evaluation of library composition, and (3) the possibility of "freezing" the library to map its composition at any moment.

The weak point in reasoning about the equilibration of imine-based systems lies in the fragility of the imine bond and the inability to switch off the reaction to "freeze" the equilibrium for performing a valid analysis. The process of imine exchange does not require any catalyst and occurs over practically the whole pH range; what is more, the equilibrium position depends strongly on the pH.[8] The method of choice for blocking further equilibration involves irreversibly reduc-

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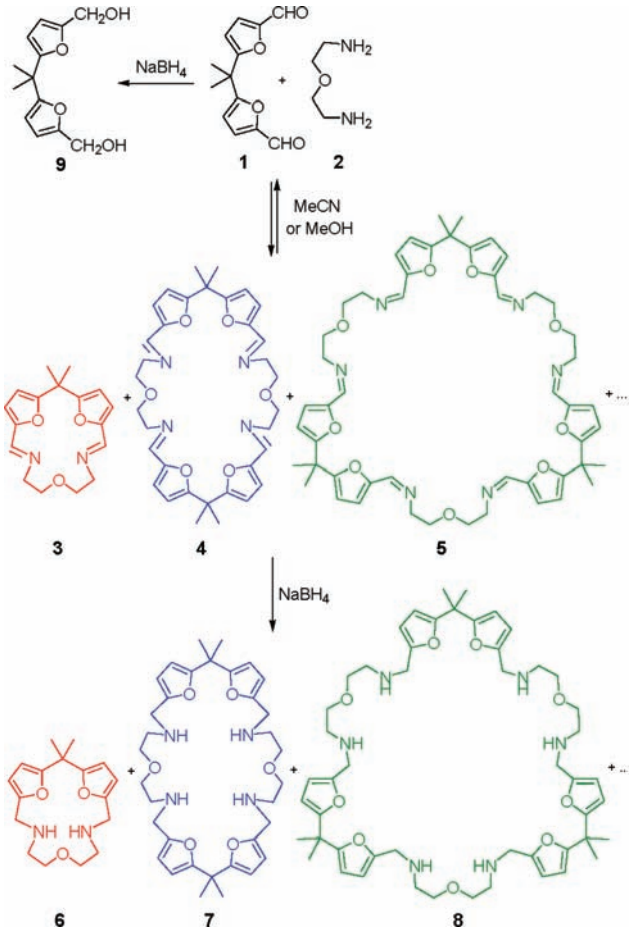
Scheme 1. Formation of the (**1** + **2**) Imine Library and Its Transformation into the Secondary Library of Amines



ing imines into the corresponding amines with use of some conventional reagents, the most popular and cheapest of which is $NaBH_4$.[7] This approach is related to two controversies. First, there is a tacit assumption that such a transformation allows for conversion of all the imine compounds at the same rate, without disturbing the product distribution and thus biasing the template effect. Second, reduction with $NaBH_4$ requires an external source of protons to proceed,[9] and no procedure allowing the application of DCC for imines in an aprotic solvent has yet been reported.

The aim of this paper is to report the findings of basic experiments concerning thermodynamic control and reversibility in libraries of macrocyclic imines, and the influence of the reduction conditions on the composition of the mixture of reduction products; that mixture will be called a secondary library of amines. On this basis, we propose a set of procedures to make sure that the composition of the library of imines is properly reflected by the composition of the library of amines.

Drawing upon our previous experience,[10] as a model process we selected the reaction of the furan-derived dialdehyde **1** with the aliphatic diamino ether **2**. This system ensures a good solubility of all the library members in acetonitrile and in methanol up to 100 mM (Scheme 1). A remarkable feature of the system described in this paper is that it is very sensitive to templation with sodium salts ($NaClO_4$, NaNCS), thus serving as a good model system to investigate the possible influence of the reduction step, performed with an excess of $NaBH_4$.

The libraries were prepared by simply mixing substrates **1** and **2** (0.05 mM each) in a proper solvent on a 1-mL scale. After an equilibration period of 2 days, the imine DCLs were reduced with $NaBH_4$ (5 molar equivs). In the case of MeCN, this was followed by the addition of 1 mL of 1% TFA in water (v/v) to satisfy the need for a source of protons. We found RP-HPLC to be a very convenient and useful method for analyzing secondary amine libraries, allowing very good and reproducible resolution of the amine mixture in less than 30 min, without any workup or sample pretreatment. The chromatograms of the amine libraries from the nontemplated reactions, in both solvents used, showed a predominance of macrocycles of types [2+2] **7** and [3+3] **8**, whereas [1+1] **6** and diol **9**, being products of the reduction of the parent dialdehyde **1**, were merely traces among some other low-concentration, unidentified substances (Table 1, entry 1; Table 2 entry 1). From the library formed in MeOH, macrocycles **6** and **7** could be isolated in 34% and 10% yield, respectively.

The addition of even a small amount of $NaClO_4 \cdot H_2O$ to a nontemplated library in MeCN resulted in a dramatic change in library composition and amplification of the [1+1] macrocycle **3** (Table 1). As little as 0.1 molar equiv raised its population from 3% to 14% with respect to the sum of all compounds **6**−**9** (Table 1, entry 2). Such high library sensitivity to template content suggests the possibility of very precisely controlling its composition and following these changes. The addition of 1 molar equiv of $NaClO_4 \cdot H_2O$ to the library in MeCN converted almost all the library members to a single component **3** (Table 1, entry 5). Similar effects were observed in methanol (Table 2); in this case, higher amounts of the template were required for the effective amplification of the [1+1] macrocycle **3**.

Strong affinity of sodium to [1+1] macrocycle **3** was supported by X-ray analysis. **3**·$NaClO_4$ complex was obtained by slow ether diffusion into the $NaClO_4 \cdot H_2O$ templated (**1** + **2**) library (Figure 1). In the solid state, Na^+ fits well in the macrocyclic cavity, being simultaneously bound by all five heteroatoms present in the imine **3**.

On the other hand, we must stress again that sodium cation was added to every library (including the "nontemplated" one) in huge amounts accompanying the reducing agent (as $NaBH_4$, 5 molar equivs), but this time without affecting the [1+1] macrocycle population. Such a "selective" influence raises a question that, in our opinion, exceeds the limits of the particular macrocycle synthesis presented here. This is the question about the mutual influence of results of the

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Table 1. Templation in the (**1** + **2**) DCL in MeCN[a]

entry	$NaClO_4 \cdot H_2O$ [molar equiv]	product ratio [%][b] [1+1] **6**	[2+2] **7**	[3+3] **8**	diol **9**
1	0	3	55	39	3
2	0.1	14	48	34	4
3	0.25	26	42	28	4
4	0.5	53	28	17	2
5	1	100	0	0	0

[a] HPLC of the secondary amine libraries. [b] Ratio to the sum of compounds **6**−**9**; other low-abundant library members were neglected.

Table 2. Templation in the (**1** + **2**) DCL in MeOH[a]

entry	$NaClO_4 \cdot H_2O$ [molar equiv]	product ratio [%][b] [1+1] **6**	[2+2] **7**	[3+3] **8**	diol **9**
1	0	2	64	29	5
2	0.25	10	59	26	5
3	0.5	16	55	24	5
4	1	28	47	20	5
5	5	79	14	3	5
6	10	91	4	0	5

[a] HPLC of the secondary amine libraries. [b] Ratio to the sum of compounds **6**−**9**; other low-abundant library members were neglected.

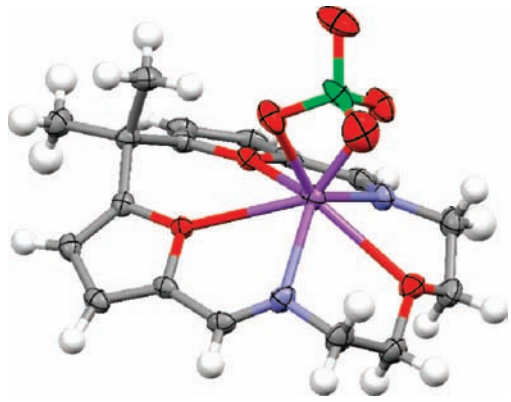

Figure 1. X-ray structure of **3**·$NaClO_4$ (thermal ellipsoids at the 50% probability level; oxygen = red, nitrogen = blue, chlorine = green, sodium = violet, carbon = gray, hydrogen = white; anion disorder and disordered solvent molecules were removed for clarity).

macrocyclization and reduction steps and the possibility of quantitative measurement of the equilibrium concentrations of imines on the basis of the secondary amine library composition.

Sodium cation "selectivity" may be rationalized by differences in the reaction kinetics of imine formation and reduction. To estimate the reduction kinetics, we employed UV spectrometry. The imine library members (including parent dialdehyde **1**) have a maximum of absorbance in the region of about 280 nm, and ring-conjugated double bond reduction shifts the maximums down to about 220 nm. UV analysis revealed that, in methanol, reduction takes less than *1 min* to transform the whole imine library into the resulting secondary amine library.[11] Such results stand in contrast to typical procedures reported for the reduction of imines to amines. This 1-min estimation should be considered an upper limit and it results from a practical experimental limitation. For the reaction in MeCN, we observed a similar robustness if only 1% TFA in water (v/v) was added following the reducing agent. By contrast, the macrocyclization time for a nontemplated library was estimated to be about 60 min in MeOH and about 6 h in MeCN. Such differences in the reaction rates ensure the real "freezing" of the imine concentrations in the amine library.[12]

The next step in developing the combinatorial methodology is to prove that the library is indeed under thermodynamic control. Reversibility is an inherent feature of the imination reaction, but such experiments clearly test the validity of procedures, especially the reaction times proposed. Again, sodium cation was chosen as a template for such transformations.

If the system is in fact governed by thermodynamics, its terminal state should be independent of the pathway leading to it. The chromatogram of the secondary amine library obtained by reduction of the nontemplated imine library (**1** + **2**) in MeCN is presented in Scheme 2a, illustrating the predominance of the [2+2] and [3+3] macrocycles. Such a library was then templated with 2 molar equiv of $NaClO_4 \cdot H_2O$ and allowed 2 days of equilibration, leading exclusively to the [1+1] macrocycle, formed at the expense of all the other library members (Scheme 2b). The outcome was precisely the same as when the template was added simultaneously with the substrates (Table 1, entry 6). To obtain conclusive proof of thermodynamic control over the macrocyclization, in the next series of experiments we deactivated the Na^+ by adding 15-crown-5 (15-c-5), a well-known strong ligand for this cation.[13] Introduction of the crown ether brought about a dramatic change in library composition; the [1+1] macrocycle **3** disappeared in favor of its higher analogues (Scheme 2c). A "blank test" performed by adding 15-crown-5 to the nontemplated library confirmed that the additive had no impact on the system. Such experiments prove that the system is truly (and exclusively) under thermodynamic control and the procedures involved eliminate kinetic disturbances and any side reactions. What is more, this proves that we can stimulate the system many times without losing its adaptive behavior. Finally, the templates do not need to be removed from the mixture, but just properly deactivated. The same set of experiments were performed with methanol employed as a solvent; full reversibility was also observed in this case.

Having in hand a useful method for library construction and analysis, we employed it in the synthesis of macrocycles (Scheme 3). Diamine **6** was easily obtained in 84% yield

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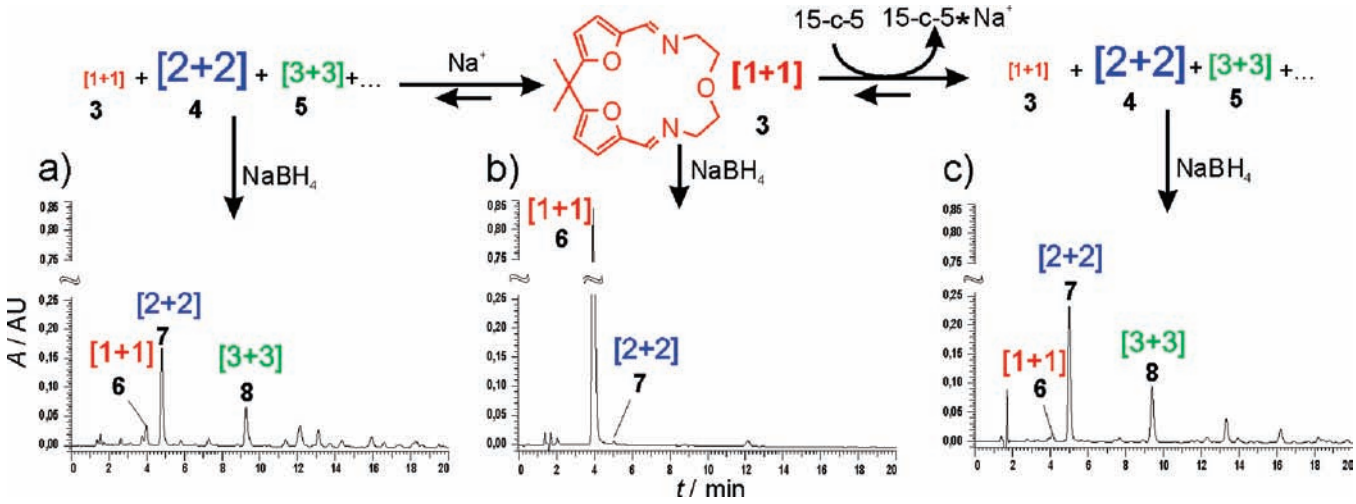
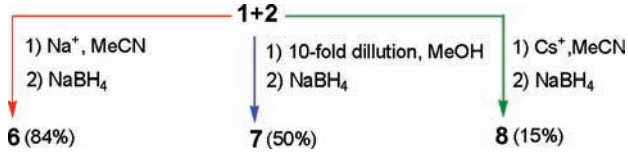
Scheme 2. Multiple Templation Experiments in the (**1** + **2**) Library in MeCN: Chromatograms of Secondary Libraries of Amines[a]



[a] Key: (a) the nontemplated library; (b) the same library to which 2 molar equivs of $NaClO_4 \cdot H_2O$ was added; (c) the former library to which 10 molar equivs of 15-crown-5 (15-c-5) was added.

from the (**1** + **2**) library in MeCN templated with 2 molar equiv of $NaClO_4 \cdot H_2O$.

Scheme 3. Amplification of Various Macrocycles from the (**1** + **2**) Library



We also looked for the conditions under which the two other macrocycles [2+2] **4** and [3+3] **5** would be amplified. Utilizing cations of the first and second group of the Periodic Table as templates, however, we found that none of them stimulated the library toward the [2+2] macrocycle. Instead, it could be significantly amplified by a 10-fold decrease in the concentration of the substrates down to 5 mM (Scheme 3). The corresponding amine [2+2] **7** was isolated in 50% yield from the (**1** + **2**) library in methanol, accompanied by macrocycle **8** (10%). This concentration-dependence offers an unusually attractive (i.e., easily applicable) possibility of library composition control. The 48-membered macrocycle (**5**) was found to be amplified upon templation of a (**1** + **2**) library in MeCN with CsNCS. The corresponding hexaamine **8** was isolated in 15% yield, accompanied by 17% of [2+2] **7** and 12% of [1+1] **6**.

In conclusion, we state that it is possible to precisely measure the equilibration of imines based on the composition of the resulting secondary amine library. The imine mixture can be easily and multiply directed toward the desired thermodynamic product, while not just templates, but also reaction medium and reagent concentrations play a vital role and can be used for efficient macrocycle synthesis. It is our conviction that the model problem solution presented here has the advantage of generality. Extending the results presented here to DCLs containing other aromatic aldehydes (e.g., furan, thiophene, pyrole) is the subject of ongoing research.

Supporting Information Available: Procedures of libaries formation and reduction; macrocycles **6**−**8** and diol **9** syntheses and chractierization data, HPLC and UV experiments procedures, and crystallographic information file for the **3**•$NaClO_4$ complex. This material is available free of charge via the Internet at http://pubs.acs.org.

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