Molecular Recognition

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A "Dial-A-Receptor" Dynamic Combinatorial Library**

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Dynamic combinatorial chemistry (DCC)[1] is an increasingly popular tool for the discovery and exploration of systems which involve molecular recognition, including synthetic receptors,[2] ligands and substrates for biomolecules,[3] mechanically interlocked structures,[4] self-assembling materials,[5] self-replicators,[6] sensors,[7] protein folding,[8] self-sorting systems,[9] and catalysts.[10] New reactions and methods for generating dynamic combinatorial libraries (DCLs) are continuously appearing.[11] DCLs are also developing into powerful workhorses for systems chemistry.[1j,k,12] In a DCL all the members continuously exchange building blocks with one another, thus resulting in a product distribution which is under thermodynamic control. When an external molecule (template) is added to the system, the library composition changes in favor of the compounds which bind the template. While many examples of template effects using DCC have been reported,[1–10] usually only one or a few library members are amplified upon addition of the template. This scarce amplification also applies to DCLs of synthetic receptors. For nearly all the DCLs reported thus far it remains largely unpredictable whether a specific guest will be able to find and amplify a receptor within it. Receptor libraries that reliably produce hosts for a certain class of guests have not yet been reported. We now show that a continuous range of six different receptors of increasing size may be selectively amplified by exposing a library, made from only two simple building blocks, to a large range of different templates in aqueous solution. This library showed amplification of one or more of these receptors for nearly all 30 investigated amine and ammonium ion guests covering a wide range of shapes and sizes. Thus, this library provides a generic starting point for the development of synthetic receptors for this important class of compounds in water.

In previous work we discovered that exposing small DCLs made from building block **1** to spermine as a template, resulted in the amplification of tetramer $(\mathbf{1})_4$ (Figure 1).[13] In a separate study we found that DCLs made from dithiol **2** also gave a tetrameric receptor $[(\mathbf{2})_4]$ when exposed to adamantane derivative **31**.[14] We reasoned that by mixing **1** and **2** we should be able to access all mixed tetramers $(\mathbf{1})_3(\mathbf{2})$, $(\mathbf{1})_2(\mathbf{2})_2$, $(\mathbf{1})(\mathbf{2})_3$, and potentially larger mixed macrocycles such as pentamers. Thus, we mixed the building blocks **1** and **2** in an equimolar ratio (5 mM total) in a borate buffer (pH 8.4) in the presence of air.

The thiols oxidized to disulfides in the course of three days (representative control experiments revealed that the library compositions do not change after two days; see Figure S6 in the Supporting Information) and the compositions of the resulting DCLs were analyzed using LC-MS. Without the addition of any template the composition was dominated by the statistically most likely $(\mathbf{1})_2(\mathbf{2})_2$ tetramers (multiple isomers; see the Supporting Information). Encouragingly, also all the other tetramers (including all possible isomers) could be detected, albeit only in small quantities. In addition to these macrocycles, two different [2]catenanes were detected by LC-MS, the previously reported $(\mathbf{2})_4$-$(\mathbf{2})_4$[14] and the new heterocatenane $(\mathbf{1})(\mathbf{2})_3$-$(\mathbf{2})_4$.

We then proceeded to make DCLs in the presence of a range of 30 different amine and ammonium ion templates, most of them of biological relevance (Figure 2). After the individual DCLs were stirred for three days at room temperature the samples were analyzed by HPLC (see the Supporting Information). Nearly all of the 30 templates were able to amplify one or more receptors. The only exceptions are templates **27** and **28** which were poorly soluble. Moreover, most templates induced a unique response in the DCL (Figure 3 and see the Supporting Information for all the chromatograms). The response of a DCL to a template is routinely analyzed in terms of the amplification factors (AFs) of the individual receptors. AFs are defined as the concentration of the receptor in the presence of the template over the concentration in the absence of the template.

However, comparing the AFs of different receptors, which are present at very different concentrations, within a single library in the absence of the template is not very meaningful. For example, a compound that already contains half the library material in the absence of the template cannot have an AF larger than 2, while a compound that only contains 1 % of the untemplated library material can have an AF of up to 100. To compare amplification factors between different receptors we introduce a normalized amplification factor (AF_n), defined by Equation (1).

$$AF_n = ([A]_T - [A]_0)/([A]_{max} - [A]_0) \quad (1)$$

Herein, $[A]_T$ and $[A]_0$ are the concentrations of the library

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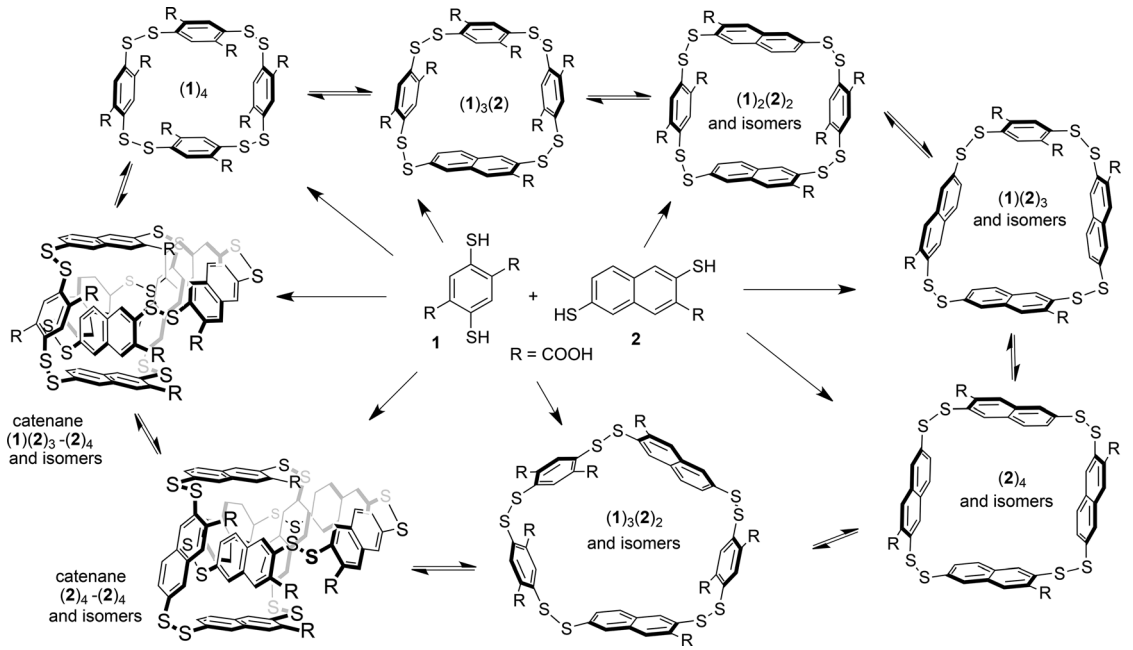

Figure 1. Mixing building blocks **1** and **2** in borate buffer pH 8.4 in presence of oxygen resulted in a dynamic combinatorial library containing several macrocycles and two [2]catenanes.

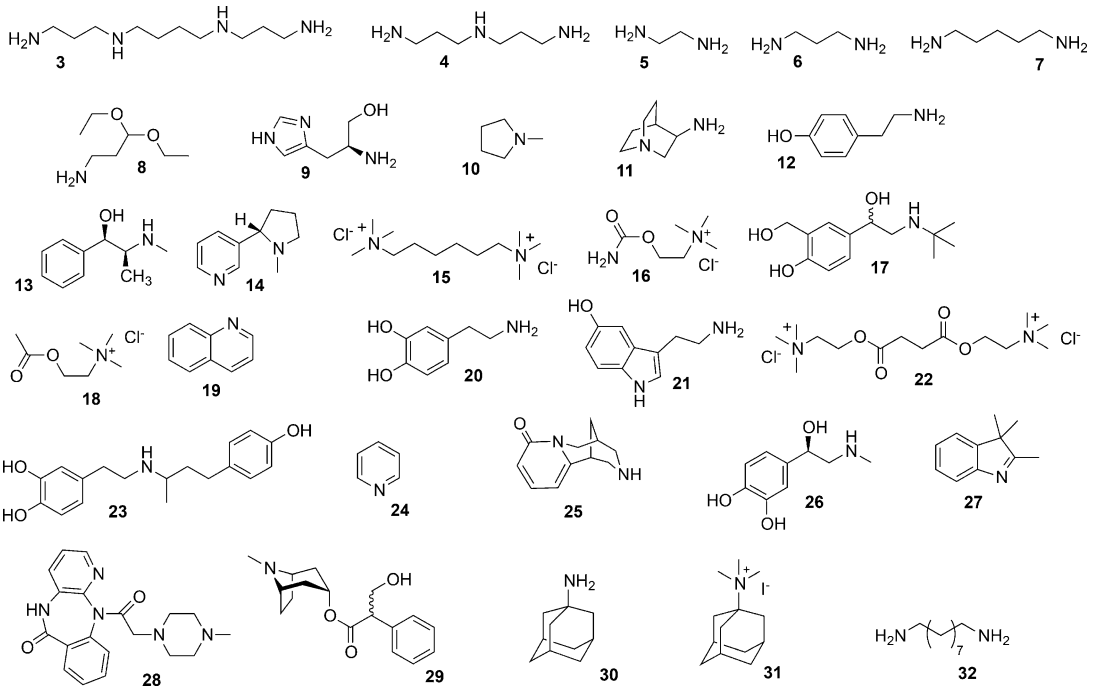

Figure 2. Templates used in the DCLs.

member A in the presence and absence of the template, respectively, and $[A]_{max}$ is the maximum possible concentration of A, based on the amounts of available building block(s). The maximum value for AF_n is 1, when $[A]_T = [A]_{max}$, while $AF_n = 0$ corresponds to the case where there is no amplification ($[A]_T = [A]_0$). Values of $AF_n < 0$ indicate that the concentration of the library member is reduced in the presence of template.

While values of AF can be determined directly from the peak areas of HPLC chromatograms based on UV-Vis detection, for AF_n it is necessary to determine the actual concentrations of the species in the library. Fortunately, the UV response generated by **1** and **2** turned out to be additive, that is, independent of the library member in which they were incorporated.[15] Therefore the concentrations of the library members could be obtained from the peak areas after the

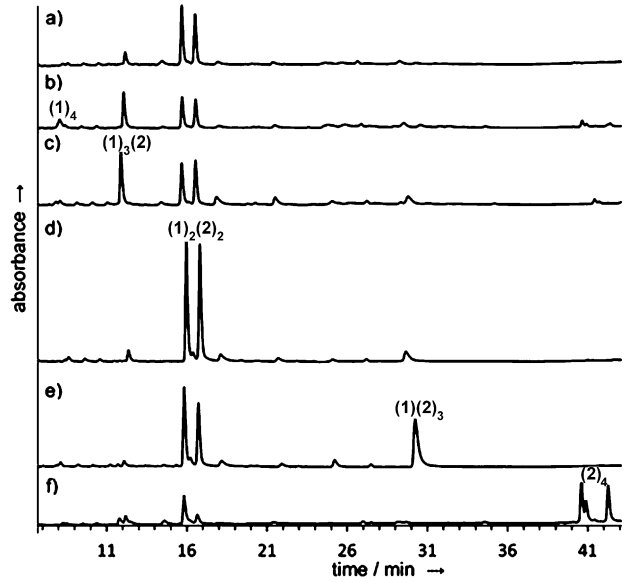

Figure 3. Partial HPLC chromatograms (260 nm) of a DCL composed of a) equimolar amounts (5.0 mM in total) of building block **1** and **2**. The DCL in the presence of 2.5 mM of b) ethylenediamine (**5**), c) 1-amino-3-3-diethoxypropane (**8**), d) tyramine (**12**), e) dobutamine (**23**), f) 1-adamantylamine (**30**). Samples were diluted with 200% volume DMSO immediately prior to analyses.

effective absorptivities of the two building blocks had been determined (see the Supporting Information for details).

The AF_n values of the various macrocycles for all templates are shown in Table 1. The various isomers of the macrocycles of the same overall building block composition are grouped together and treated as one because in the vast majority of the cases (90%) the isomers respond similarly to the introduction of individual templates. Values for $AF_n \geq 0.09$ (shown in bold) reveal that all the expected tetrameric receptors are amplified by selected subsets of templates. As the templates increase in size or bulkiness they tend to amplify the larger macrocycles. The maximum amplification of the smallest receptor $(\mathbf{1})_4$ is obtained with spermine (**3**), while cadaverine (**7**) is most efficient at amplifying $(\mathbf{1})_3(\mathbf{2})$. Tyramine (**12**) is best for $(\mathbf{1})_2(\mathbf{2})_2$, dobutamine (**23**) is best for $(\mathbf{1})(\mathbf{2})_3$, 1-adamantylamine (**30**) is best for $(\mathbf{2})_4$, and atropine (**29**) induces a modest amplification of the pentameric receptor $(\mathbf{1})_3(\mathbf{2})_2$. In most cases amplification appears to be selective for one or several receptors which have similar sizes. However, there are a few exceptions. The thin templates **3**, **4**, **6**, and **7** not only amplify the small macrocycles $(\mathbf{1})_4$ and $(\mathbf{1})_3(\mathbf{2})$ but also the large macrocycle $(\mathbf{2})_4$. However, the amplification of $(\mathbf{2})_4$ is strongly reduced upon lowering the template concentration to stoichiometric levels (where templating is more selective for the best binders[16]), whereas the amplification of the smaller macrocycles is much less affected (see Table S5 in the Supporting Information), thus suggesting that the small macrocycles are the stronger binders. Furthermore, the amplification of $(\mathbf{2})_4$ is facilitated by the fact that much of **1** is taken up in the small macrocycles, thus liberating **2**. Another exception is 1,9-diaminononane (**32**), which amplifies the relatively small oligomer $(\mathbf{1})_3(\mathbf{2})$ as well as the larger oligomers $(\mathbf{1})(\mathbf{2})_3$ and $(\mathbf{2})_4$. We speculate that the elongated shape may allow two of the $(\mathbf{1})_3(\mathbf{2})$ receptors to be bound to a single template.

We performed our template screening using a 1:1 ratio of **1** and **2**, which puts restraints on the amplifications of library members with building block compositions that do not match this ratio. When the aim is to isolate specific receptors from the DCLs it becomes important to lift such restraints, which is possible by adjusting the building block ratio to match the composition of the receptor. For example, with template **23** we obtained $AF_n = 0.38$ for $(\mathbf{1})(\mathbf{2})_3$ when using an equimolar amount of **1** and **2**, while we obtained $AF_n = 0.44$ for the same receptor when we used a 1:3 ratio of **1** and **2**. More importantly, while the receptor corresponded to 29% of the total library material in the original DCL, it constituted 61% of library material in the biased DCL.

The data in Table 1 were obtained using a modest excess of the template (1:2 template to building block ratio, which translates into a 4:1 template to homotetramer ratio). Under

Table 1: Normalized amplification factors (AF_n) for the six receptors upon addition of a given template (2.5 mM) to a DCL made from **1** and **2** (2.5 mM each). $AF_n > 0.09$ are shown in bold.

Template		$(\mathbf{1})_4$	$(\mathbf{1})_3(\mathbf{2})$	$(\mathbf{1})_2(\mathbf{2})_2$	$(\mathbf{1})(\mathbf{2})_3$	$(\mathbf{1})_3(\mathbf{2})_2$	$(\mathbf{2})_4$
3	spermine	**0.70**	**0.13**	−0.52	0.01	−0.03	**0.44**
4	bis(3-aminopropyl)amine	**0.37**	**0.13**	−0.51	0.01	−0.03	**0.57**
5	ethylenediamine	**0.26**	**0.24**	−0.18	0.03	−0.02	0.04
6	1,3-diaminopropane	**0.32**	**0.43**	−0.39	0.02	−0.03	**0.39**
7	cadaverine	0.04	**0.52**	0.04	0.00	−0.03	**0.31**
8	1-amino-3,3-diethoxypropane	0.09	**0.39**	−0.06	0.05	−0.02	0.04
9	histidinol	0.04	**0.25**	**0.57**	0.00	−0.03	0.03
10	1-methylpyrrolidine	0.03	**0.18**	0.03	0.04	−0.02	0.00
11	3-aminoquinuclidine	0.03	**0.15**	**0.15**	0.06	−0.02	0.01
12	tyramine	0.06	0.02	**0.92**	0.04	−0.03	0.00
13	(−)ephedrine	0.03	−0.03	**0.45**	0.05	−0.01	0.00
14	nicotine	0.04	−0.01	**0.39**	0.09	−0.01	0.00
15	hexamethonium chloride	0.03	**0.10**	**0.34**	0.08	−0.03	n.d.[a]
16	carbamoylcholine chloride	0.03	0.00	**0.33**	0.06	−0.02	n.d.[a]
17	salbutamol	0.02	−0.05	**0.31**	0.00	0.00	0.01
18	acetylcholine chloride	0.03	0.00	**0.31**	**0.14**	−0.02	0.01
19	quinoline	0.04	0.00	**0.28**	0.00	0.00	0.04
20	dopamine	0.03	0.06	**0.26**	−0.02	−0.02	0.00
21	serotonine	0.00	−0.05	**0.24**	0.00	−0.02	0.06
22	succinylcholine chloride	0.04	0.01	**0.24**	**0.10**	0.03	0.00
23	dobutamine	0.02	−0.06	**0.28**	**0.38**	−0.02	0.00
24	pyridine	0.04	0.02	**0.17**	0.01	−0.02	0.00
25	cytisine	0.04	0.07	**0.16**	0.05	−0.01	0.02
26	(−)-epinephrine	0.03	0.01	**0.09**	0.01	−0.02	0.00
27	trimethylindolenine	0.03	−0.01	0.01	−0.02	0.01	0.00
28	pirenzepine	0.00	−0.02	−0.02	0.04	0.02	0.01
29	atropine	0.01	−0.02	−0.23	0.07	**0.09**	0.04
30	1-adamantylamine	0.02	0.05	−0.31	−0.02	0.00	**0.79**
31	ATMA	−0.01	0.00	−0.29	0.00	0.02	**0.64**
32	1,9-diaminononane	0.08	**0.16**	−0.40	**0.24**	−0.03	**0.59**

[a] n.d. = macrocycle not detected.

conditions of excess template, amplification is biased towards those library members which the system can produce in largest quantities.[16] Thus, $(\mathbf{1})_2(\mathbf{2})_2$ will be more readily amplified than $(\mathbf{1})_3(\mathbf{2})$ and $(\mathbf{1})(\mathbf{2})_3$, which are in turn more readily amplified than $(\mathbf{1})_4$ and $(\mathbf{2})_4$. Hence, selective amplification of either of the homotetramers must reflect strong binding affinity. Indeed, from our previous work we know that the templates **3** and **31** bind strongly to receptors $(\mathbf{1})_4$ and $(\mathbf{2})_4$, respectively (binding constants are shown Table 2). However, for templates that induce the strongest amplification of $(\mathbf{1})_2(\mathbf{2})_2$ it is not necessarily the case that this receptor is also the strongest binder among the ones listed in Table 1. To illustrate this we investigated the binding affinity of the various receptors for templates **11**–**14**, which all amplify $(\mathbf{1})_2(\mathbf{2})_2$. Binding affinities were determined from library distributions obtained at nine different template concentrations using DCLFit.[17] Some of the thus obtained numbers were validated against binding affinities determined by ITC using isolated samples of selected receptors (obtained as mixtures of isomers). The results (Table 2) show that the data obtained using DCLFit and ITC agree within the range of the up to 2 kJ mol^{-1} deviation (a factor 2.2 in binding constant) that may be expected.[17]

Table 2: Equilibrium constants (K_a in M^{-1}) for binding of selected templates to different macrocycles.

Template	Method	$(\mathbf{1})_4$	$(\mathbf{1})_3(\mathbf{2})$	$(\mathbf{1})_2(\mathbf{2})_2$	$(\mathbf{1})(\mathbf{2})_3$	$(\mathbf{2})_4$
3	ITC[13]	4.5×10^7	n.m.[a]	n.m.[a]	n.m.[a]	n.m.[a]
11	DCLFit	2.2×10^4	2.9×10^4	7.8×10^3	5.4×10^3	3.1×10^3
12	DCLFit[b]	6.2×10^4 (4.6×10^4)	4.1×10^4 (4.0×10^4)	9.8×10^4 constrained	5.8×10^4 constrained	n.d.[a]
	ITC	n.m.[a]	n.m.[a]	1.3×10^5	1.0×10^5	n.m.[a]
13	DCLFit[b]	4.0×10^3 (1.1×10^4)	2.5×10^3 (5.8×10^3)	9.9×10^3 constrained	2.0×10^4 constrained	n.d.[a]
	ITC	n.m.[a]	n.m.[a]	1.6×10^4	2.5×10^4	n.m.[a]
14	DCLFit	3.7×10^3	3.2×10^3	3.8×10^3	3.0×10^3	n.d.[a]
31	other[14]	n.m.[a]	n.m.[a]	n.m.[a]	n.m.[a]	1×10^7

[a] n.d. = not detected, n.m. = not measured. [b] Values within parentheses were fitted by constraining the values of the other binding constants to those obtained by ITC.

The amplification data for template **11** point towards $(\mathbf{1})_3(\mathbf{2})$ and $(\mathbf{1})_2(\mathbf{2})_2$ as strong binders. Since amplification will be biased towards $(\mathbf{1})_2(\mathbf{2})_2$, this suggests that $(\mathbf{1})_3(\mathbf{2})$ should be the stronger binder of the two receptors, and this turned out to be the case (Table 2). It is interesting to see that $(\mathbf{1})_4$ has also a high affinity, even though it is hardly amplified, because mixed-building-block receptors of comparable affinity can be produced by the system in larger quantities, thus maximizing the overall binding energy.[16] Template **12** selectively amplifies receptor $(\mathbf{1})_2(\mathbf{2})_2$ and, indeed, binds this receptor best, even though the selectivity is not as high as a naive inspection of the amplification data might have suggested. Template **13** shows less pronounced selectivity in amplification and is a case where the amplification data do not reflect binding affinity. Both ITC and DCLFit analysis indicate that $(\mathbf{1})(\mathbf{2})_3$, and not $(\mathbf{1})_2(\mathbf{2})_2$, is the stronger binder. Template **14** shows comparable affinities for both $(\mathbf{1})(\mathbf{2})_3$ and $(\mathbf{1})_2(\mathbf{2})_2$.

In conclusion, our results show that a simple library made from **1** and **2** is capable of providing a suitable receptor platform for all of the soluble amine and ammonium guests that we tested, thus presenting a generic system for the recognition of amines and ammonium ions in water. This is the first report of a DCL that provides a continuous range of receptors for a wide range of guest sizes and shapes. Guest binding is achieved using a limited range of noncovalent interactions: hydrophobic interactions with the aromatic rings of **1** and **2** and possibly also the sulfur atoms and interactions with the mostly deprotonated carboxylic acid groups. Thus, it is not surprising that a given receptor may be amplified to a similar extent by a range of different templates. We expect that an expansion of the recognition potential of the building blocks, while maintaining the generic platform, will lead to more template-specific recognition. Research in this direction is currently underway in our laboratory.

Experimental Section

General methods: Building blocks **1**,[13] **2**,[14] and template **31**[18] were synthesized following literature procedures. All the other templates were obtained from commercial sources and used without further purification. HPLC analyses were performed using an Agilent 1100 series HPLC and LC-MS using a HPLC-MS from Thermo Scientific, LCQ Fleet series. Acetonitrile was purchased from Biosolve. Formic acid was purchased from Sigma–Aldrich. Analyses were performed using a reversed-phase HPLC column (Kromasil C8, 4.6 × 150 mm, 5 μm) injecting 3 μL of a DCL sample that had been diluted with 200% volume DMSO immediately prior to analyses. A flow rate of 1 mL min^{-1} was used. The mobile phase consisted of a mixture of acetonitrile and doubly distilled water (both containing 0.1% formic acid), using the following gradient: (0 min: 30% CH_3CN; 5 min: 40% CH_3CN; 30 min: 70% CH_3CN; 35 min: 70% CH_3CN; 40 min: 95% CH_3CN; 50 min: 95% CH_3CN; 55 min: 30% CH_3CN). Negative ion mass spectra were acquired in ultrascan mode using electrospray ionization.

Dynamic combinatorial library preparation: Equimolar amounts of building blocks **1** and **2** (5 mM overall concentration) were dissolved in borate buffer (50 mM) and the pH value was adjusted to 8.4 by addition of an appropriate volume of a 1M solution of NaOH. An aliquot corresponding to 2.5 mM of each template (dissolved in 50 mM borate buffer, pH 8.4) was added separately and the mixtures were allowed to oxidize and equilibrate at room temperature. The DCLs were analyzed after three days.

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