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Research Article

Static Combinatorial Chemistry: A High-Pressure Approach to the Synthesis of Macrocyclic Benzoamide Libraries

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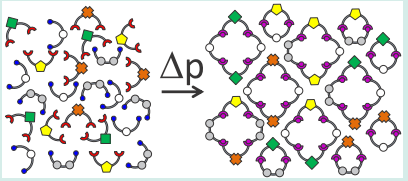
ABSTRACT: We investigated the yield and distribution of macrocyclic products formed in combinatorial libraries (CLs) obtained via double-amidation reactions of methyl diesters with α,ω-diamines. The application of the static combinatorial chemistry (SCC) approach allowed us to generate a large number of macrocyclic diamides and tetraamides in single experiments. We show that high-pressure conditions accelerate the macrocyclization process but also have a great impact on the distribution of macrocyclic products in the presented libraries, promoting the formation of macrocyclic compounds and eliminating the linear ones. The distribution of macrocyclic products was also found to be strongly dependent on the structural features of the substrates employed. Furthermore, in three- and four-substrate CLs we observed the formation of a new type of hybrid tetraamides consisting of three different components.



KEYWORDS: *static combinatorial chemistry, high pressure, macrocyclization, macrocyclic amides*

INTRODUCTION

Pressure is one of the main factors, apart from temperature, that affect the direction and rate of chemical reactions. Principally, conducting a chemical transformation under high-pressure conditions is beneficial for entropy reasons, which are crucial in the preorganization processes. As a consequence, the direction of chemical reactions carried out under high-pressure conditions is determined by the volume of activation, defined as the difference between the molar volumes of the transition state and substrates ($\Delta V^* = V_{TS} - V_S$). Notably, reactions characterized by a negative activation volume ($\Delta V^* < 0$) are accelerated by pressure, whereas those with $\Delta V^* > 0$ are inhibited.[1−3] Consequently, this strategy has proved to be particularly useful for reactions that are inefficient under thermal conditions for steric or stereoelectronic reasons.[4−9] To date, the remarkable input of the high-pressure technique has been observed in reactions such as condensation, addition, and elimination, in various type of cycloadditions,[10] and also in organocatalysis[11,12] as well as in metal catalysis.[13−16] In addition to the high-dilution technique,[17,18] template effects,[19−21] and metathesis,[22,23] high pressure is valuable tool in the macrocyclization process, since it prevents unfavorable entropy effects, accelerates the formation of cyclic products, and eliminates the linear ones.

Searching for efficient pathways to obtain macrocyclic compounds, which can find applications in supramolecular chemistry as molecular receptors,[24,25] sensors,[26−28] and catalysts,[29−33] is one of the main topics of our long-term research. We previously developed two synthetic procedures addressing this problem: macrocyclization under high-pressure conditions via double quaternization of diamines by α,ω-diiodide compounds[34−36] and via double amidation of dimethyl esters by α,ω-diamines.[37]

It is worth mentioning that remarkable progress in the construction of challenging supramolecular architectures and devices is possible through the application of combinatorial chemistry tools. The ability to combine multiple molecular building blocks and form various structures in a single experiment is a highly desirable strategy because of the lower costs and shorter synthesis times. Thus, the creation of such combinatorial libraries (CLs) has found wide application, e.g., in the pharmaceutical industry to search for potential drugs that are difficult to obtain by the classic approach via often tedious synthetic pathways.[38−41] In the static combinatorial chemistry (SCC) approach, libraries of many different derivatives are obtained as a result of irreversible reactions, where it is impossible to reproduce substrates from already-formed products. In addition, the library formed must be fully representative, i.e., it must contain all of the products obtainable from the given substrates. To date, SCC has been the most successful in peptide synthesis, where the variety of building blocks is limited to the set of natural α-amino acids.[42] In the case of macrocyclization processes, the overwhelming majority of reports in the literature present the dynamic combinatorial chemistry (DCC) approach based on the reversible formation of imines, disulfides, or boronic

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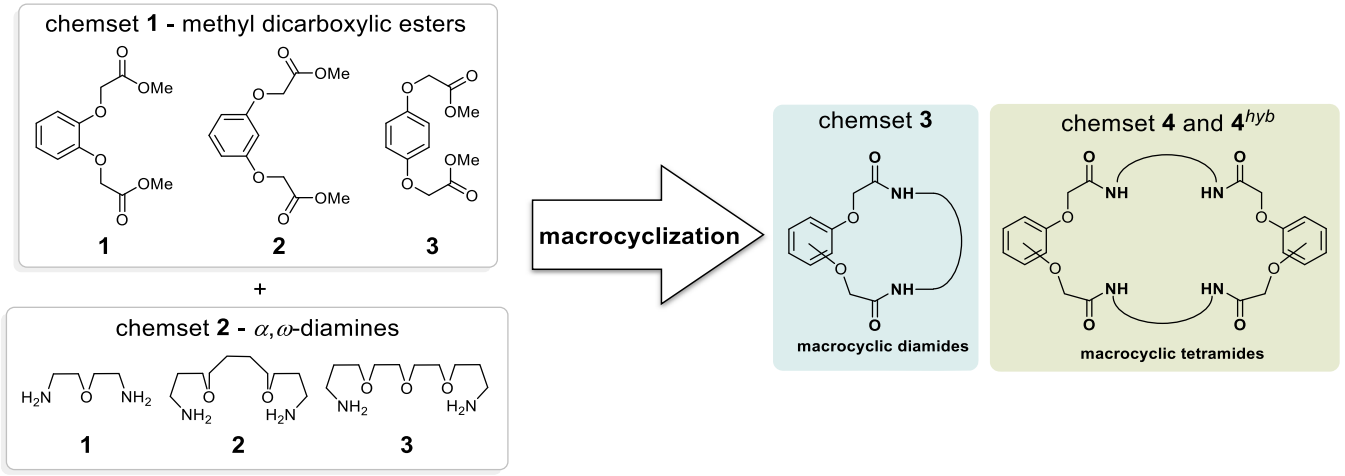
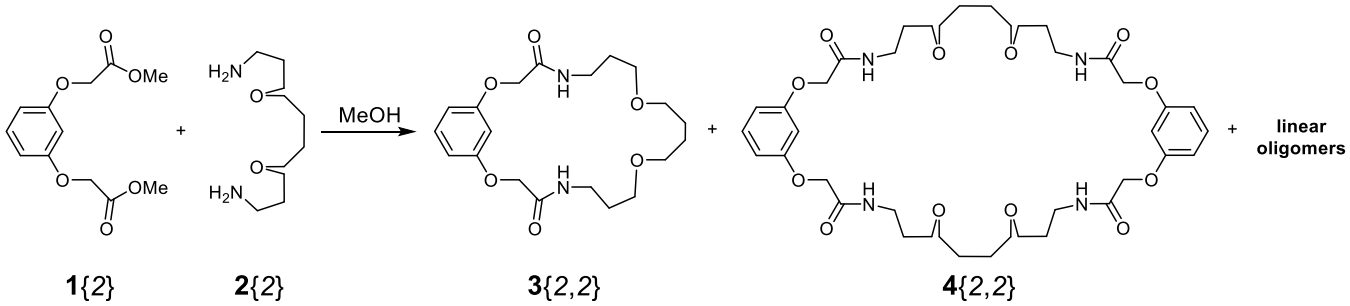


Figure 1. Substrates used in the macrocyclization reaction and schematic representation of the SCLs formed.

Scheme 1. Model Reaction



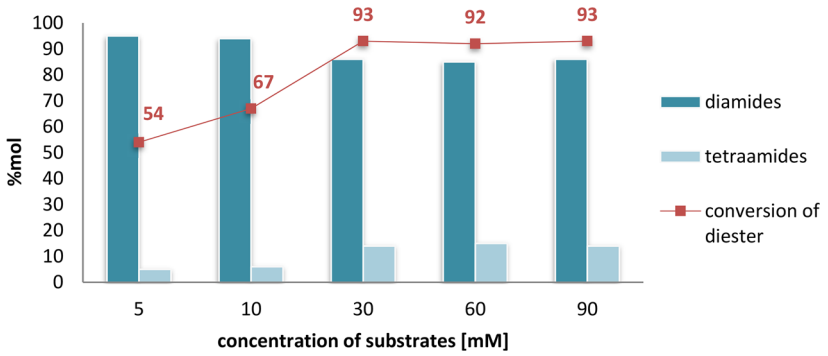


Figure 2. Influence of the concentration on the model reaction carried out for 168 h

esters.[43−45] On the other hand, the application of the SCC approach remains much less explored, probably because of the difficulties in using this complex method for such a demanding process, since linear products (oligomers), once formed, no longer participate in the creation of desired products, which as a result decreases the yield of macrocycle formation. However, in many cases the formation of irreversible covalent bonds outperforms the dynamic approach. In the literature we can find mainly three types of processes based on macrocyclization reactions generating valuable and complex static CLs (SCLs), namely, macrocyclization on a solid support,[46,47] macrocyclization using multicomponent reactions,[48,49] and depolymerization leading to macrocyclic compounds.[50,51]

In this work, we decided to combine the positive effects of high pressure on the macrocyclization reaction with combinatorial chemical tools. Here we demonstrate representative examples of the effect of high pressure on the formation of combinatorial libraries. Furthermore, although this approach is a relatively unexplored area of chemistry, it can afford several practical advantages in the challenging synthesis of macrocyclic compounds.

RESULTS AND DISCUSSION

We recently demonstrated that inorganic salts have a great impact on the formation of macrocyclic benzoamides via the double-amidation reaction of methyl dicarboxylic esters with α,ω-diamines.[52] On the basis of these results, herein we investigate the distribution of the macrocyclic products of this reaction, namely, macrocyclic diamides and tetraamides, in two-, three-, and four-substrate CLs formed under atmospheric and high-pressure conditions. To study these processes, we chose two chemsets of substrates, i.e., methyl dicarboxylic

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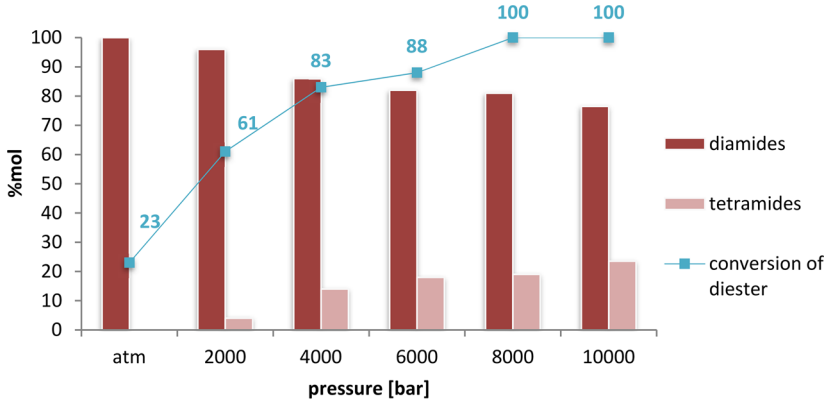

Figure 3. Influence of high pressure on the model reaction carried out for 24 h.

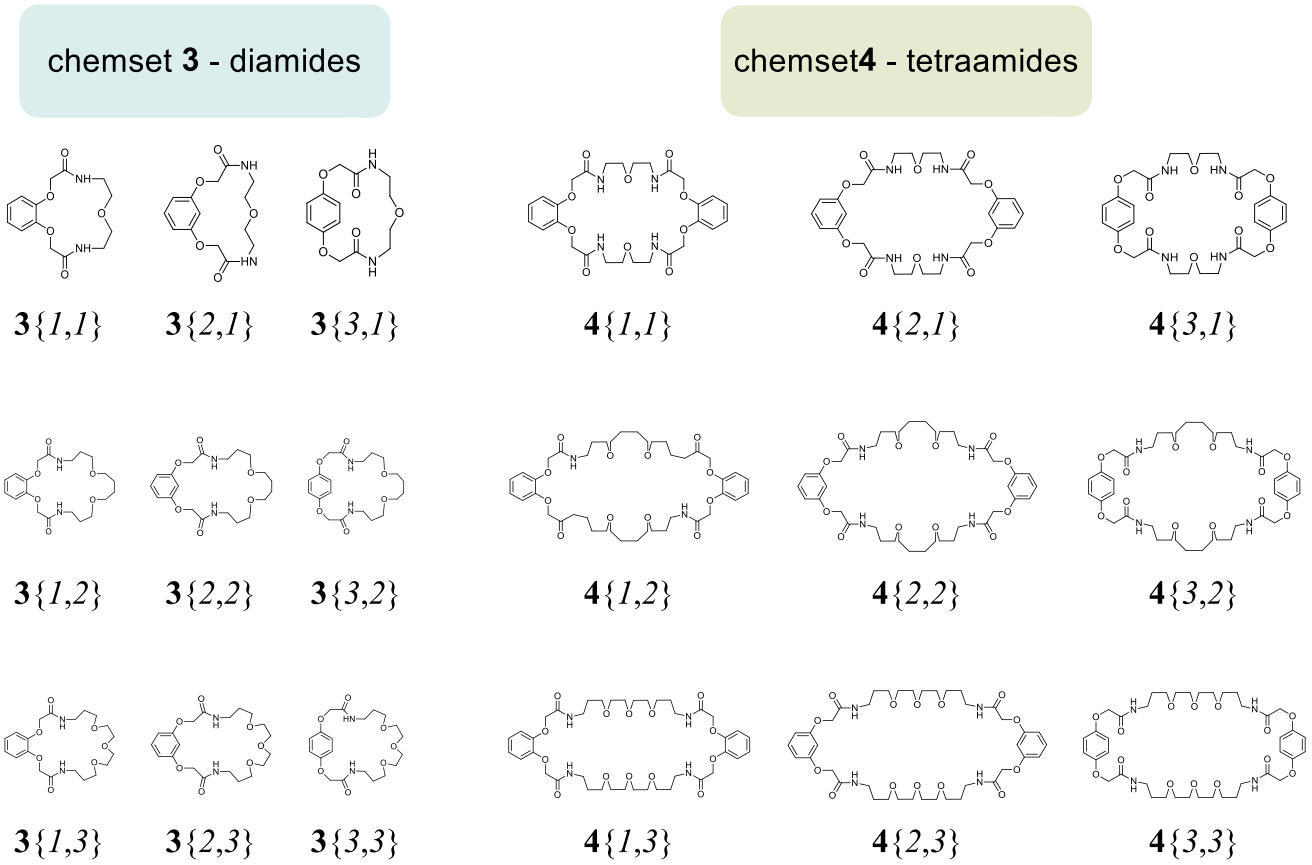

Figure 4. Main products formed after macrocyclization reaction.

esters (chemset **1**) and *α,ω*-diamino ethers (chemset **2**) (Figure 1).

We started our investigations with the optimization of the double-amidation reaction conditions. As a model substrates we chose diester **1**{*2*} and diamine **2**{*2*} characterized by optimal structural factors (diester geometry and diamine chain length) to provide the formation of both macrocyclic products: di- and tetraamides (Scheme 1).

Initially, we explored the distribution of macrocyclic products and conversion of diester **1**{*2*} at five different concentrations in the range of 5−90 mM under ambient pressure and temperature conditions using methanol as a solvent (Figure 2). All of the reactions were carried out for 168 h because of their low rate, a characteristic feature of macrocyclization. We found that a substrate concentration above 30 mM results in ∼93% conversion of diester **1**{*2*}, but in addition to the desired macrocyclic di- and tetraamides, we detected small amounts of linear oligomers as side products. On the other hand, a lower substrate concentration, imitating high-dilution conditions, reduces the amounts of linear products and macrocyclic tetraamides but nevertheless results in unsatisfactory conversion below 67%. Analyzing these outcomes, we choose 30 mM as an optimal concentration.

With these results in hand, we determined the influence of high-pressure conditions on the model reaction. Diester **1**{*2*} and diamine **2**{*2*} were dissolved in methanol (C = 30 mM), and the reaction was carried out under different pressure conditions (2−10 kbar) at room temperature. Taking into

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Table 1. Two-Substrate SCLs of Macrocyclic Benzoamides Obtained under 1 bar and 10 kbar[a]

Entry	Reagents		Conversion of diester [%]		Molar ratios of products [mol%]			
					1 bar, t=168 h		10 kbar, t=24 h	
			1 bar	10 kbar	Diamides	Tetraamides	Diamides	Tetraamides
1	**1**{*1*}	**2**{*1*}	80	87	**3**{*1*,*1*} 99.5	**4**{*1*,*1*} 0.5	**3**{*1*,*1*} 95.0	**4**{*1*,*1*} 5.0
2		**2**{*2*}	93	88	**3**{*1*,*2*} 85.0	**4**{*1*,*2*} 15.0	**3**{*1*,*2*} 78.0	**4**{*1*,*2*} 22.0
3		**2**{*3*}	98	92	**3**{*1*,*3*} 88.0	**4**{*1*,*3*} 12.0	**3**{*1*,*3*} 76.0	**4**{*1*,*3*} 24.0
4	**1**{*2*}	**2**{*1*}	92	90	**3**{*2*,*1*} 77.0	**4**{*2*,*1*} 23.0	**3**{*2*,*1*} 68.5	**4**{*2*,*1*} 31.5
5		**2**{*2*}	93	89	**3**{*2*,*2*} 85.0	**4**{*2*,*2*} 15.0	**3**{*2*,*2*} 76.5	**4**{*2*,*2*} 23.5
6		**2**{*3*}	100	90	**3**{*2*,*3*} 95.0	**4**{*2*,*3*} 5.0	**3**{*2*,*3*} 78.0	**4**{*2*,*3*} 22.0
7	**1**{*3*}	**2**{*1*}	88	75	**3**{*3*,*1*} 33.0	**4**{*3*,*1*} 67.0	**3**{*3*,*1*} 16.5	**4**{*3*,*1*} 83.5
8		**2**{*2*}	93	89	**3**{*3*,*2*} 85.0	**4**{*3*,*2*} 15.0	**3**{*3*,*2*} 81.0	**4**{*3*,*2*} 19.0
9		**2**{*3*}	98	90	**3**{*3*,*3*} 89.0	**4**{*3*,*3*} 11.0	**3**{*3*,*3*} 79.0	**4**{*3*,*3*} 21.0

[a]Changes in high-pressure libraries are specified (increases in green, decreases in red).

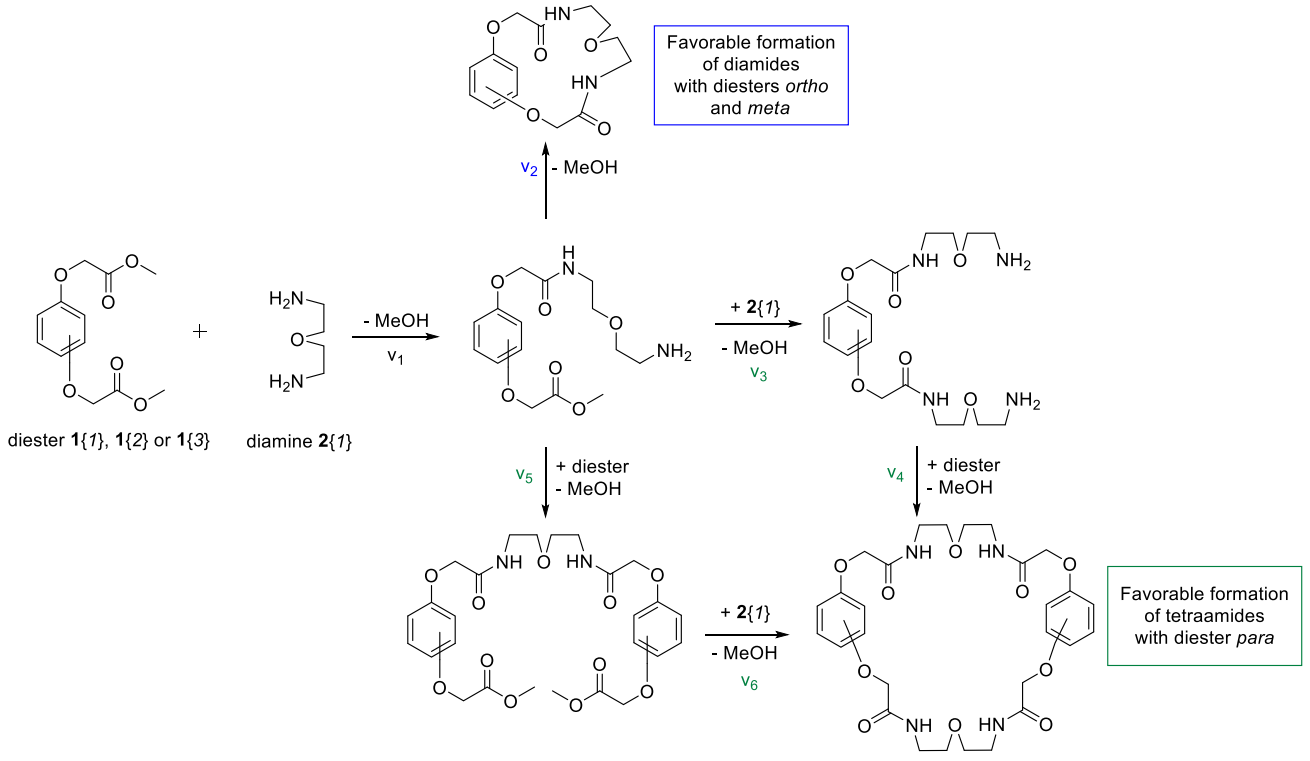

Figure 5. Proposed mechanism of the macrocyclization reaction.

account the previously reported examples of macrocyclization under high-pressure conditions, we decided to carry out the reactions over 24 h. Subsequently, these results were compared to reference reaction leads under atmospheric pressure for the same period of time (24 h), as shown in Figure 3. One can note that high-pressure conditions strongly increase the conversion of diester **1**{2}. Quantitative conversion was reached under 8 and 10 kbar after only 24 h, which means that the reaction rate was accelerated about 7-fold compared with atmospheric pressure. Moreover, with an increase in pressure we observed significant difference in the distribution of products: the content of tetraamide **4**{2,2} in the reaction mixture increased. From the synthetic point of view, this information can be particularly useful because of the difficulty of accessing large macrocyclic compounds (>30-membered). Thus, we chose 10 kbar as the optimal pressure for the formation of CLs. Additionally, using the optimal conditions we carried out the high-pressure experiment on a 5-fold scale using 50 mL Teflon ampules (see the Supporting Information). In that case we observed a slightly higher conversion of the diester (95%), but the distribution of macrocyclic diamides and tetraamides remained unchanged.

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Table 2. Three-Substrate SCLs of Macrocyclic Benzoamides Obtained under 1 bar and 10 kbar[a]

Entry	Reagents			Molar ratios of products [mol%]			
				1 bar, t=168 h		10 kbar, t=24 h	
				Diamides ^{S}	Diamides ^{L}	Diamides ^{S}	Diamides ^{L}
1	**1**{*1*}	**2**{*1*}	**2**{*2*}	**3**{*1,1*} 65	**3**{*1,2*} 32	**3**{*1,1*} 56	**3**{*1,2*} 39
2		**2**{*1*}	**2**{*3*}	**3**{*1,1*} 53	**3**{*1,3*} 45	**3**{*1,1*} 50	**3**{*1,3*} 47
3		**2**{*2*}	**2**{*3*}	**3**{*1,2*} 33	**3**{*1,3*} 61	**3**{*1,2*} 36	**3**{*1,3*} 58
4	**1**{*2*}	**2**{*1*}	**2**{*2*}	**3**{*2,1*} 31	**3**{*2,2*} 61	**3**{*2,1*} 27	**3**{*2,2*} 62
5		**2**{*1*}	**2**{*3*}	**3**{*2,1*} 24	**3**{*2,3*} 71	**3**{*2,1*} 29	**3**{*2,3*} 58
6		**2**{*2*}	**2**{*3*}	**3**{*2,2*} 39	**3**{*2,3*} 56	**3**{*2,2*} 45	**3**{*2,3*} 47
7	**1**{*3*}	**2**{*1*}	**2**{*2*}	**3**{*3,1*} 0	**3**{*3,2*} 84	**3**{*3,1*} 0	**3**{*3,2*} 81
8		**2**{*1*}	**2**{*3*}	**3**{*3,1*} 0	**3**{*3,3*} 91	**3**{*3,1*} 0	**3**{*3,3*} 86
9		**2**{*2*}	**2**{*3*}	**3**{*3,2*} 41	**3**{*3,3*} 52	**3**{*3,2*} 48	**3**{*3,3*} 44
10	**2**{*1*}	**1**{*1*}	**1**{*2*}	**3**{*1,1*} 93	**3**{*1,2*} 7	**3**{*1,1*} 67	**3**{*1,2*} 28
11		**1**{*1*}	**1**{*3*}	**3**{*1,1*} 99	**3**{*1,3*} 0	**3**{*1,1*} 92	**3**{*1,3*} 2
12		**1**{*2*}	**1**{*3*}	**3**{*1,2*} 86	**3**{*1,3*} 0	**3**{*1,2*} 72	**3**{*1,3*} 3

[a]Changes in high-pressure libraries are specified (increases in green, decreases in red). Fluctuations of up to 2 mol % were ignored as no change. The conversion of diesters was nearly 100% for each reaction. The results obtained for macrocyclic tetraamides have been omitted for clarity. The superscripts ^{S} and ^{L} denote the smaller and larger macrocyclic diamides, respectively.

The influence of rising pressure on the yield and distribution of products was investigated in two-, three-, and four-substrate CLs created from variously mixed members from chemsets **1** and **2**. The composition of each library was analyzed by reversed-phase HPLC utilizing a recently reported procedure and the collection of macrocyclic products shown in Figure 4.[52]

The molar ratios of macrocyclic products observed in two-substrate libraries under atmospheric and high-pressure conditions are shown in Table 1. Analyzing the composition of libraries under atmospheric pressure, one can observe that the structure of the substrates strongly affects the distribution of macrocyclic products. This is particularly noticeable for libraries created with the participation of the shortest diamine, **2**{*1*}, and esters with different proximity of reactive centers. During the reaction of diamine **2**{*1*} with diester **1**{*1*}, because of the small spread angle of the reacting groups (*ortho* geometry), the formation of the diamide is promoted. Therefore, macrocyclization occurs much faster than in the reactions with another molecule of diamine or diester ($v_2 \gg v_3$; $v_2 \gg v_4$ and $v_2 \gg v_5$; and $v_2 \gg v_6$), as shown in Figure 5. A similar relationship is observed for diester **1**{*2*} possessing ester groups at the *meta* positions. However, in the case of the reaction with **1**{*3*}, characterized by a *para* arrangement of the ester groups, the content of tetraamide **4**{*3,1*} is twice as high as that of diamide **3**{*3,1*}, which is a consequence of too much stress in the smaller macroring. It can be postulated that the rate of the macrocyclization reaction is much lower than the rates of the individual subsequent reactions necessary to form the tetraamide (i.e., $v_2 \ll v_3$; $v_2 \ll v_4$; and $v_2 \ll v_5$ and $v_2 \ll v_6$) (Figure 5). In libraries composed of the longer diamines **2**{*2*} and **2**{*3*}, we noted the favorable formation of diamides over tetraamides in all cases. These results indicate that the rate of formation of macrocyclic products depends primarily on the structure of the substrates, which determines the size and stretch in the corresponding macrorings.

Conducting the same reactions under high-pressure conditions reduces the reaction time by almost 7 times, which is undoubtedly an advantage of this approach. On the other hand, in all of the libraries under 10 kbar pressure, we observed the formation of similar main products, but the content of tetraamides increased in all of the reaction mixtures. For example, in the case of the library formed from diester **1**{*1*} and diamine **2**{*1*} (Table 1, entry 1), we noted an increase in the amount of tetraamide **4**{*1,1*} from 0.5 mol % to 5.0 mol %. Moreover, for diester **1**{*2*} and diamine **2**{*3*}, the formation of macrocyclic tetraamide **4**{*2,3*} was over 4 times more effective under high pressure (Table 1, entry 6) than under atmospheric pressure. A noteworthy outcome was observed for the library formed from diester **1**{*3*} and diamine **2**{*1*} (Table 1, entry 7), where the formation of tetraamide **4**{*3,1*} is even more favorable than under atmospheric pressure because of its more flexibile and larger ring compared with the tight macroring of diamide **3**{*3,1*}.

In three-substrate libraries (Table 2), the total content of tetraamides also increased under high pressure, but not as significantly as in two-substrate libraries. On average, we noticed a 4% increase in tetraamide content, from ∼6 mol % (1 bar) to ∼10 mol % (10 kbar) in a single library. Interestingly, because of competition between two diamines, we also noticed that high-pressure conditions affected the distribution between macrocyclic diamides with smaller or larger cavities obtained from the corresponding diamines. In the majority of three-substrate libraries, the content of the larger macrocyclic diamide decreases. In only one library (Table 2, entry 9) did we observe that under high-pressure conditions the type of the main product switched from **3**{*3,3*} to **3**{*3,2*}. Opposite results were observed in libraries with diester competitions, where the

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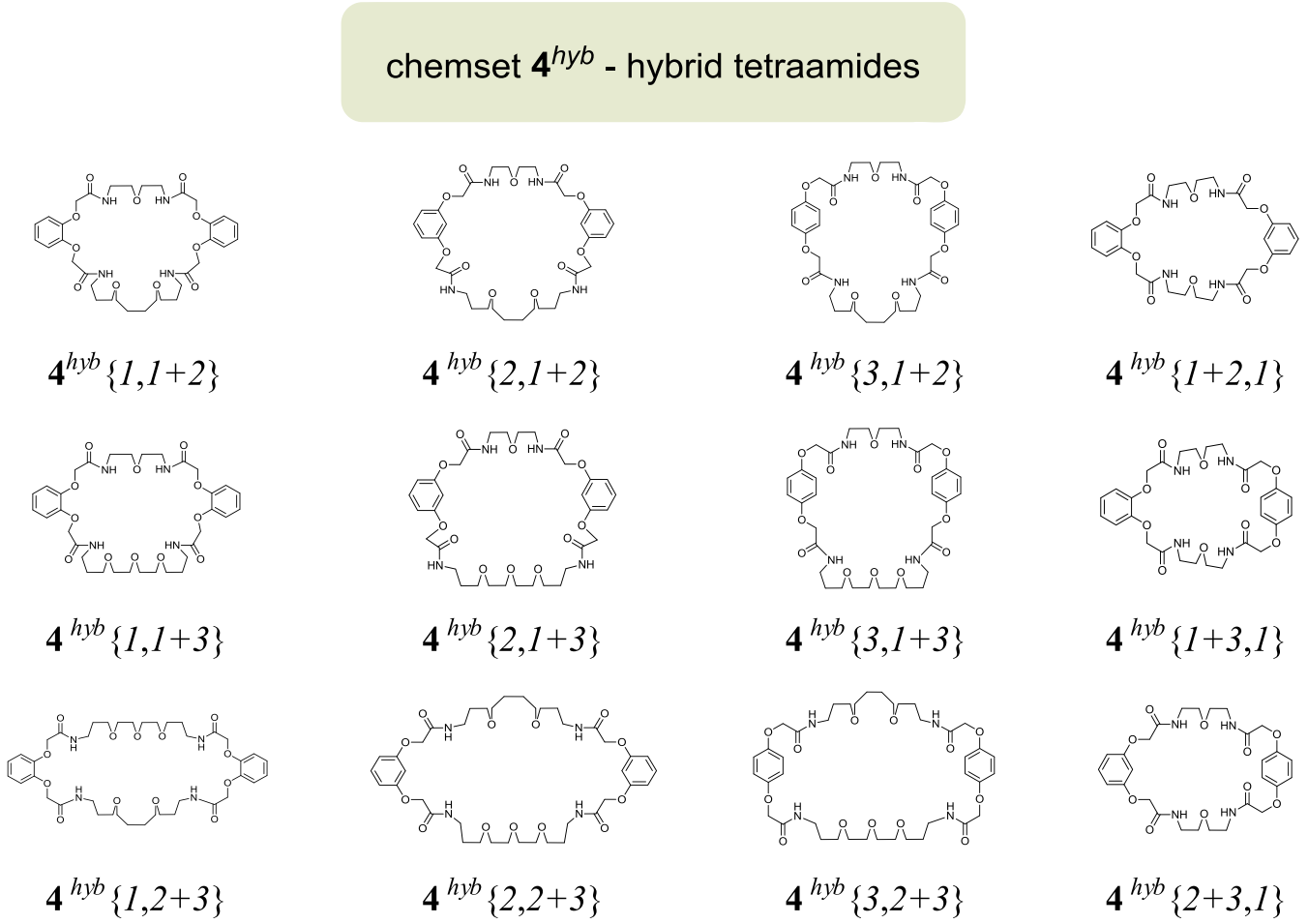

Figure 6. Macrocyclic hybrid tetraamides formed in three- and four-substrate libraries.

Table 3. Four-Substrate SCLs of Macrocyclic Benzoamides Obtained under 1 bar and 10 kbar[a]

Entry	Reagents		Molar ratios of products [mol%]					
			1 bar, t=168 h			10 kbar, t=24 h		
			Diamides S	Diamides M	Diamides L	Diamides S	Diamides M	Diamides L
1	**1**{*1*}	**2**	**3**{*1,1*} 41.3	**3**{*1,2*} 20.7	**3**{*1,3*} 35.7	**3**{*1,1*} 39.3	**3**{*1,2*} 22.0	**3**{*1,3*} 35.8
2	**1**{*2*}	**2**	**3**{*2,1*} 13.5	**3**{*2,2*} 37.5	**3**{*2,3*} 45.4	**3**{*2,1*} 13.8	**3**{*2,2*} 38.6	**3**{*2,3*} 43.7
3	**1**{*3*}	**2**	**3**{*3,1*} 0.0	**3**{*3,2*} 41.2	**3**{*3,3*} 53.9	**3**{*3,1*} 0	**3**{*3,2*} 47.8	**3**{*3,3*} 46.9
4	**2**{*1*}	**1**	**7** 93.0	**13** 6.3	**19** 0.0	**7** 84.0	**13** 15.5	**19** 0.0

[a]Changes in high-pressure libraries are specified (increases in green, decreases in red). Fluctuations of up to 2 mol % were ignored as no change. The conversion of diesters was nearly 100% for each reaction. The results obtained for macrocyclic tetraamides have been omitted for clarity. The superscripts ^{S} and ^{L} denote the smaller and larger macrocyclic diamides, respectively.

content of large-sized macrocyclic diamides increased (Table 2, entries 10−12).

Analyzing the three-substrate libraries, we can also draw a conclusion that the length of the diamine and relative position of the ester groups (geometric factors) determine the lack of statistical distribution of macrocyclic products, much as in the case of two-substrate libraries. What is more, these combinatorial libraries contained unusual macrocyclic hybrid tetraamides (chemset $\mathbf{4}^{hyb}$), as shown in Figure 6. Their presence was proven by UPLC−MS analysis.

The four-substrate libraries are the most complex we studied, which is why there are many factors that have an influence on their composition. In these libraries we also observed the formation of hybrid tetraamides from chemset$\mathbf{4}^{hyb}$. In all of the libraries (Table 3) only trace amounts of tetraamides were detected, and we did not observe any improvement in their formation using high-pressure conditions. Also in libraries 1 and 2 (Table 3, entries 1 and 2), we did not observe significant changes in the distribution of diamides in going from atmospheric pressure to high pressure. Only in library 3 (Table 3, entry 3) did we note a change in the

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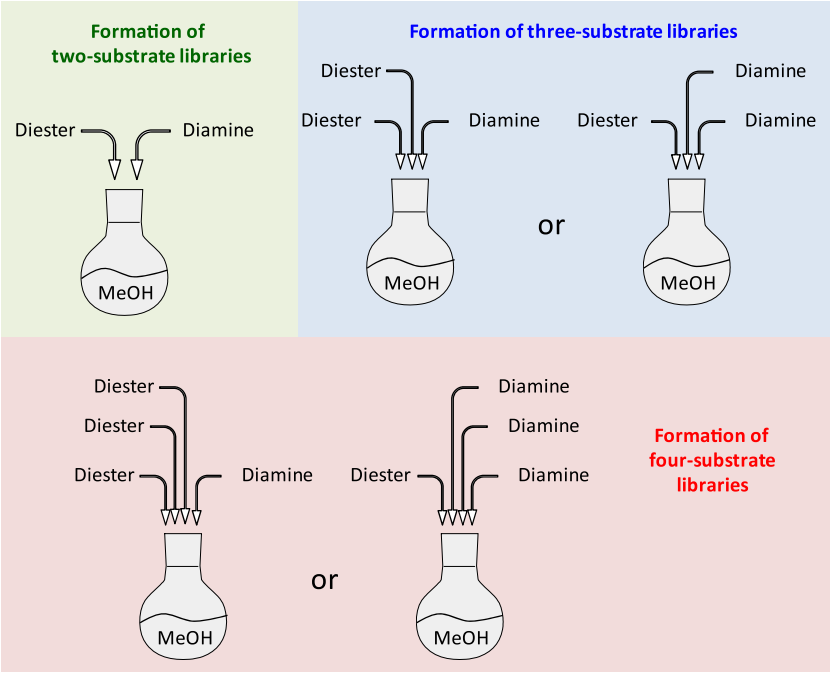

Figure 7. Formation of combinatorial libraries.

main product under 10 kbar, from diamide **3**{*3*,*3*} to **3**{*3*,*2*}. In terms of diamine competitions (like those seen for the three-substrate libraries), in four-substrate libraries we observed that the high pressure promoted the formation of the smaller macrocyclic diamide, decreasing **3**{*3*,*2*} (Table 3, entry 3). Moreover, in the case of diester competition, the amount of the larger macrocyclic diamide increased (Table 3, entry 4), which is in contrast to the results obtained for three-substrate libraries.

CONCLUSIONS

In this work, we investigated the distribution of macrocyclic products formed in SCLs, employing a double-amidation reaction under atmospheric and 10 kbar pressure. We found that the geometries of the diester (chemset **1**) and diamine (chemset **2**) combined with high-pressure conditions strongly affected the proportions of products formed (chemsets **3**, **4**, and $\mathbf{4}^{hyb}$). Most of all, we observed the acceleration of the macrocyclization rate under 8−10 kbar, so the reaction time was shortened from 168 h to just 24 h. The influence of high-pressure conditions can be easily observed in two-substrate CLs, where the amount of macrocyclic tetraamides significantly increased. With increasing complexity of the libraries, the impact of high pressure may be obscured by specific geometrical factors of the substrate. However, high pressure has an impact on the proportions of the macrocycles formed, including control of the main products in the reaction mixtures and the size of the cavity. We were also able to extend this branch of SCC to hybrid tetraamides (chemset $\mathbf{4}^{hyb}$), obtaining macrocyclic compounds with over 30 members, which are difficult to synthesize because of the unfavorable entropy change. Additionally, the presented approach allows for the formation of small libraries of macrocyclic compounds in a single experiment and their testing using HPLC and UPLC−MS. In particular, this method could be used to identify promising molecular receptors or catalysts. Evaluation of the described strategy allows for better and rational control over the formation of desired macrocyclic products, which are obtained much more quickly than with classical methods.

EXPERIMENTAL PROCEDURES

General Methods. Commercially available HPLC-grade methanol was used as a solvent during the formation of combinatorial libraries. Reactions under atmospheric pressure were performed in round-bottom flasks with stirring for 168 h. Reactions under high pressure were performed for 24 h in Teflon ampules using a U101 high-pressure apparatus with a hydraulic press, commercially available from Unipress (Warsaw, Poland), which can operate at up to 15 kbar. A scheme and photographs of a typical piston−cylinder apparatus and ampules are presented in Figure S1.

Formation of Combinatorial Libraries. As shown in Figure 7, two-substrate libraries were prepared by dissolving in methanol (10 mL) one diester from chemset **1** (0.3 mmol) and one diamine from chemset **2** (0.3 mmol).

Three-substrate libraries were prepared by dissolving in methanol (10 mL) two diesters from chemset **1** (0.3 mmol of each diester) and one diamine from chemset **2** (0.3 mmol) or one diester from chemset **1** (0.3 mmol) and two diamines from chemset **2** (0.3 mmol of each diamine).

Four-substrate libraries were prepared by dissolving in methanol (10 mL) three diesters from chemset **1** (0.3 mmol of each diester) and one diamine from chemset **2** (0.3 mmol) or one diester from chemset **1** (0.3 mmol) and three diamines from chemset **2** (0.3 mmol of each diamine).

HPLC and UPLC Analyses. The referenced benzoamides (chemsets **3** and **4**) were synthesized as previously described, and the libraries were analyzed by HPLC on a Bionacom Velocity C18-2 column (4.6 mm × 250 mm, grain size 5 μm) at 25 °C at a flow rate of 1 mL/min with gradient elution (25% → 50% acetonitrile in water in 30 min).[52] To identify all of the macrocyclic hybrid tetraamides (chemset $\mathbf{4}^{hyb}$), the UPLC−MS method was used (MALDI SYNAPT G2-S HDMS (Waters) connected with an Acquity UPLC (Waters) at 25 °C at a flow

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rate of 1.5 mL/min with gradient elution (25% → 50% acetonitrile in water in 30 min).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscombsci.0c00024.

Schematic and photos of the high-pressure equipment and copies of UPLC−MS chromatograms (PDF)

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Author Contributions

The manuscript was written through contributions of all authors. All of the authors approved the final version of the manuscript.

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Notes

The authors declare no competing financial interest.

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