Facile acetal dynamic combinatorial library†‡

Dvora Berkovich-Berger and N. Gabriel Lemcoff*

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We herein report our first results on the use of simple acetalation chemistry in the service of dynamic combinatorial libraries (DCLs); the reaction between triethylene glycol and 4-nitrobenzaldehyde afforded a DCL of more than 15 cyclic and acyclic species; all of which were separated and characterized; the smaller macrocyclic compounds were successfully amplified by the use of ammonium ions.

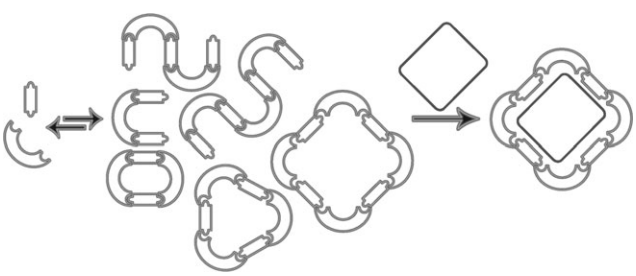
At the basis of any recognition process we usually come across well defined, preassembled cavities of the right dimensions and shapes, *i.e.*, the lock-and-key principle. Small structural changes between the free and complexed host brings about small entropic changes that may, in consequence, produce a more stable assembly. Many key processes in chemical and biological mechanisms are based on this principle and have major consequences on the reaction outcome. Thus, finding the precise host for the specific guest has significant implications and much effort has been directed towards this area of research. A dynamic combinatorial chemistry[1] provides a useful mechanism for the search of the right supramolecular assembly. Reversible bonding of the initial building blocks, and the consequent complex equilibria which are established, form the dynamic library components. The DCLs thus formed are an attractive tool for screening molecules with molecular recognition properties and amplifying them. The increase of the concentration of selected species in response to the introduction of a template is commonly referred to as ''amplification'' (Scheme 1).

Dynamic combinatorial chemistry has been applied successfully in the development of synthetic receptors and has proven to be a practical method that not only allows the identification of new host molecules but also provides a facile synthetic route towards these sometimes complex molecules. Fitting examples are the macrocyclic receptors produced by hydrazone exchange,[2] such as the *[2]-catenane* isolated by Sanders, Otto and co-workers,[2e] an extremely complex receptor with a remarkable affinity and selectivity for acetylcholine. These results highlight the power of the DCL strategy by effectively amplifying an unpredictable candidate as a very strong receptor for a biologically active compound. DCLs are also very versatile. It has been shown, for instance, that more than one reversible reaction can be used in the same library,[3] and also that the number of components in a DCL can be vast, for example, Miller and co-workers recently reported a library containing more than 10 000 molecules, the largest DCL to date.[4]

The acid-catalyzed reaction between carbonyls and alcohols to give acetals is a classical and much studied reaction with several synthetic applications,[5] although somewhat secluded to the protective group role. Rapid equilibrium, accessible and inexpensive reagents and well-known methodologies make it an extremely good candidate for creating DCLs. Furthermore, ''freezing'' a dynamic library of acetals is readily achieved by addition of base and neutralization of the acid catalyst. Nonetheless, the detrimental lability of acetals and the formation of water during the equilibration period present a challenging problem when creating an acetal DCL. Perhaps because of this there are but a few reports in the literature for the use of this type of simple bonding in DCLs. Up to date, only two examples of cyclic acetal DCLs are known. The first was put forward by Fuchs, Stoddart and co-workers and produced chiral polyethers based on threitol[6] while the second example was a DCL of cyclophane Ag^+ receptors equilibrated by means of acid-catalyzed transacetalation of formaldehyde acetals by the Mandolini group.[7] To the best of our knowledge, there are no examples in the literature for the creation of acetal DCLs by straightforward combination of aldehydes and alcohols.

Thus, commercially available triethylene glycol and 4-nitrobenzaldehyde were employed to generate an acetal dynamic library that could theoretically contain both oligomers and macrocycles (denoted $\mathbf{O}_n$ and $\mathbf{M}_m$, respectively) using sulfuric acid as the catalyst (Scheme 2). The presence of hemiacetal species was discounted due to the lower stability of the hemiacetal function.

Electron-poor aromatic aldehydes were chosen as starting materials because of their inherent propensity to form stable



Scheme 1 Illustration of amplification in a dynamic combinatorial library upon external addition of a specific template to an equilibrated mixture.

Department of Chemistry, Ben-Gurion University of the Negev, P.O. Box 653, Beer-Sheva, 84105, Israel. E-mail: lemcoff@bgu.ac.il; Fax: (+97)-8-6461740; Tel: (+97)-8-6461196

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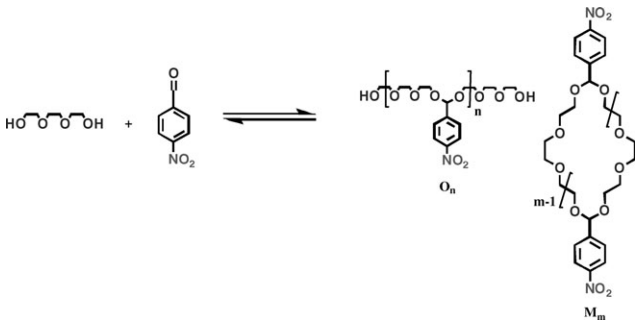

Scheme 2 A DCL built by acetalation of *p*-nitrobenzaldehyde using triethyleneglycol. $\mathbf{O_1}$ is the 2 + 1 oligomer and $\mathbf{M_1}$ is the 1 + 1 macrocycle (smallest possible members).

acetals. The effect of electron-withdrawing groups on aromatic acetals has been covered in the relevant literature and it has been shown that the destabilization of the benzylic carbocation hinders acetal hydrolysis.[8–11] Triethyleneglycol was selected as the alcohol counterpart since the smallest cyclic member of such a library would contain an 11-membered ring, a thermodynamically disfavored moiety, diminishing the formation of an entropically favored 1 : 1 cyclic compound ($\mathbf{M_1}$). Additionally the macrocycles formed by ethylene glycol oligomers have the advantage of mimicking crown ethers and their cation complexation ability,[12] an advantageous property when designing host compounds.

To generate the library, the mixture was refluxed in toluene with a catalytic amount of sulfuric acid under azeotropic distillation conditions. After 20 h the library was fully equilibrated and 70% of the aldehyde had been converted into acetals (according to ^{1}H NMR analysis). A series of distinct acetal peaks were observed (Fig. 1) indicating that several acetalic compounds were obtained. The library was then quenched by the addition of potassium carbonate and the mixture separated by preparative HPLC. Most gratifyingly, we were able to separate and fully characterize the complex mixture that contained more than 15 library members; both cyclic and acyclic. The different fractions were analyzed both by MALDI-TOF (see ESI‡) and ^{1}H NMR as shown in Fig. 2.

As one of the main attributes of dynamic combinatorial libraries is the ability to regenerate a full library out of a small

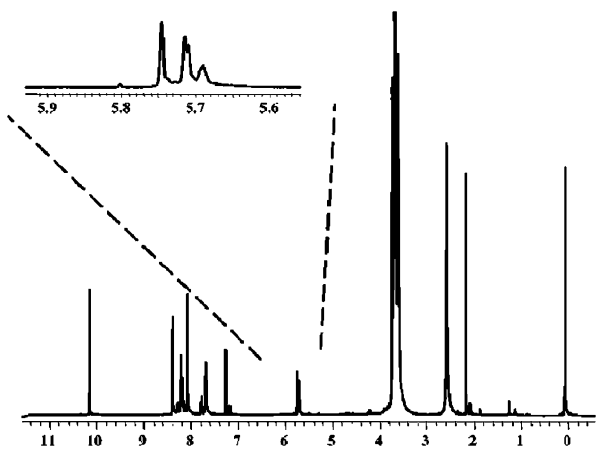

Fig. 1 ^{1}H NMR of *p*-nitrobenzaldehyde and triethyleneglycol DCL.

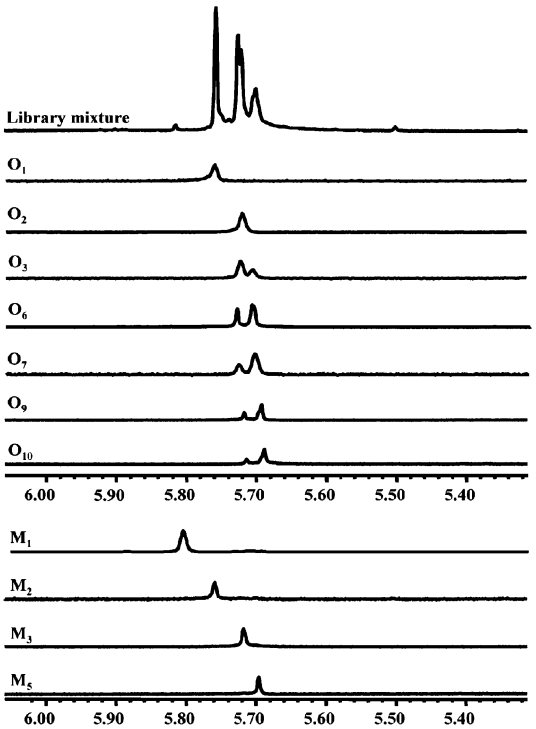

Fig. 2 ^{1}H NMR spectra (acetal region) of the library mixture after separation by preparative HPLC.

subgroup we exposed an acetalic oligomer to library equilibration conditions. Accordingly, a fraction taken from preparative HPLC containing 13 mg of the $\mathbf{O_6}$ oligomer was heated in deuterated toluene for 48 h with sulfuric acid as catalyst. NMR and MALDI-TOF analysis before and after the addition of catalyst show the regeneration of the library, albeit not exactly the same library was obtained due to the different stoichiometry of starting materials (see ESI‡).

Finally the effect of organic cations as possible amplification templates was tested. Several ammonium ions were used to test the generality of the effect: dibenzyl ammonium hexafluorophosphate ($DBAPF_6$), tetrabutyl ammonium iodide (TBAI); tetraoctylammonium bromide (TOAB) and paraquat (DMV). After reaching equilibrium a 25 molar percent of ammonium ion template was added to the library mixture. Samples were taken 24 h and 3 days after the salt addition. To our satisfaction, significant changes in concentrations were observed. For most templates used an amplification of the macrocycles $\mathbf{M_1}$, $\mathbf{M_2}$ and $\mathbf{M_3}$ were detected at the expense of other library members (see ESI†). For $DBAPF_6$ $\mathbf{M_1}$ was amplified about 10-fold and $\mathbf{M_2}$ was augmented 2.5-fold. Table 1 and Fig. 3 display the results obtained for $DBAPF_6$. The amplification of the macrocycles provided a larger amount of compounds $\mathbf{M_1}$ and $\mathbf{M_2}$ which were readily crystallized and their structures solved§ (Fig. 3, right side insets).

The association constant for $DBAPF_6$ with $\mathbf{M_2}$ was calculated by NMR titration to be about 2×10^2 M^{-1} (see ESI‡) in accordance to similar complexes of crown ether analogs with quaternary ammonium ions shown in the literature.[13] No shift of the benzyl signal could be observed when $DBAPF_6$ was titrated with $\mathbf{O_2}$.

Table 1 Several library members before and after amplification by $DBAPF_6$

Library member	HPLC t_R/min	% in equilibrated library[a]	% after 24 h templation	% after 3 days templation
$\mathbf{O_1}$	3	14.7	2.1	1.5
$\mathbf{M_1}$	4.3	5.6	51.9	56.4
$\mathbf{O_5}$	5.15	2.6	0.7	0.5
$\mathbf{M_2}$	5.3	2.0	5.6	4.35
$\mathbf{O_6}$	6.4	5.4	1.3	2.1
$\mathbf{M_3}$	7.2	1.6	1.05	0.65
$\mathbf{O_7}$	8.2	2.1	0.2	0.36
$\mathbf{M_4}$	9.6	0.8	0.5	0.5
$\mathbf{O_9}$	14.5	0.15	0.1	0.2

[a] Due to a ~6-fold absorbance coefficient of 4-nitrobenzaldehyde over acetal derivatives, calculations were done by combining integrals of peaks both in the full HPLC chromatograms and NMR spectra of the fractions that contained all the 4-nitrobenzaldehyde.

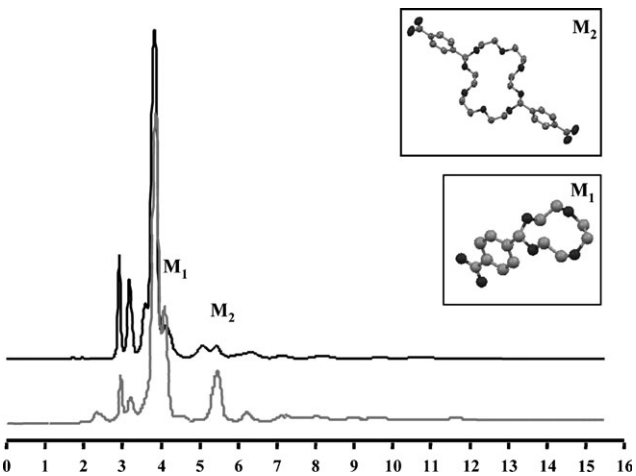

Fig. 3 Preparative HPLC of the library before (top) and after amplification by $DBAPF_6$ template (bottom). The X-ray structures of $\mathbf{M_1}$ and $\mathbf{M_2}$ are shown on the right side insets.

In conclusion we have shown that the simple reaction between alcohols and aldehydes is fitting for creating dynamic combinatorial libraries and may be used as the structural framework for this type of assemblies. A new acetal dynamic combinatorial library was thus established and analyzed. The library at equilibrium is composed of at least 15 members, either oligomers or macrocycles, as shown by NMR and mass spectra. The dynamic nature of the DCL was demonstrated by re-equilibration of a single library member to regenerate a full library. Furthermore, the anticipated association and amplification of macrocycles was detected by the addition of ammonium ions, as expected for crown ether analogues.

The simplicity of acetalation reactions paves the way for an extensive use of this method in the creation of novel dynamic combinatorial libraries. We are currently working on raising the degree of complexity of the acetal libraries by using tri- and tetrafunctional starting materials (alcohols and aldehydes), and also by the introduction of additional recognition functions orthogonal to the acetal equilibrium conditions.

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Notes and references

§ *Crystal data*: $\mathbf{M_1}$ structure: $C_{13}H_{17}NO_6$, $M = 283.28$, orthorhombic, space group *Pbca*, $a = 15.714(3)$, $b = 8.2622(15)$, $c = 20.989(4)$ Å, $V = 2725.1(9)$ Å^3, $Z = 8$, 14 250 reflections measured, 2704 unique ($R_{int} = 0.060$), from which 1288 were used in the calculations. The final R was 0.0484. $\mathbf{M_2}$ structure: $C_{26}H_{34}N_2O_{12}$, $M = 566.55$, triclinic, space group $P\bar{1}$, $a = 7.166(3)$, $b = 7.306(3)$, $c = 13.515(6)$ Å, $V = 687.7(5)$ Å, $Z = 1$, 4010 reflections measured, 2721 unique ($R_{int} = 0.025$), from which 2047 were used in the calculations. The final R was 0.0728.

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