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Chloride-Assisted Peptide Macrocyclization

Nikolina Vidović,[§] Gordan Horvat,[§] Davide Riva, Tamara Rinkovec, Nikola Cindro, Vladislav Tomišić,* and Giovanna Speranza*

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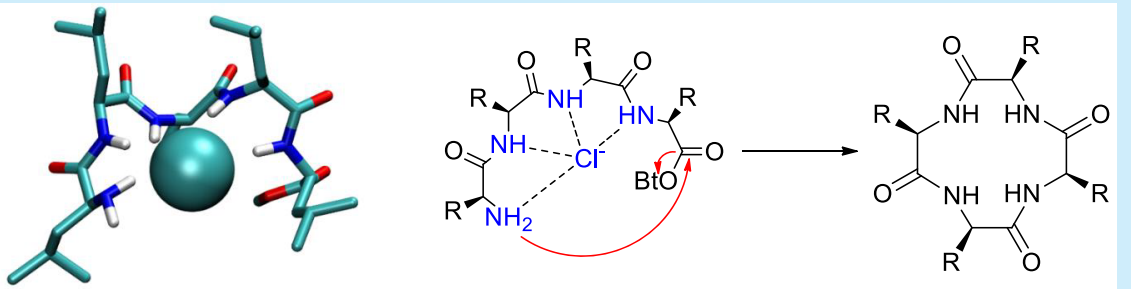

ABSTRACT: The role of the Cl^- anion as a templating agent for the synthesis of cyclopeptides was assessed through the preparation of three new homocyclolysines and other six cyclic peptides by head-to-tail lactamization. Isolated yields of products obtained by chloride-templating approach were considerably higher than those gained by a cation-promoted procedure, whereby, in some cases, only the anion-assisted synthesis yielded the desired cyclopeptides.

Starting from the isolation of the antibiotic gramicidin S, the first biologically active cyclopeptide identified in 1944, cyclic peptides have attracted an increasing interest, because of their unique chemical and biological properties.[1−4] When the polypeptide chain is constrained into a cyclic structure, both reduction of the conformational flexibility and an increased resistance to in vivo enzymatic degradation result. As a consequence, cyclic peptides generally exhibit improved metabolic stability and bioavailability, as well as enhanced binding affinity and selectivity toward receptors, compared to their more-flexible linear analogues. These features make cyclic peptides promising lead compounds for drug discovery and excellent tools for understanding complex biological processes such as protein−protein and generally host−guest interactions.[4,5] So far, beside naturally occurring peptides comprising a cyclic backbone, thousands of cyclic peptides have been prepared via chemical synthesis and many of them are endowed with potent biological activities such as antifungal, antibacterial, antineoplastic, insecticidal, anti-inflammatory, and melanin production inhibitory effects.[2,6]

However, the synthesis of cyclic peptides, especially late-stage cyclization step, continues to represent a significant synthetic challenge, although efforts to develop improved methods for their preparation have grown exponentially in recent years.[1−4,7−10] Regardless of the macrocyclization strategy, the main factor that affects the success of a ring closure reaction is the conformational preorganization, that is the ability of a linear precursor to bring its reactive termini in close spatial proximity.[4,11] A favorable conformation facilitating the intramolecular cyclization process may be achieved by incorporating turn-inducing structural elements along the polypeptide chain[12] and/or by using an external template such as metal ions.[1,4] The latter approach relies on the well-documented capacity of cyclopeptides to act as ionophores binding metal ions in vivo and in solution.[11,13−17] Several examples of metal ion-assisted peptide macrocyclization are known.[4,18−20]

Herein, we report that not only cations but also anions are able to act as directing agents for promoting the cyclization of linear peptides. As a part of a long-term project on supramolecular receptors for cations and anions,[21] we have ventured into the synthesis of functionalized homocyclopeptides, i.e., cyclic peptides with multiple occurrences of a single amino acid residue bearing a substituent on the side chain, which enables the design of receptors with specific binding properties.

To this aim, as a first approach, we prepared tetralysine, pentalysine, and hexalysine (**1**−**3**; see Scheme 1) via the standard solution-phase peptide synthesis, using the orthogonally protected lysine derivatives (CbzHN-Lys(Boc)-COOH and H_2N-Lys(Boc)COOMe) as building blocks, and repeated steps of condensation/deprotection as depicted in Scheme 1.

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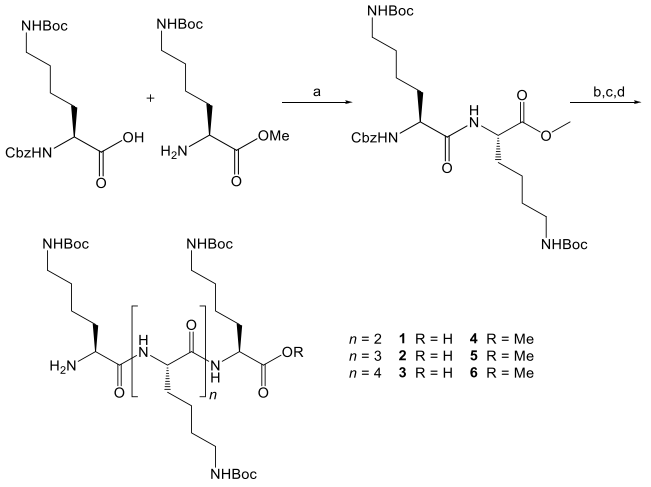
Scheme 1. Synthesis of Compounds 1−6: (a) HOBt, EDCxHCl, TEA, DMF; (b) H_2, Pd/C, EtOH; (c) CbzLys(Boc)-OH, HOBt, EDCxHCl, TEA, DMF; and (d) LiOH and MeOH, Followed by H_2, Pd/C, EtOH[a]



[a]Steps b and c were repeated two, three, and four times for tetralysine (**1**), pentalysine (**2**), and hexalysine (**3**), respectively. To prepare **4**−**6**, methyl ester protecting groups were not removed in step d.

Compounds **1**, **2**, and **3** were submitted to cyclization under the experimental conditions reported by Ye et al.,[18,19] i.e., in highly diluted *N*,*N*-dimethylformamide (DMF) solution (ca. 10^{-4} M) using 3-(diethoxyphosphoryloxy)-1,2,3-benzotriazin-4(3H)-one (DEPBT) as the coupling reagent, triethylamine (TEA) as the base, and LiCl, NaCl, $NaClO_4$, or sodium tetraphenylborate (NaTPB) salts as sources of metal ions to promote head-to-tail lactamization. The corresponding cyclic peptides (**cyclo-1**, **cyclo-2**, and **cyclo-3**) were isolated in poor to modest yields (15%−35%; see Table 1) with no epimerization observable by nuclear magnetic resonance (NMR) spectroscopy.

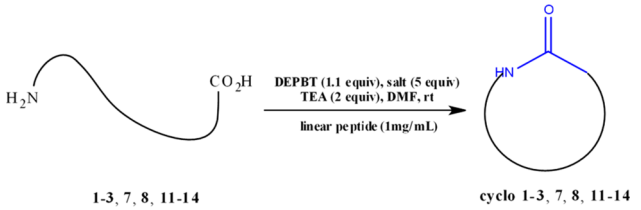
In order to thermodynamically characterize ion-assisted conformational preorganization, we used methyl-ester derivatives **4**−**6** (Scheme 1) as model compounds of peptides **1**−**3**. Complexation affinity of linear peptide derivatives toward Li^+, Na^+, and K^+ cations was investigated by means of microcalorimetric and ^{1}H NMR titrations in DMF.

Unexpectedly, in microcalorimetric titrations of **4**−**6** with $LiClO_4$, $NaClO_4$, and $KClO_4$ no significant heat effect was observed (see Figures S7, S9−S11, and S14 in the Supporting Information), which indicated that no binding occurred or that the complexation reaction was isoenthalpic. Analogous results were obtained when the same experiments were performed on the corresponding derivatives of the linear peptides **7** and **8** (Scheme 2), i.e., the pentaleucine methyl ester (**9**) and Phe-Leu-Leu-Phe-Leu-Leu methyl ester (**10**), both lacking functionalized side chains (see Figures S17−S19, as well as S22−S24 in the Supporting Information for details regarding the synthesis of these substrates).

Low binding abilities of **4**−**6**, **9**, and **10** for Na^+ cations in dimethylformamide (DMF) were also confirmed by ^{1}H NMR titrations. Upon the stepwise addition of sodium perchlorate to a deuterated DMF peptide solutions, no significant change of the chemical shifts of the ligand protons resulted (see Figures S28 and S29 in the Supporting Information).

On the basis of these findings, the question arose as to which species in ion-assisted cyclization by alkali metal in DMF

Table 1. Yields of Cyclization Reaction of the Linear Precursors Assisted by Different Salts



	Yield (%)			
linear peptide[a]	LiCl/NaCl	NaTPB	TEACl	$NaClO_4$
K4 (**1**)	21[b]	8	47	0
K5 (**2**)	35[c]	26	43	0
K6 (**3**)	15[c]	10	17	0
L5 (**7**)		15	52	0
(FLL)$_2$ (**8**)	<5[c]	6	23	<5
I4 (**11**)	<5[b]	<5	18	0
I5 (**12**)	11[c]	<5	26	0
S5 (**13**)	21[c]		29	
F5 (**14**)			46	

[a]For all linear precursors, except **13**, cyclization reactions were performed also in the presence of TEAOAc and without the addition of salts. The presence of cyclic products was not observed in either case. [b]LiCl. [c]NaCl.

actually reacted with the linear precursors, bringing the C-terminus and the N-terminus closer to each other. Taking into account the recently reported chloride-templated synthesis of pseudopeptidic macrocycles,[22,23] the possible role of this anion in promoting the amide-bond formation in the preparation of 12- to 18-membered cyclic peptides (**cyclo-1**−**cyclo-3**) can be envisaged.

To test the hypothesis that the cyclization process is actually promoted by the interaction of the Cl^- anion with the linear precursors, we repeated the synthesis of cyclopeptides from compounds **1**−**3** and prepared six additional cyclic peptides—**cyclo-7**, **cyclo-8**, and **cyclo-11**−**cyclo-14** (for details, see the Supporting Information)—from the corresponding linear precursors **7** and **8** and **11**−**14** (Scheme 2), under the same experimental conditions as described above, and by using various salts (see Table 1) as the sources of the ions assisting the ring closure.

As reported in Table 1, the highest yields of cyclization reactions were obtained in the presence of a strongly coordinating anion (tetraethylammonium chloride, TEACl) and the lowest in the presence of weakly coordinating anions (NaTPB and $NaClO_4$). Between these yields were those obtained when LiCl or NaCl were used. In these cases, the templating effect of the Cl^- anion seems to be less efficient, probably as a result of ion pairing of the anion with its counterion.[24] When cyclization experiments were conducted using pentaphenylalanine (**14**) as a starting material and TEACl, or two other chloride salts containing large inert cations—namely, tetrabutylammonium chloride (TBACl) and benzyltriethylammounium chloride—almost the same yields of the cyclic product (**cyclo-14**) were obtained (see Table S3 in the Supporting Information). Finally, without added salts, or in the presence of tetraethylammonium acetate (TEAOAc), no formation of cyclic products was detected. Data in Table 1 indicate that, for all linear precursors, an improvement in the cyclization yields due to the chloride-templating effect has been observed. Such an increase is remarkable in the case of

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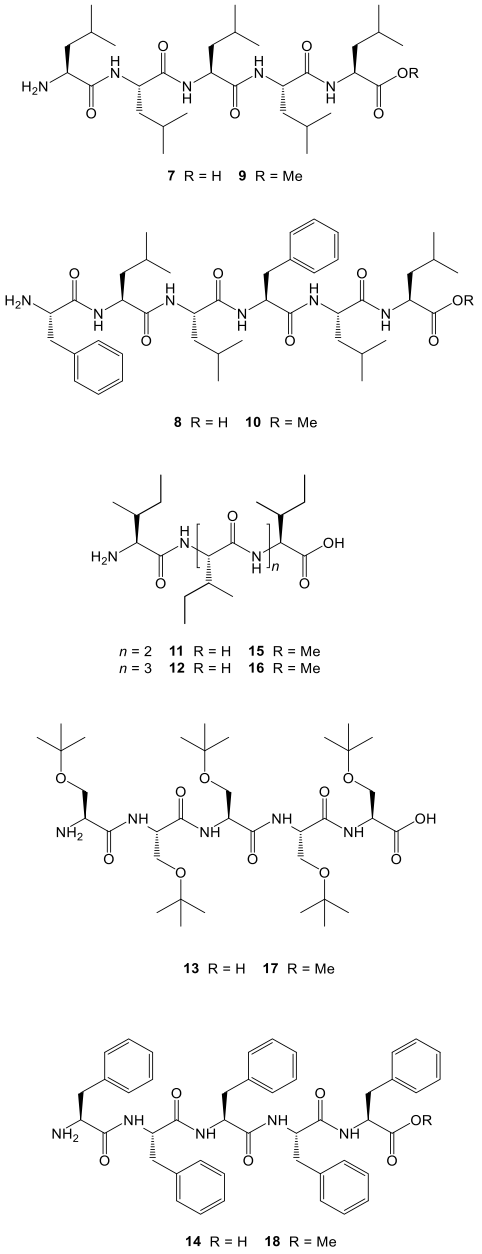
Scheme 2. Structures of Linear Precursors 7, 8, 11−14 and Their Methyl Esters 9, 10, and 15−18



the linear peptides **1** and **7** (from 8% to 47% and from 15% to 52%, going from NaTPB to TEACl, respectively), and somewhat lower but still significant in the case of the remaining substrates. That can be considered as particularly important, taking into account that cyclic tetrapeptides and pentapeptides are generally difficult to prepare and that sequences rich in Lys(Boc) are troublesome to cyclize.[12,25] The highest yield (52%) was observed for **cyclo-7**. This value is far greater than that recently reported[26] (3%) for a head-to-tail macrocyclization of pentaleucine (**7**) in the absence of any ion template.

Among all coupling systems tested (see Table S2 in the Supporting Information), DEPBT, which is a reagent frequently selected to avoid racemization,[27] showed far better results, in terms of the reaction yield. However, it is worth noting that no cyclization occurs with DEPBT in the absence of salt additives (Table S1 in the Supporting Information), thus suggesting the crucial role of the salt-induced preorganization for the successful cyclization of linear peptides.

No detectable NMR signal splitting, indicative of epimerization, in any of recorded spectra was observed. Cyclopeptides bearing amino acids with compact residues showed C_n symmetry (see Figures S37−S44, S55, and S56 in the Supporting Information), which was expected, whereas complex proton spectra were observed for peptides having bulky side chains such as **cyclo-11−cyclo-13**.[28,29] These spectra also showed significant temperature and solvent dependences (Figure S52 and S54 in the Supporting Information), which could be explained by slow interconversion between nonsymmetrical conformers.[28]

The affinity of linear peptide methyl-ester derivatives **4−6**, **9**, **10**, and **18** toward the Cl^- anion was investigated by microcalorimetric titrations in DMF using TEACl. During calorimetric experiments, the addition of TEACl to the peptide solution resulted in the data (see Figure 1, as well as Figures S6, S13, S16, S21, and S26 in the Supporting Information) from which the stability constants and complexation reaction enthalpies and entropies were derived (see Table 2). The

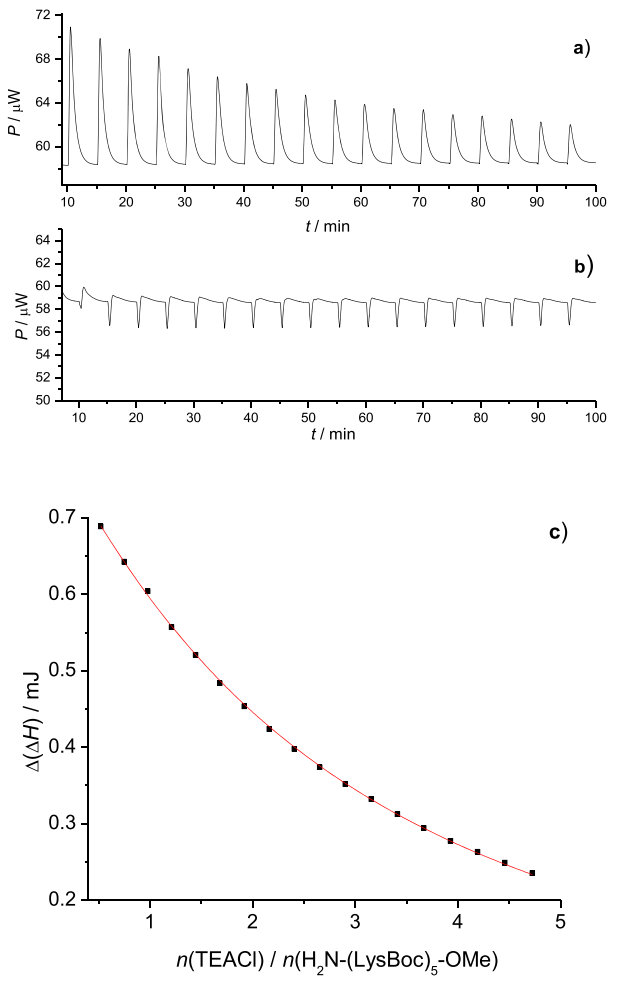


Figure 1. (a) Microcalorimetric titration of H_2N-$(LysBoc)_5$-OMe (**5**) (c = 4.90 × 10^{-3} M) with TEACl (c = 0.1027 M) in DMF in the presence of $TBAClO_4$ (c = 0.0498 M) at θ = 25 °C; (b) microcalorimetric titration of $TBAClO_4$ (c = 0.0498 M) with TEACl (c = 0.1027 M) in DMF at θ = 25 °C; and (c) dependence of successive enthalpy change on $n(Cl^-)/n(H_2N$-$(LysBoc)_5$-OMe (**5**)) ratio. [Legend: (■) measured values and (—) calculated values.]

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Table 2. Thermodynamic Parameters for Complexation of Linear Peptides with Chloride Anions in DMF at 25 °C Determined by Microcalorimetric and ^{1}H NMR Titrations[a]

peptide	log K ± SE[b]	$\Delta_r G°$ ± SE (kJ mol^{-1})	$\Delta_r H°$ ± SE (kJ mol^{-1})	$\Delta_r S°$ ± SE (J K^{-1} mol^{-1})
H_2N-(LysBoc)$_4$-OMe (**4**)	1.51 ± 0.01	−8.61 ± 0.05	2.50 ± 0.09	37.3 ± 0.2
	1.05 ± 0.01[c]	−5.99 ± 0.06		
H_2N-(LysBoc)$_5$-OMe (**5**)	1.47 ± 0.07	−8.4 ± 0.4	4.4 ± 0.9	43 ± 2
	1.26 ± 0.05[c]	−7.2 ± 0.3		
H2N-(LysBoc)$_6$-OMe (**6**)	1.68 ± 0.03	−9.6 ± 0.2	2.8 ± 0.3	41.7 ± 0.4
	1.74 ± 0.06[c]	−9.9 ± 0.3		
H_2N-(Leu)$_5$-OMe (**9**)	1.459 ± 0.008	−8.33 ± 0.05	6.2 ± 0.1	48.7 ± 0.3
	2.12 ± 0.04[c]	−12.1 ± 0.2		
H_2N-(PheLeuLeu)$_2$-OMe (**10**)	2.06 ± 0.03	−11.8 ± 0.2	1.9 ± 0.2	46.0 ± 0.1
	1.89 ± 0.02[c]	−10.8 ± 0.1		
H_2N-(Phe)$_5$-OMe (**18**)	1.54 ± 0.04	−8.8 ± 0.3	2.5 ± 0.2	37.6 ± 0.2

[a]SE = standard error of the mean (N = 3). [b]K is given in units M^{-1}. [c]Obtained by ^{1}H NMR titrations.

corresponding log K values were in the range of 1.5−2.1, indicating that all ligands had similar affinities toward the Cl^- anion. All reactions were slightly endothermic and entropy-driven, most probably because of the entropically favorable anion desolvation upon its coordination by the backbone amide groups.

The binding of the Cl^- anion was also observed in ^{1}H NMR titrations of peptide ligands **4**−**6**, **9**, and **10** with TEACl in DMF-d_7, where significant downfield shifts of amide NH and α-protons occurred after the addition of chloride solution (see Figure 2, as well as Figures S30−S33 in the Supporting Information). From the recorded ^{1}H NMR spectra, the stability constant of peptide-chloride complexes were determined and agreed very well with those obtained via microcalorimetry (see Table 2).

NMR analysis clearly showed that the conformational preorganization of linear precursors occurred upon the addition of chloride salt. The addition of TEACl resulted in the NOE signals of amide protons of pentaphenylalanine methyl ester (**18**) showing interactions with each other and indicating that these groups were in close proximity upon the chloride binding (see Figure S58 in the Supporting Information).

Note that the cyclization processes proceeded even in the presence of bulky anions, such as tetraphenylborate (Table 1), but with much lower yields, compared to those performed via the addition of TEACl. That could be tentatively explained by taking into account that interactions of linear peptide H_2N−(LysBoc)$_5$−OMe (**5**) and TPB was (surprisingly) observed in the course of the corresponding NMR titration (see Figure S34 in the Supporting Information), although the shifts of the proton signals were much smaller than in the case of the titration with TEACl. That indicated weak, but still existing, interaction of tetraphenylborate with the linear peptide, which could lead to the formation of the cyclic product.

An additional indication that the Cl^- ion plays a key role in the ring closure reactions (Scheme 3) came from the study of the corresponding macrocyclization reaction kinetics. Cyclization experiments of pentaphenylalanine (**14**) were performed using an increasing concentration of TEACl (from 2 equiv to 100 equiv). Higher concentration of TEACl caused faster macrocyclization reaction and its larger final yield, as evidenced by both quantitative ^{1}H NMR and TLC analysis (see Figure 3, as well as Figures S2−S5 in the Supporting Information). Moreover, the reaction was performed in the presence of $AgClO_4$ to sequester chlorides, whereby that equimolar

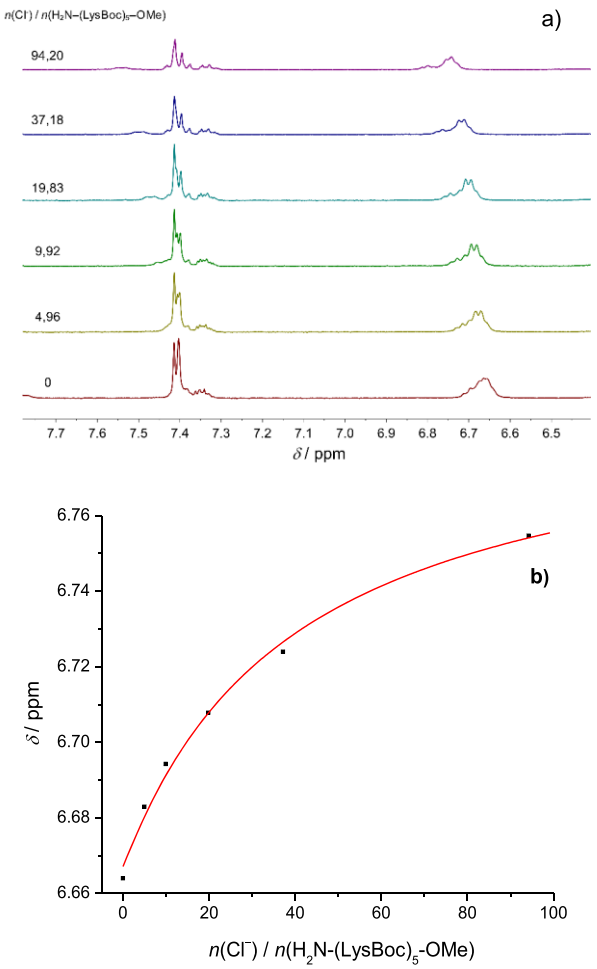

Figure 2. (a) ^{1}H NMR titration of H_2N-(LysBoc)$_5$-OMe (**5**) (c = 1.16 × 10^{-3} M) with TEACl (c = 0.287 M) in DMF−d$_7$ at θ = 25 °C; and (b) dependence of chemical shift of protons on $n(Cl^-)/n(H_2N$-(LysBoc)$_5$-OMe (**5**)) ratio. [Legend: (■) measured values and (—) calculated values.]

amount of this salt, with respect to chlorides, was added to the reaction mixture 4 h after mixing of the reactants. Indeed, a substantial reduction of the reaction rate was observed, which can be clearly seen in Figure S1 in the Supporting Information.

Moreover, the templating effect of halides other than chloride was investigated. A significant decrease of the reaction

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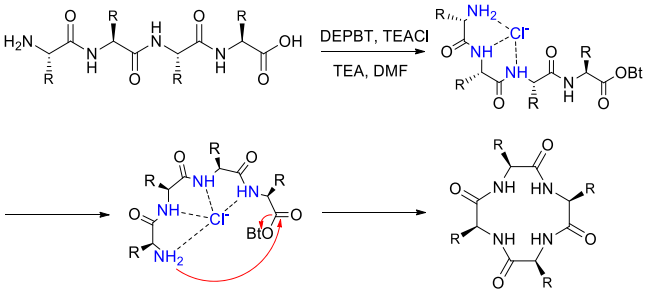
Scheme 3. Proposed Mechanism of the Anion-Assisted Macrocyclization of Peptides



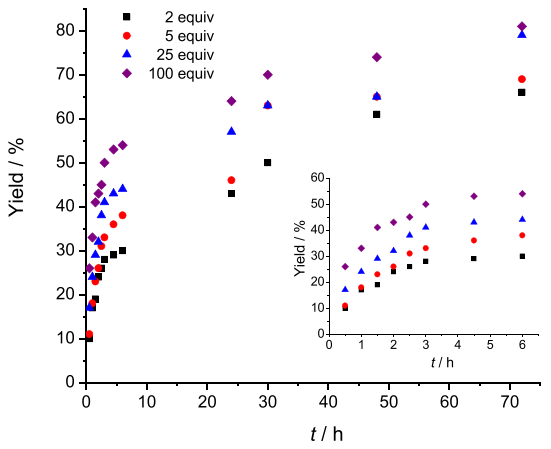


Figure 3. Kinetics of cyclization of compound **14** (1.40×10^{-3} M) in the presence of DEPBT coupling reagent (1.54×10^{-3} M) and TEACl in DMF. The inset shows kinetic traces recorded during the first 6 h after mixing of the reactants.

yield of **cyclo-14** formation was observed going from TBACl (74%) to TBABr (21%) and TBAI (5%) by quantitative TLC analysis (see Table S3 in the Supporting Information). Such a templating effect ($Cl^- > Br^- > I^-$) was in agreement with the results reported for the preparation of pseudopeptidic macrocycles.[23]

Structural characterization of chloride-peptide complexes of ligands **4**–**6**, **9**, and **10** was also performed via molecular dynamics (MD) simulations with explicit solvent molecules. In these simulations, it was found that the Cl^- ion was coordinated by all backbone amide groups and *N*-terminal amine group of the peptides (Table S4 in the Supporting Information), which was experimentally corroborated by the NOE interactions of amide protons in chloride complexes of compound **18** (see Figure S58 in the Supporting Information). Such binding resulted in the cyclic conformation of the linear peptide adequate for the subsequent cyclization reaction (see Figure 4, as well as Figures S35 and S36 in the Supporting Information). In the course of the MD simulations of the ligands with bound Na^+ cations, complex dissociation was observed in all cases. This indicated that the binding of the Na^+ cation by the peptides was weak or nonexistent, which was in agreement with the experimental results.

The above findings suggest that (i) Cl^- ions are directly involved in peptide folding (Scheme 3) and (ii) the mechanism of head-to-tail cyclization suggested by Ye et al.[18] should be at least partially revised.

To conclude, head-to-tail macrocyclizations of three homolysines (**1**–**3**) and six other peptides (**7**, **8**, **11**–**14**),

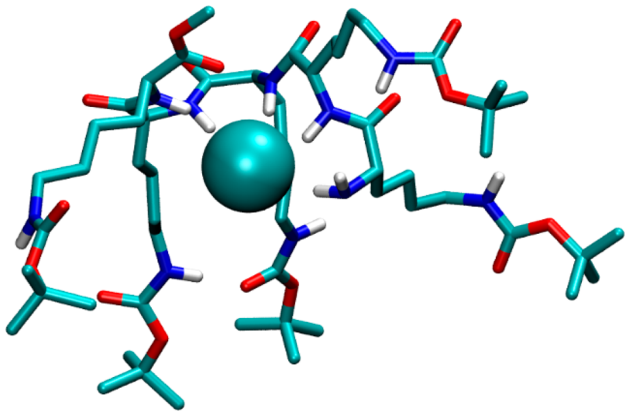


Figure 4. Structure of H_2N-Lys(Boc)$_5$-OMe (**5**)-Cl^- complex obtained by MD simulation in DMF. Carbon-bound hydrogen atoms are omitted for the sake of clarity.

performed in the presence of different salts (LiCl, NaCl, NaTPB, $NaClO_4$, TEACl, TEAOAc), suggested a role of the Cl^- anion in the conformational preorganization of reactive ends of the linear precursors. Complexation of methyl-ester derivatives (**4**–**6**, **9**, and **10**) with different cations and the Cl^- anion was studied by microcalorimetric and NMR titrations, indicating a high affinity of the compounds studied toward the Cl^- ion. These findings were strengthened by the results of MD simulations. Although anion recognition by cyclopeptides is well-documented[30] and several examples of the use of anions as directing agents for the synthesis of a wide range of inorganic and organic assemblies are known,[31] to the best of our knowledge, no example of anion-templated synthesis of cyclopeptides has been reported so far. Using this approach, in the present work, nine cyclopeptides—three of them being Boc-protected homolysines—were obtained in moderate to high yields.

Work is underway to gain more-detailed insights into the role of cations/anions in affecting the ring closure of linear peptides.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c00036.

Experimental procedures (synthesis and physicochemical measurements); NMR, HRMS, and IR spectra; ITC and ^{1}H NMR titrations data; results of molecular dynamics simulations (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

Giovanna Speranza − *Dipartimento di Chimica, Università degli Studi di Milano, 20133 Milano, Italy*; Email: giovanna.speranza@unimi.it

Vladislav Tomišić − *Department of Chemistry, Faculty of Science, University of Zagreb, 10000 Zagreb, Croatia*; orcid.org/0000-0002-1191-2123; Email: vtomisic@chem.pmf.hr

Authors

Nikolina Vidović − *Dipartimento di Chimica, Università degli Studi di Milano, 20133 Milano, Italy*

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Gordan Horvat − *Department of Chemistry, Faculty of Science, University of Zagreb, 10000 Zagreb, Croatia*
Davide Riva − *Dipartimento di Chimica, Università degli Studi di Milano, 20133 Milano, Italy*
Tamara Rinkovec − *Department of Chemistry, Faculty of Science, University of Zagreb, 10000 Zagreb, Croatia*
Nikola Cindro − *Department of Chemistry, Faculty of Science, University of Zagreb, 10000 Zagreb, Croatia*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.0c00036

Author Contributions

[§]These authors contributed equally.

Notes

The authors declare no competing financial interest.

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