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Complete List of Authors:	Kanagaraj, Kuppusamy; Shanghai University, College of Chemistry Wang, Rui; Shanghai University Zhao, Ming-Kai; Shanghai University Ballester, Pablo; ICREA, Rebek, Jr., Julius; Scripps Research Institute, The Skaggs Institute for Chemical Biology Yu, Yang; Shanghai University, Chemistry

Selective Binding and Isomerization of Oximes in a Self-assembled Capsule

Kuppusamy Kanagaraj,[1] Rui Wang,[1] Ming-Kai Zhao,[1] Pablo Ballester,[3] Julius Rebek, Jr.,[1,2] Yang Yu*,[1]

[1] Center for Supramolecular Chemistry & Catalysis and Department of Chemistry, College of Science, Shanghai University, Shanghai 200444, China.

[2] Skaggs Institute for Chemical Biology and Department of Chemistry, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, CA 92037, USA

[3] Institute of Chemical Research of Catalonia (ICIQ), The Barcelona Institute of Science and Technology (BIST), 43007 Tarragona, Spain; Catalan Institution for Research and Advanced Studies (ICREA), 08010 Barcelona, Spain

KEYWORDS: Capsules, Induced isomerization, Binding selectivity, Oxime isomerization.

ABSTRACT: A series of straight-chain (C7-C13) alkyl-*O*-methyl aldoximes (R-C(H)=NOMe) were synthesized with various functional groups at the remote ends (alkenes, halogen, -COOH and NH_2). Their isomers about the C=N bond showed ~ 60-40 % *E-Z* ratio in organic solutions. Surprisingly, their confinement in a water-soluble capsule with benzoselenodiazole walls shows high selectivity for the *cis*- / *Z*-isomer. Their relative affinities for the chalcogen-bonded capsule at room temperature depends mainly on the guest chain length and functional groups. A chain length of 14 heavy atoms showed especially high *E or Z*-isomers (>99%) selective separation using water-soluble capsule. *E-Z* isomerization has occurred only in the capsular cavity at room temperature, and has accelerated in 10 orders by sonication. The proposed unprecedented *Z*-isomer selective binding, separation and *E-Z* isomerization are supported by NMR, DOSY and computational studies.

Container compounds provide unique environments and unconventional pathways for chemical processes involving confined small molecules.[1-9] The constrained, finite volumes and shapes inside the container hosts differ starkly from the practically infinite spaces in the bulk solution outside. Water-soluble container hosts such as cavitands and capsules offer additional extremes to potential guests: they present guests with aromatic-lined, hydrophobic interiors and polar, hydrophilic environments in the solvent. The contrasts are likely to give flexible guests choices between different arrangements in space - conformations - in the two environments. Conformational isomerization of molecules can be triggered by thermal, chemical, or photochemical energy[4-9,10] and earlier we used the constraints of a hydrogen-bonded capsule in organic media to alter ring-chain isomerization of guests.[11,12,13,14] Here, we present the effects of confinement on oxime ethers in a chalcogen bonded, water-soluble capsule. The capsule is used to shift equilibria between *E* and *Z* isomers and assist their separation under mild conditions.

We recently prepared and characterized[15] the water-soluble cavitand, **Se** (Figure 1). Like the corresponding sulfide and telluride congeners introduced by Diederich,[16] the **Se** cavitand can engage in dimerization to **Se•Se**, driven by the self-complementary arrangement for chalcogen bonding of the benzoselenodiazole units on the rim and the filling of space. Guests of various lengths can form complexes, either as the cavitand (**Se**:guest) or capsule (**Se•Se**:guest).[15] Suitably functionalized cavitands are known to dimerize to capsules *via* H-bonding,[13] halogen bonding,[14] or chalcogen bonding (Figure 1) when appropriate guests are available.[15,16]

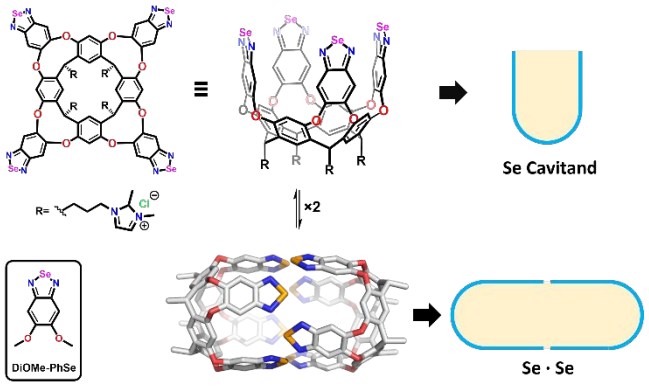
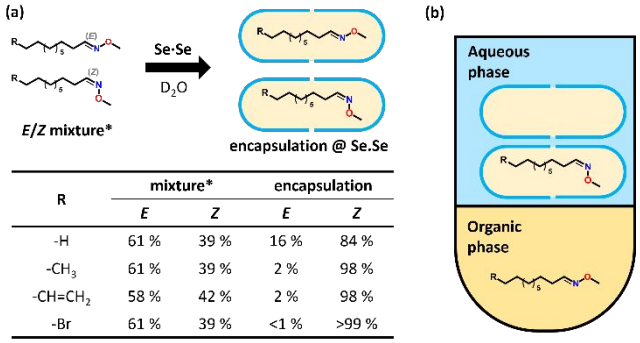


Figure 1. Cavitand **Se** self-assembled to capsule **Se•Se** through chalcogen bonding. (Top) Structure of cavitand **Se** and its cartoon representation. (Bottom) crystal structure and cartoon representation of capsule **Se•Se**. Hydrogen atoms and alkyl chains are omitted for clarity. Structure of **DiOMe-PhSe** used as a control.

The **C=N** bonds of imines and oximes typically exist as geometrical isomers *Z*-/*Cis*-/*Syn*- and *E*-/*Trans*-/*Anti*-.[17,18] The isomers of imines interconvert quite rapidly at RT whereas oximes (**NOH**) and oxime ethers (**NOMe**) are more stable and undergo isomerization with catalysts (Bronsted or Lewis acids, metal ions, *etc.*), and thermal or photochemical interventions.[19-21] The *E*/*Z* isomers of **NOMe** have different physical and chemical properties and play important roles in biological processes.[22] Further, separation of *E*/*Z*-isomer of oximes ethers with the highly substituted aryl groups was possible using simple chromatographic techniques, whereas more sophisticated instruments are required for alkyl oxime ethers.[19-22]



R	mixture*		encapsulation	
	E	*Z*	*E*	*Z*
-H	61 %	39 %	16 %	84 %
-CH_3	61 %	39 %	2 %	98 %
-$CH{=}CH_2$	58 %	42 %	2 %	98 %
-Br	61 %	39 %	<1 %	>99 %

Figure 2. (a) Selective encapsulation of oxime ethers by the **Se** cavitand. The encapsulations were carried out with the guests (0.5 equiv. as mixtures of *Z* and *E*-alkyl-*O*-methyl oximes in CD_3CN) and **Se** (1 mM in D_2O). The ratios of guest isomers in the **Se•Se** capsule were determined by ^1H NMR (600 MHz, 298 K). (b) Simple separation of *Z*- and *E*-isomers of oxime ethers by selective encapsulation. The separations were carried out with the guests (1.0 equiv. as mixtures of *Z* and *E*-alkyl-*O*-methyl oximes in CD_3CN) and **Se** (1 mM in D_2O). *mixture of isomers in organic solvent.

Binding, *Z*-isomer selectivity and separation of alkyl oxime ethers

Alkyl aldehyde **NOMe** derivatives with various remote functions were synthesized from the corresponding alkyl alcohols through sequential reactions steps of oxidation to the aldehydes followed oximation (See SI for details). The oximes were obtained as a mixture of *Z*- (~40%) and *E*- (~60%) isomers and characterized by ^1H and ^{13}C NMR and HRMS analysis (see Table S1, Figures 2, S4-S72). Addition of **C10NOMe** or **C11NOMe** (0.5 equiv., 60 mM in CD_3CN) containing 39% of *Z*-isomer and 61% of *E*-isomer to the **Se** cavitand in D_2O (1 mM), was followed by sonication (7h, See SI, Section 1.4). The encapsulation complexes were evaluated by ^1H NMR: *Z*/*E*- @ **Se•Se** 98% / 2% for **C11NOMe** and 84% / 16% for **C10NOMe**, by integration of the upfield-shifted signals in NMR spectra (Figures 2, 3 and S76, S77). However, alkyl-*O*-methyl oximes with different chain lengths, **(C7-C13)NOMe** and *Z*/*E* ratios gave a chain length-dependent *Z*-isomer selectivity in **Se•Se** (Table S1, Figures S76 and S77). Oximes of 14 C,N,O-atom length (**C11NOMe**) gave the highest *Z*-isomer selectivity for the **Se•Se** capsule.

The selective encapsulation of the *Z*-isomer oxime ethers was confirmed by the binding study of *Z*- and *E*-**C11NOMe** separately (Figures S89-S91) and COSY studies (Figures S92). Complexes **C11NOMe@Se•Se** were characterized by integration of the host methine protons and guest protons (Figures S90 and S91), calculated chemical shifts (Figures S93 and S94). We used diffusion-ordered NMR spectroscopy (DOSY) measurements (Figures S100 and S101) to show that the **Se** cavitand binds **NOMe** guests to form capsules in aqueous medium. The previously reported capsule complex **4,4'-dimethybiphenyl@Se•Se**, was used as an internal standard. When mixed with **C11NOMe@ Se•Se**, the complexes showed similar diffusion co-efficients and kinetic stabilities (Figure S101).[15]

The chemical shifts and the structures of the **NOMe** guests in the **Se•Se** cavity were predicted from the initial peak assigned to *E*/*Z*-isomers from ^1H-^1H COSY spectrum (Figures S86 and S92). Calculated upfield shifts (-Δδ ppm) of **NOMe@Se•Se** capsule complex are given in Scheme 1a and Figures S87, S88, S93, S94, S98 and S99. In the **Se•Se** cavity, the predominant *Z*-isomer showed smaller -Δδ value than *E*-isomer, because the OCH_3 groups of **NOMe** guests interacted differently with aromatic panels/walls of **Se**. Interestingly, the central (-CH_2-) units of the alkyl chain inside **NOMe@Se•Se** showed large induced shifts (-Δδ) due to their location near the polarizable, chalcogen atoms in the middle of the capsule.

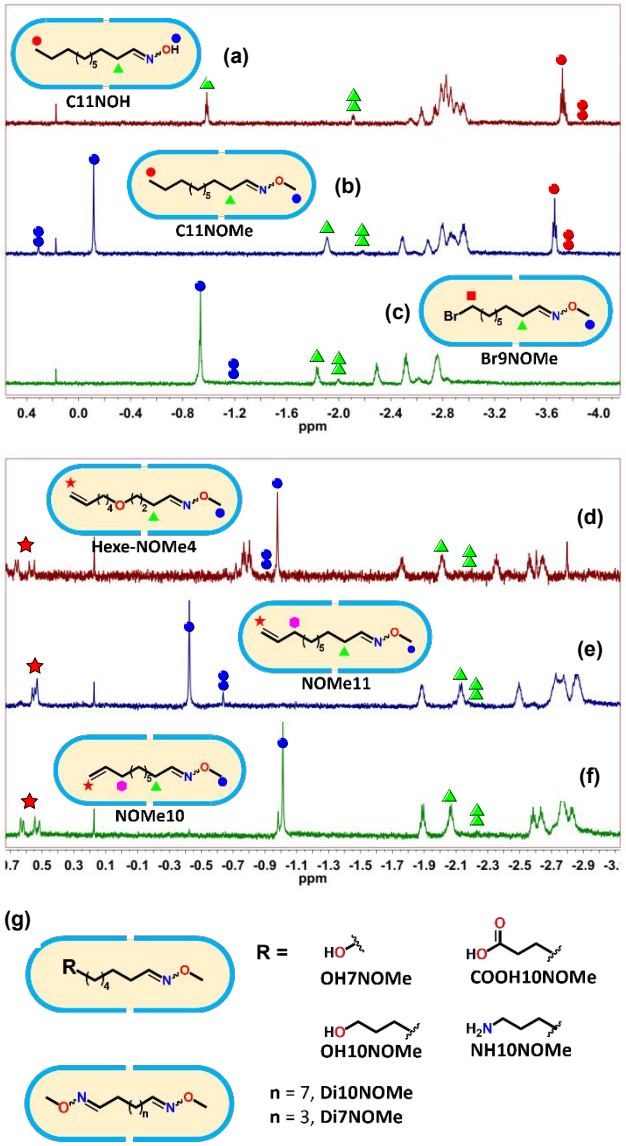
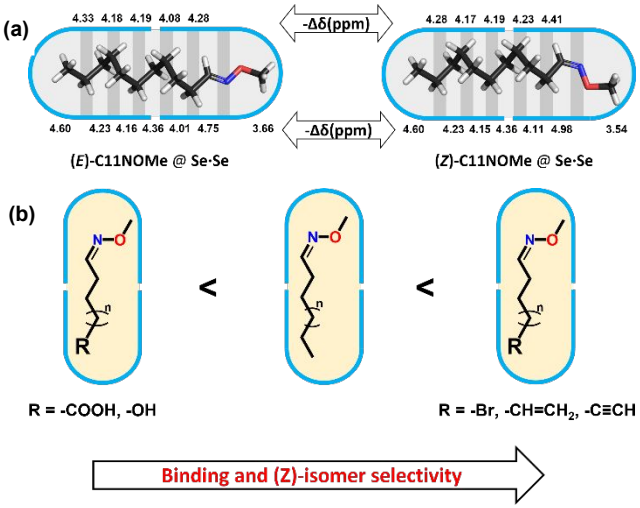


Figure 3. Comparison of upfield portions of the ^1H NMR spectra of functional alkyl-*O*-methyl oximes guests in **Se•Se** (600 MHz, 25 °C) and its cartoon representation. (a) **C11NOH**, (b) **C11NOMe**, (c) **Br9NOMe**, (d) **Hexe-NOMe4**, (e) **NOMe11**, (f) **NOMe10**, and (g) cartoon representation of the binding modes and/or patterns of functional oximes guests in **Se•Se**. The **Se** cavitand (1 mM in D_2O) were mixed with **R-NOMe** derivatives (0.5 equiv. in CD_3CN). The ratios were determined by ^1H NMR integration (600 MHz, 298 K). The NMR signals of bound *Z* and *E*-isomers has noted in spectra with the respective symbols of single and double marks respectively.

The study was extended to the effects of functional groups (alkenes and halides) remote from the **NOMe** termini (Figure 2). The *Z*-isomer selectivity of the alkene derivative, **C11NOMe** was 98% and the **BrC9NOMe** derivative was 99% in the **@Se•Se** capsule. The selectivity may involve attractive

interactions, like π-π and halogen-π interactions,[20] or merely reflect more crowding with the rigid terminal alkene or the larger bromide.

We also examined variations in guests. The "-*O*-" heteroatom at the middle of the alkyl chain in **Hexe-NOMe4** (Figure 3) shows 89% of *Z*-isomer in the **Se•Se** capsule. Guests with terminal hydrophilic groups like -OH, -COOH and -NH_2 (**OH10NOMe, OH7NOMe, COOH10NOMe** and **NH10NOMe**) showed only weak binding to the **Se•Se** capsule or exchanged rapidly (Figures S82, S83, S84, and S85). However, the simple oxime, (**C11NOH**) shows good binding with a *Z*-isomer selectivity of 77% inside the **Se•Se** capsule complex (Figures 3a, S78, and S79). **Bis-NOMe** functional derivatives, **Di7NOMe** and **Di10NOMe** showed moderate binding with upfield- shifted signals in their ^{1}H NMR spectra (Figures S82 and S83). The roles played by the remote functions and the *Z*-isomer selectivity for the **Se•Se** capsule are summarized in Scheme 1.



Scheme 1. (a) Cartoon representations of **Se•Se**: *E*/*Z*-**C11NOMe**, 2:1 capsular complexes in D_2O; the chemical shifts of *E*/*Z*-**C11NOMe** (D_2O, 600 MHz, 298 K) and the upfield shifts (-Δδ) calculated from bound signals and "free guest" in D_2O. (b) Cartoon representation for alkyl-*O*-methyl oxime derivatives (14 atoms) @ **Se•Se** in D_2O, and the relative binding and *Z*-isomer selectivity of remote functions.

The preferred encapsulation of the *Z*-isomer oxime ethers was confirmed by adding the various equivalents (0.25-2.5 equiv. with respect to [**Se•Se**]) of *E*/*Z*-**C11NOMe** (Figures S151-S152) and NMR determination of these isomers (Figures S149-S150). The *Z*-Isomer has a higher affinity (K_A, 1.3 x 10^3 M^{-1}) than the *E*-isomer (0.88 x 10^3 M^{-1}) but is weaker than the alkyl guest **C11** (Scheme S6 and Figures S107-S110). Both isomers are taken in by the cavitand but the *Z* isomer is rapidly capped by a second cavitand to form a capsule. This leaves the *E* isomer free and it can be extracted from the mixture with $CDCl_3$.

The *Z*-isomers of alkyl-*O*-methyl oximes have higher affinity for the capsule than the *E*-isomers, which provides a simple means of separation: simple extraction by $CDCl_3$ removes the uncomplexed *E*-isomer (Figures 2b and 4a). Then removing the D_2O followed by EtOAc extraction or addition of the linear alkyl guest **C11** followed by $CDCl_3$ releases the *Z*-isomer (Figures S153-S154 and S140-S141). The *Z*-isomer selectivity for other **NOMe** derivatives was studied and quantified by NMR before and after extraction (Table S1). The recovered **Se** could be used through more than 6 recycles (Table S1).

E-Z isomerization by water-soluble capsule

We observed that binding occurs rapidly upon mixing of **Se** and **NOMe** derivatives, preferentially complexing the *Z*-isomer rather than *E*-isomer (Figures S151-S152). The *E*-complex is also formed along with the *Z*-complex, but in lesser amounts than it appears in the bulk solution (Figures S151-S152 and S98-S99), *so isomerization must occur.* The less stable *E*-complex (more strained form) might be converted to the *Z*-complex in the constrained hydrophobic environment. That is, the isomerization may be mediated by **Se** or **Se•Se**. Or the isomerization could take place in free solution and the host takes up the *Z*-isomer selectively.

Various control experiments were undertaken. Initially, the *E*/*Z*-ratio and isomerization of **C11NOMe** was studied in $CDCl_3$ as a function of temperature (Figure S102). The *E*/*Z*-ratio of the **NOMe** derivatives in organic solvents under the complexation reaction conditions was independent of temperature (298-328 K). VT-NMR studies of the @**Se•Se** complexes in D_2O solution showed that the *E*/*Z*-ratio is stable from 298-368 K (Figures S103 and S104). Peak broadening indicated that complexation and de-complexation of the guest occurs at higher temperatures.

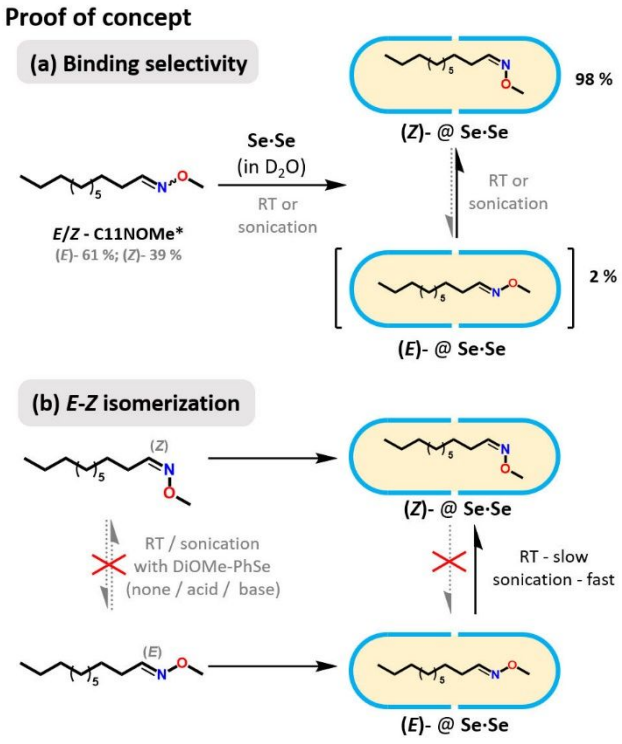


Figure 4. Cartoon representation for proof of concept for separations (a) Selective encapsulation of *E*/*Z*-oxime ether mixtures by the **Se•Se**, (b) Binding of pure *E* and *Z*-oxime ether by the **Se•Se**, and mediated *E*-*Z* isomerization. *mixture of *E* and *Z*-isomers.

Control compound **DiOMe-PhSe** was synthesized and characterized by ^{1}H and ^{13}C NMR and HRMS (Scheme S3,

Figures S50, S51 and S52). Isomerization of *E*/*Z*-**C11NOMe** with **DiOMe-PhSe** was studied (along with additives like catalytic amounts of D_2O, acid, base, *etc.,*) under the various conditions in DMSO-d_6 under sonication or RT at different time intervals (Figures S142-S148). The ratio of *E/Z* was not altered and confirmed that the hydrophobic cavity with the fixed size and shape is responsible for this *E-Z* selective isomerization.

Given these results and the behavior of **DiOMe-PhSe @***E*/*Z*-**C11NOMe**, we tried other competition studies (Scheme S6, and Figures S105-S112). Typical alkane guests of chain length **C8-C14** are bound with **Se** and form capsular complex (Figures S74 and S75). However, **C11** was selectively captured by **Se** from a mixture containing **C11**, **C11NOMe**, and **C12NOMe** (Scheme S6, and Figures S105-S112). After sonication of the above mixture, *E*/*Z* ratio (free **NOMe** derivatives in aqueous medium) was not altered. Further, **NOMe** derivative containing 14 atoms in their chain length showed better binding in the cavity of **Se•Se** than those with longer or shorter lengths (Scheme S7, Figure S105 and S106). Isomerization of *E-Z* or *Z-E* of **C11NOMe** did not occur using **Se•Se@C11** either with or without sonication in D_2O at RT (Scheme S8 and Figures S136-S139) as confirmed by extraction experiments (Figures S140-S141).

The *Z*-isomer of **C11NOMe** (>1 equiv.) shows selective and strong binding towards **Se•Se** of 98%, while the less stable *E*-isomer complex is formed in about 2% (Figures 3b, 4a, and S151-152). The capsule complex distribution varies on immediate mixing with respect to different ratios of H and G (Figures S97-S98 and S151-S152). We found *E-Z* isomerization occurred only in the capsular cavity of **Se** with and without sonication in D_2O at RT (Figures S130-S133). The rate of *E-Z* isomerization is accelerated by the sonication compared with RT (Figures S134-S135). With increased time, the complexed *E*-isomer converts to the more stable *Z*-isomer in the capsule.

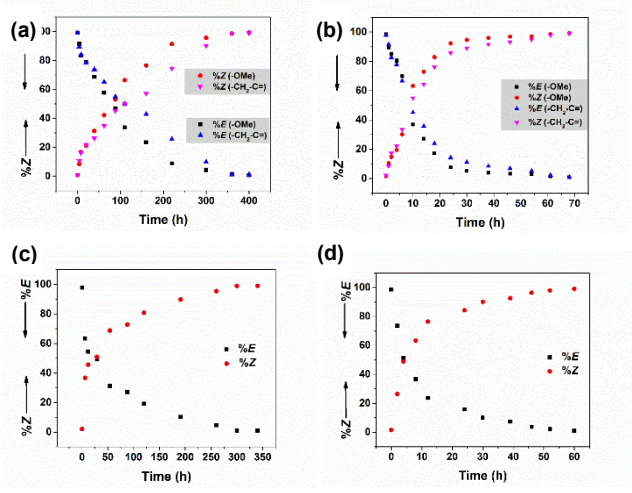


Figure 5. Representative *E-Z* isomerization kinetic data of (a) and (b) **C11NOMe** and (c) and (d) **Br9NOMe** mediated by **Se•Se** in D_2O, (a) and (c) at RT, (b) and (d) under sonication at RT. A marked acceleration of *Z*-isomer (red circle for –OMe signal, magenta triangles for $–CH_2–C=$ signal), and decrease of the *E*-isomer (black squares for –OMe signal, blue triangles for $–CH_2–C=$ signal) was calculated from the up-field shifted signals in ^1H NMR. The isomerization were carried out with the *E*-oxime guests (in CD_3CN, 0.5 equiv.) and **Se** (1 mM in D_2O).

The *E-Z* isomerization (and *vice versa*) of **C11NOMe** was studied in the capsular cavity with and without sonication in D_2O at RT (Figures 5, and S113-S129). Representative *E-Z* isomerization results of **C11NOMe** and **Br9NOMe** are given in Figure 5. The *Z*-isomer does not revert to the *E*-isomer (Figures S115-S116, S119-S120, S123-S124 and S127-S128), whereas *E*-isomer isomerizes to *Z*-isomer (Figures S113-S114, S117-S118, S121-S122 and S125-S126). The confined hydrophobic capsular cavity of **Se•Se**, strongly influences the *E-Z* isomerization at RT and the sonication accelerated the rate 8-10 fold. The *E* isomer goes into the cavitand and is rapidly capped when the chain coils. Then, on prolonged sonication, the isomerization to the (shorter) *Z* isomer occurs to relieve some gauche interactions along the chain (complexation→ alkyl chain coiling → relieve some gauche interactions → isomerization). The *E-Z* isomerization has a calculated half-life of 2-3 hours (Figures 5 and S129). **Br9NOMe** shows faster *E-Z* isomerization than the **C11NOMe** derivative, perhaps due to additional interactions with the capsular environment (Figure 5 and S129).[20]

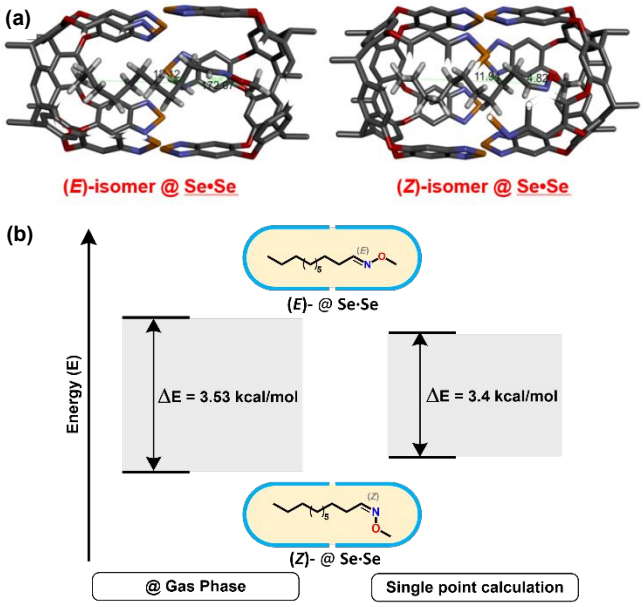


Figure 6. (a) DFT optimized structure (BP86-D3bj dev2SVP level) of ***E*/*Z*-C11NOMe** @ **Se•Se** and (b) the energy levels, and interfacial plots of the proposed complexes.

Computational studies were undertaken to confirm the binding selectivity for the *Z*-isomer, **C11NOMe** and the *E-Z* isomerization mediated by **Se** capsule. At the DFT level of theory (BP86-D3bj dev2SVP) the encapsulation complex of the *Z*-isomer @ **Se•Se** is energetically more favorable by 3.4-3.5 kcal/mol (single point and in the gas phase) Figure 6.

The studies confirmed that, the **Se•Se** cavity binds *Z*-isomer **NOMe** guests of 14 atoms length (**C11NOMe**) with high selectivity (Figure 4a). Further, this study provides the evidence for a conformational restriction, stability of *E*/*Z*-**NOMe** isomers within the **Se•Se** capsule that drive this *Z*-isomer selectivity. The bound *Z*-isomer is favored suggesting that the complex of the *E*-isomer is destabilized by *gauche* interactions in the coiled conformation of the bound guest.[23] The encapsulated *E*-isomer converted slowly at RT or more rapidly upon sonication (Figures 4 and 5).

Summary and outlook

The shape-space and weak intermolecular forces control the guest *E/Z* equilibria conformations in this water-soluble yet hydrophobic confined space. Ultimately, container compounds are expected to be useful in stabilizing reactive intermediates and controlling reaction selectivity.[13,24-27] The cavity of **Se•Se**, selectively binds the *Z*-isomer of alkyl-*O*-methyl oximes derivatives (with 14 heavy atoms in length), and these bound and unbound isomers were separable by simple extraction using organic solvents. The cavitand **Se** was recovered and reused for more than 6 cycles without loss of selectivity. Selective binding was established by various control experiments and computational results.

The *Z*-isomer complex has selective binding in **Se•Se** (~98%) along with the less stable *E*-isomer (~2%). The *E-Z* isomerization occurs in the capsular cavity slowly at RT and is accelerated 8-10 fold by sonication. Isomerization to the (shorter) *Z*-isomer likely occurs to relieve some *gauche* interactions along the chain. The behavior of confined guests in the capsular cavity may relate to their behavior in biological receptors.

ASSOCIATED CONTENT

Supporting Information. The Supporting Information is available free of charge via the Internet at http://pubs.acs.org.

Synthesis and characterization of **Se** cavitand and **NOMe** derivatives; NMR spectra for all synthesized compounds and competitive binding studies; computational data, and all experimental details (PDF).

AUTHOR INFORMATION

Corresponding Author

***Yang Yu** - Center for Supramolecular Chemistry & Catalysis and Department of Chemistry, College of Science, Shanghai University, Shanghai 200444, China.
https://orcid.org/0000-0001-5698-3534

Author

Kuppusamy Kanagaraj - Center for Supramolecular Chemistry & Catalysis and Department of Chemistry, College of Science, Shanghai University, Shanghai 200444, China.
https://orcid.org/0000-0002-9263-1277

Rui Wang - Center for Supramolecular Chemistry & Catalysis and Department of Chemistry, College of Science, Shanghai University, Shanghai 200444, China.
https://orcid.org/ 0000-0001-7116-6006

Ming-Kai Zhao- Center for Supramolecular Chemistry & Catalysis and Department of Chemistry, College of Science, Shanghai University, Shanghai 200444, China.

Pablo Ballester - Institute of Chemical Research of Catalonia (ICIQ), The Barcelona Institute of Science and Technology (BIST), 43007 Tarragona, Spain; Catalan Institution for Research and Advanced Studies (ICREA), 08010 Barcelona, Spain.
https://orcid.org/ 0000-0001-8377-6610

Julius Rebek, Jr. - Center for Supramolecular Chemistry & Catalysis and Department of Chemistry, College of Science, Shanghai University, Shanghai 200444, China, and Skaggs Institute for Chemical Biology and Department of Chemistry, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, CA 92037, USA
https://orcid.org/0000-0002-2768-0945

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ABBREVIATIONS

CCR2, CC chemokine receptor 2; CCL2, CC chemokine ligand 2; CCR5, CC chemokine receptor 5; TLC, thin layer chromatography.

REFERENCES

1. A.J. Kirby, *Angew. Chem. Int. Ed.,* **1996**, *35*, 706-724.
2. D. Ringe, and G.A. Petsko, *Science*, **2008**, *320*, 1428-1429.
3. (a) R. Cacciapaglia, S. Di Stefano, and L. Mandolini, *Acc. Chem. Res.*, **2004**, *37*, 113-122. (b) H. Takezawa, K. Shitozawa, and M. Fujita, *Nat. Chem.,* **2020**, *12*, 574-578.
4. (a) V. Serreli, C.-F. Lee, E.R. Kay, and D.A. Leigh, *Nature,* **2007**, *445,* 523-527. (b) M. Li, L.-J. Chen, Y. Cai, Q. Luo, W. Li, H.-B. Yang, H. Tian, and W.-H. Zhu, *Chem*, **2019**, *5*, 634-648. (c) K. Ohara, M. Kawano, Y. Inokuma, and M. Fujita, *J. Am. Chem. Soc.,* **2010**, *132*, 30-31. (d) E.R. Kay, D.A. Leigh, F. Zerbetto, *Angew. Chem. Int. Ed.,* **2006**, *46*, 72-191. (e) K. Wang, X. Cai, W. Yao, D. Tang, R. Kataria, H.S. Ashbaugh, L.D. Byers, and B.C. Gibb, *J. Am. Chem. Soc.,* **2019**, *141*, 6740-6747. (f) S. Kuwahara, Y. Suzuki, N. Sugita, M. Ikeda, F. Nagatsugi, N. Harada, and Y. Habata, *J. Org. Chem.,* **2018**, *83*, 4800-4804.
5. (a) Y. Inokuma, M. Kawano, and M. Fujita, *Nature Chem.,* **2011**, *3,* 349-358. (b) J.H. Jordan, and B.C. Gibb, *Chem. Soc. Rev.,* **2015**, *44*, 547-585. (c) A. Parthasarathy, L.S. Kaanumalle, and V. Ramamurthy, *Org. Lett.,* **2007**, *9(24)*, 5059-5062. (d) C.M. Hong, D.M. Kaphan, R.G. Bergman, K.N. Raymond, and F.D. Toste, *J. Am. Chem. Soc.,* **2017**, *139*, 8013-8021.
6. (a) M. Xue, Y. Yang, X. Chi, Z. Zhang, and F. Huang, *Acc. Chem. Res.,* **2012**, *45*, 1294-1308. (b) K. Ohara, Y. Inokuma, and M. Fujita, *Angew. Chem. Int. Ed.,* **2010**, *49(32)*, 5507-5509. (c) S. Erbas-Cakmak, D.A. Leigh, C.T. McTernan, and A.L. Nussbaumer, *Chem. Rev.,* **2015**, *115*, 10081-10206. (d) M. Li, L.-J. Chen, Z. Zhang, Q. Luo, H.-B. Yang, H. Tian, and W.-H. Zhu, *Chem. Sci.,* **2019**, *10*, 4896-4904. (e) Y. Zhou, Y. Chen, P.-P. Zhu, W. Si, J.-L. Hou, and Y. Liu, *Chem. Commun.,* **2017**, *53*, 3681-3684. (f) L. Jin, C. Jingzhi, H. Wenhao, and C. Xu, *Chin. J. Org. Chem.*, **2018**, *38(6)*, 1507-1515.
7. (a) H. Wu, Y. Chen, L. Zhang, O. Anamimoghadam, D. Shen, Z. Liu, K. Cai, C. Pezzato, C.L. Stern, Y. Liu, and J.F. Stoddart, *J. Am. Chem. Soc.,* **2019**, *141*, 1280-1289. (b) X. Yan, J.-F. Xu, T.R. Cook, F. Huang, Q.-Z. Yang, C.-H. Tung, and P.J. Stang, *PNAS*, **2014**, *111(24)*, 8717-8722. (c) Z.-T. Shi, Y.-X. Hu, Z. Hu, Q. Zhang, S.-Y. Chen, M. Chen, J.-J. Yu, G.-Q. Yin, H. Sun, L. Xu, X. Li, B.L. Feringa, H.-B. Yang, H. Tian, and D.-H. Qu, *J. Am. Chem. Soc.,* **2021**, *143*, 442-452. (d) T. Hao, Y. Yang, W. Liang, C. Fan, X. Wang, W. Wu, X. Chen, H. Fu, H. Chen, and C. Yang, *Chem. Sci.,* **2021**, *12*, 2614-2622.
8. (a) T. Caneva, L. Sperni, G. Strukul, and A. Scarso, *RSC Adv.,* **2016**, *6*, 83505-83509. (b) M.R. Sullivan, and B.C. Gibb, *Org. Biomol. Chem.,* **2015**, *13*, 1869-1877. (c) F.-Q. Li, Q.-L. Yu, Y.-H. Liu, H.-J. Yu, Y. Chen, and Y. Liu, *Chem. Commun.,* **2020**, *56*, 3907-3910.
9. (a) H. Sunohara, K. Koyamada, H. Takezawa, and M. Fujita, *Chem. Commun.,* **2021**, *57*, 9300-9302. (b) A.M. Raj, and V. Ramamurthy, *Org. Lett.,* **2017**, *19(22)*, 6116-6119. (c) V. Blanco, D.A. Leigh, and V. Marcos, *Chem. Soc. Rev.,* **2015**, *44*, 5341-5370. (d) D.A. Leigh, J.K.Y. Wong, F. Dehez, and F. Zerbetto, *Nature*, **2003**, *424*, 174–179. (e) E. Kudo, K. Sasaki, S. Kawamata, K. Yamamoto, and T. Murahashi, *Nat. Commun.,* **2021**, *12,* 1473.

10. T. Yoshihiko, M. Hiroaki, S. Hirochika, and T. Katsumi, *Bull. Chem. Soc. Jpn.,* **1989**, *62(7)*, 2213-2218.
11. (a) T. Iwasawa, E. Mann, and J. Rebek, Jr., *J. Am. Chem. Soc.,* **2006**, *128*, 9308-9309. (b) M.-M. Tang, K. Kanagaraj, J. Rebek Jr., and Y. Yu, **2022**, *17*, e202200466.
12. (a) Y.-S. Li, L. Escobar, Y.-J. Zhu, Y. Cohen, P. Ballester, J. Rebek Jr., and Y. Yu, *PNAS*, **2019**, *116(40)*, 19815-19820. (b) H.-B. Zhang, K. Kanagaraj, J. Rebek, Jr., and Y. Yu, *J. Org. Chem.*, **2021**, *86*, 8873-8881. (c) K. Kanagaraj, J. Rebek Jr., and Y. Yu, *Green Syn. Cat.,* **2022**, 10.1016/j.gresc.2022.10.005.
13. (a) M. M. Conn, and J. Rebek Jr., *Chem. Rev.,* **1997**, *97*, 1647-1668. (b) Y.-Q. Chen, H.-W. Guan, K. Kanagaraj, J. Rebek, and Y. Yu, *Chin. Chem. Lett.,* **2022**, *33(11)*, 4908-4911. (c) D.-H. Tuo, Y.-F. Ao, Q.-Q. Wang and D.-X. Wang, *CCS*, **2022**, *4(8)*, 2806-2815.
14. C. B. Aakeroy, A. Rajbanshi, P. Metrangolo, G. Resnati, M. F. Parisi, J. Desper, and T. Pilati, *CrystEngComm,* **2012**, *14*, 6366-6368.
15. F.-U. Rahman, D. Tzeli, I.D. Petsalakis, G. Theodorakopoulos, P. Ballester, J. Rebek Jr., and Y. Yu, *J. Am. Chem. Soc.,* **2020**, *142*, 5876-5883.
16. L.-J. Riwar, N. Trapp, K. Root, R. Zenobi, and F. Diederich, *Angew. Chem. Int. Ed.,* **2018**, *57*, 17259-17264.
17. (a) G. Wettermark, *Sv. Kem. Tidskr.,* **1967**, *79*, 24. (b) G. Wettermark in "*The Chemistry of Functional Groups*," Vol. 3, S. Patai, Ed., Wiley, London, **1969**, p 565. (c) K.A. Rykaczewski, E.R. Wearing, D.E. Blackmun, and C.S. Schindler, *Nat. Synth.,* **2022**, *1*, 24-36. (d) S.K. Kandappa, L.K. Valloli, S. Ahuja, J. Parthiban, and J. Sivaguru, *Chem. Soc. Rev.,* **2021**, *50*, 1617-1641.
18. (a) C.H. Warren, G. Wettermark, and K. Weiss, *J. Am. Chem. Soc.,* **1971**, *93(19)*, 4658-4663. (b) A. Dargelos, D. Liotard, and M. Chaillet, *Theoret. Chim. Acta (Berl.),***1975**, *38*, 79-82.
19. (a) D.Y. Curtin, E.J. Grubbs, and C. G. McCarty, *J. Am. Chem. Soc.,* **1966**, *88(12)*, 2775-2786. (b) Y. Hiroshi, A.S. Cheettu, A. Tsutomu, and O. Yasushi, *Bull. Chem. Soc. Jpn.,* **2005**, *78(10)*, 1851-1855.
20. (a) E. Fischer and Y. Frei, *J. Chem. Phys.,* **1957**, *27*, 808. (b) D.G. Anderson and G. Wettermark, *J. Am. Chem. Soc.,* **1965**, *87*, 1433. (c) S. Zilberg, and Y. Haas, *J. Photochem. Photobiol. Sci.,* **2003**, *2*, 1256-1263.
21. (a) S. Nsikabaka, W. Harb, and M.F. Ruiz-Lopez, *J. Mol. Str: THEOCHEM*, **2006**, *764*, 161–166. (b) J. Mas-Roselló1, T. Smejkal, and N. Cramer, *Science*, **2020**, *368*, 1098-1102. (c) S.Z. Vatsadze, A.V. Medvedko, S.A. Kurzeev, O.I. Pokrovskiy, O.O. Parenago, M.O. Kostenko, I.V. Ananyev, K.A. Lyssenko, D.A. Lemenovsky, G.M. Kazankov, and V.V. Lunin, *Organometallics*, **2017**, *36*, 3068-3075.
22. T. Sahyoun, A. Arrault, and R. Schneider, *Molecules*, **2019**, *24*, 2470.
23. B.W. Purse, and J. Rebek Jr., *Proc. Nat. Acad. Sci.*, **2006**, *103(8)*, 2530-2534.
24. A. Pappalardo, R. Puglisi, and G.T. Sfrazzetto, *Catalysts*, **2019**, *9*, 630.
25. C. Gaeta, P. La Manna, M. De Rosa, A. Soriente, C. Talotta, and P. Neri, *Chem. -Eur. J.,* **2021**, *13(7)*, 1638-1658.
26. L. Zhao, J. Cai, Y. Li, J. Wei, and C. Duan, *Nat. Commun.,* **2020**, *11*, 2903.
27. R.J. Hooley, J.V. Gavette, M. Mettry, D. Ajami, and J. Rebek, Jr., *Chem. Sci.,* **2014**, *5*, 4382-4387.

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