


Benchmarking Guanidinium Organosulfonate Hydrogen-Bonded Frameworks for Structure Determination of Encapsulated Guests

Anna Yusov, Alexandra M. Dillon, Mohammad T. Chaudhry, Justin A. Newman, Alfred Y. Lee,* and Michael D. Ward*

 Cite This: *ACS Materials Lett.* 2024, 6, 1906–1912

 Read Online

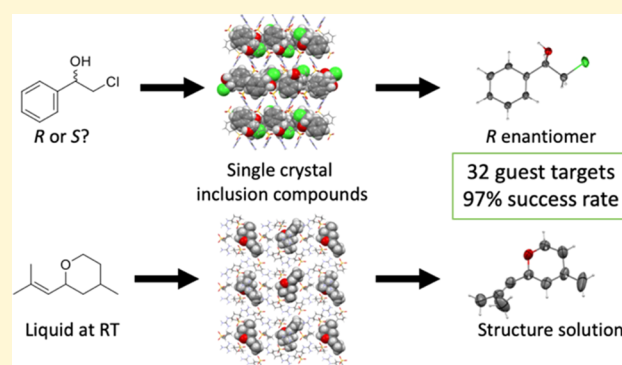
ACCESS |

 Metrics & More

 Article Recommendations

 Supporting Information

ABSTRACT: Single crystal X-ray diffraction (SCXRD) is arguably the most definitive method for molecular structure determination, but it is often challenged by compounds that are liquids or oils at room temperature or do not form crystals adequate for analysis. Our laboratory previously reported a simple, cost-effective, single-step crystallization method based on guanidinium organosulfonate (GS) hydrogen bonded frameworks for structure determination of a wide range of encapsulated guest molecules, including assignment of the absolute configuration of chiral centers. Herein, we expand on those results and report a head-to-head comparison of the GS method with adamantoid “molecular chaperones”, which have been reported to be useful hosts for structure determination. Inclusion compounds limited to only two GS hosts are characterized by low R_1 values and Flack parameters, infrequent disorder of the host and guest, and manageable disorder when it does exist. The structures of some target molecules that were not included or resolved using the adamantoid chaperones were successfully included and resolved by the GS hosts, and vice versa. Of the 32 guests attempted by the GS method, 31 inclusion compounds afforded successful guest structure solutions, a 97% success rate. The GS hosts and adamantoid chaperones are complementary with respect to guest inclusion, arguing that both should be employed in the arsenal of methods for structure determination. Furthermore, the low cost of organosulfonate host components promises an accessible route to molecular structure determination for a wide range of users.



Single-crystal X-ray diffraction (SCXRD) has been instrumental for structure determination of inorganic compounds and organic molecules dating back to Bragg in 1913¹ and Lonsdale and Whiddington in 1929.² Structure determination was further advanced by Bijvoet et al. in 1951, with the first example of determination of absolute configuration by SCXRD.³ Although nuclear magnetic resonance spectroscopy can be used for structure elucidation, SCXRD is regarded as the most definitive method, including the assignment of the absolute configuration of stereogenic centers. Compounds that are liquids at room temperature or exist only as oils, however, generally do not form crystals suitable for conventional SCXRD. The “crystalline sponge method” (CSM) employs metal–organic frameworks as hosts for target molecules to circumvent these challenges. CSM, however, can be limited by fixed pore apertures that impose a limit on guest size, as well as low occupancy and disorder of guest and solvent molecules.^{4–10} Other methods for molecular structure determination include phosphorylated macrocycle

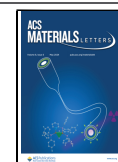
hosts,¹¹ the use of chiral MOFs,¹² and alcohols converted to sulfates followed by crystallization with guanidinium ions.¹³ Recently, our laboratory reported the use of guanidinium organosulfonate (GS) hydrogen-bonded host frameworks for structure solution of encapsulated guests using a single-step solvent-based crystallization method, affording reliable assignment of absolute configuration and relative stereochemistry for guests with stereogenic centers,^{14,15} as well as providing a structural explanation for reactive pathways.¹⁶ Later, substituted tetraaryladamantanes, a.k.a. “molecular chaperones”,^{17–22} were employed as hosts for the determination of

Received: February 23, 2024

Revised: April 3, 2024

Accepted: April 4, 2024

Published: April 10, 2024



molecular structure, including absolute configuration, for a variety of guest molecules. This method involved adding one of three different adamantoid chaperones (Figure S33) to a neat guest, in liquid form, at room temperature, heating the mixture to achieve a homogeneous solution, followed by cooling with the aim of producing a cocrystal of the adamantoid chaperone and guest.^{17,19,21} Subsequently, other research groups reported the use of GS frameworks for structure determination of target molecules,^{23,24} and very recently, a report in this journal described an anthracene-modified adamantoid molecular chaperone for structure determination of guests.²⁵

Over the past three decades, our laboratory has reported a substantial number of molecular host frameworks, built from two-dimensional hydrogen-bonded networks of guanidinium (G) and organosulfonate (S) ions (Figure 1), capable of

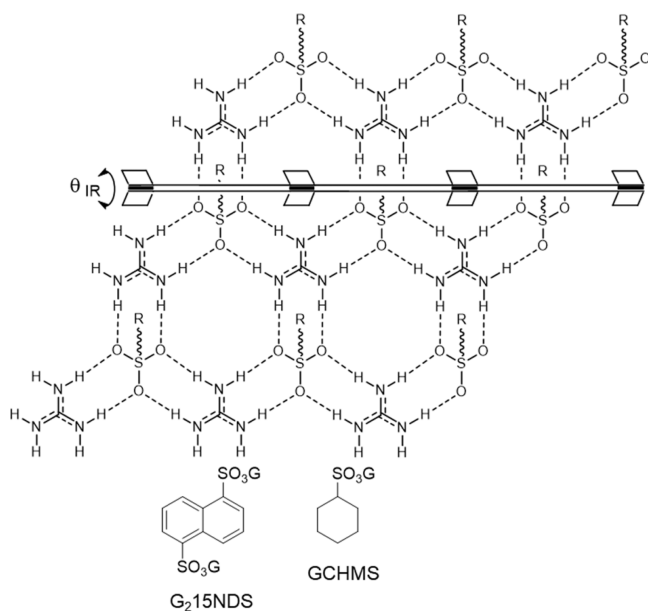


Figure 1. Top: The typical quasi-hexagonal GS sheet (top), illustrating the hydrogen-bonded “hinge” that allows facile puckering of the GS sheet allowing for “shrink-wrapping” around guests in the inclusion cavities. The R substituents on the sulfur atoms denote organic groups that can project from either side of the GS sheet. Bottom: The two guanidinium organosulfonate hosts used here.

encapsulating a wide range of guests and determining their molecular structure.^{26–30} These frameworks can adopt various architectures and pucker about hydrogen-bonding “hinges” in response to the steric demands of a target guest, enabling inclusion of a wide range of guests having various sizes and shapes in stoichiometric amounts. Framework puckering, combined with free motion of the organosulfonate residue, allows a GS host to “shrink-wrap” about the guest molecules, facilitating dense packing with associated mitigation of guest disorder. Target molecules can be included in the frameworks through a simple single-step crystallization in which a small amount of the target molecule is added to a solution of the GS framework components at room temperature. The chemical and structural diversity of organosulfonates allows for tailoring of the size, shape, and environment of the inclusion cavities.^{29,31} Approximately 500 GS inclusion compounds with well-characterized single crystal structures have been reported with more than 150 unique guests.^{28,29,32} Further-

more, the presence of sulfur atoms provides stronger anomalous scattering, which is advantageous for the assignment of an absolute configuration for target molecules with only lighter elements.

Recognizing that the attributes of the adamantoid chaperones and GS hosts may prove to be complementary with respect to structure determination, we attempted the crystallization of GS host frameworks with 32 guest targets (Figure 2). Of these 32 targets, 23 were selected from 53 attempted for the three originally reported adamantoid chaperones^{17,21} to allow for a head-to-head comparison of the two kinds of hosts. We chose to measure the performance of GS hosts against the adamantoid chaperones, because the latter employed a comprehensive library for guest inclusion and structure refinement, providing a rare opportunity for a comprehensive head-to-head comparison. Although the guest molecules were generally of low molecular weight, such compounds are often synthetic targets or intermediates that require a structure determination or confirmation. Our investigation was limited to 23 targets from the group for reasons of cost and availability. The remaining nine targets of the 32 are reported here to illustrate further the utility of the GS hosts. Collectively, the 32 targets span polar to nonpolar and aliphatic to aromatic, contain various functional groups, and have wide-ranging shapes and sizes. Although our laboratory has reported inclusion in GS hosts based on more than 100 organosulfonates,³³ we limited our investigation to only two GS hosts—guanidinium 1,5-naphthalene disulfonate (G₂1,5-NDS) and guanidinium cyclohexane monosulfonate (GCHMS)—to ensure a fair comparison with the three adamantoid chaperones.¹⁷ The occupancy of guest molecules in the GS inclusion compounds was stoichiometric, and disorder, if it exists, was manageable generally. The findings described herein show that the adamantoid and GS hosts are complementary with respect to the inclusion of target guest molecules and determination of their structure, which includes definitive assignment of the absolute configuration for guests with stereogenic centers.

Inclusion compounds with the G₂1,5-NDS host adopt a 1:1 host:guest stoichiometry (Table S5), even though the guest volumes, calculated using a simple and accurate formula,³⁴ are wide-ranging, from 58 Å³ (acetic acid, **1**) to 170 Å³ ((*R*)-(–)-carvone, **20**; (*S*)-(+)-carvone, **21**). This can be attributed to the structural compliance of the GS host, which enables the host framework to “shrink-wrap” around the target guest molecules. The G₂1,5-NDS inclusion compounds adopt the usual and previously observed simple brick architecture, which is illustrated in Figure 3 for G₂1,5-NDS⊃(*R*)-2-pentanol (**7**), with the exceptions of those with acetic acid, tetrahydrofuran, pyridine, aniline, benzonitrile, and methyl-*L*-pyroglutamate guests. G₂1,5-NDS⊃acetic acid (**1**), G₂1,5-NDS⊃pyridine (**5**), and G₂1,5-NDS⊃methyl-*L*-pyroglutamate (**22**) adopt a puckered simple brick architecture in which the GS sheets are sustained despite hydrogen bonds with the target molecules (Figure S34). In the case of compound **1**, the acetic acid guests exist as hydrogen bonded dimers nestled inside the framework cavities. G₂1,5-NDS⊃aniline (**8**) exhibits a bilayer-type architecture with hydrogen bonding between the guest and the GS sheet, with a water molecule bridging adjacent GS sheets (Figure S35), which has been previously observed.¹⁶ G₂1,5-NDS⊃benzonitrile (**10**) exhibits a bilayer architecture, but hydrogen bonds between the nitrile group of the guest and the G₂1,5-NDS host are absent. G₂1,5-

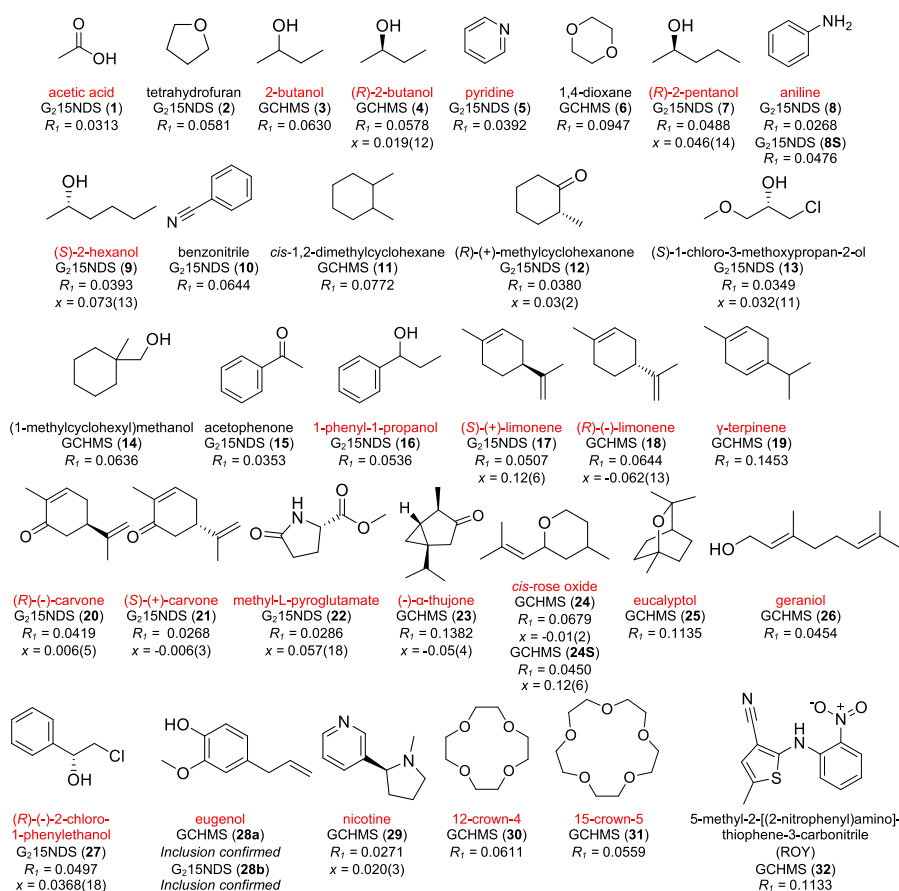


Figure 2. Target guest molecules included and fully refined in GCHMS or G_2 1,5-NDS hosts, listed in order of increasing molecular weight. The GS framework corresponding to each target molecule and the R_1 values are provided. Flack parameters (x) are provided for structures with chiral guests. The near-zero value and high precision of the Flack parameters for inclusion compounds provide confidence in the assignment of the absolute configuration. Guests denoted in red correspond to those investigated with “molecular chaperones”.^{17,21} Compound 5 contains both stereoisomers of *cis*-rose oxide in equal amounts; the stereochemistry is not denoted here for the sake of clarity. The structure of eugenol in 28a and 28b could not be resolved due to guest disorder. Examples 8S and 24S denote data collected using synchrotron radiation. Examples of the structure determination of 21 other guests (not shown here) using GS hosts have been reported elsewhere.^{14–16,23,24}

NDS \supset tetrahydrofuran (2) adopts a unique layered architecture where hydrogen bonds between the guanidinium and tetrahydrofuran molecules results in a one-dimensional ribbon in lieu of the usual GS sheet (Figure S36). Inclusion compounds 1, 2, 5, 8, 10, and 22 illustrate the tolerance of the GS frameworks and the hydrogen bonded sheet to guest molecules with hydrogen-bond donor and acceptor character.

The GCHMS host readily formed inclusion compounds with a variety of layered architectures, some new and unanticipated, in which the GS sheet is preserved except for 15-crown-5 (31), which is incorporated into the hydrogen bonded sheet through hydrogen bonding between its oxygen atoms and guanidinium protons. The pattern of the projections of the organic residues above and below each GS sheet is guest-dependent, however. This is reminiscent of previously reported inclusion compounds formed from a large collection of guanidinium arenemonosulfonates and aromatic guests that produced more than 300 inclusion compounds and four different architectures, each described by GS sheets with a unique “up–down” projection topology.²⁷ The facility of guanidinium monosulfonates for encapsulating guests can be attributed to the absence of a constraint on the registry of adjacent sheets, which provides a degree of freedom for molecular packing between the GS sheets that is not available

to disulfonates. GCHMS, reported here for the first time, is particularly adept with respect to trapping aliphatic target molecules, as illustrated for $(GCHMS)_4\supset cis$ -rose oxide (24) in Figure 3. Details of the GCHMS architectures will be reported elsewhere.

Of the 23 guests in the head-to-head comparison, 17 were included and refined in the adamantoid chaperones, whereas 22 were included and refined in the GS hosts. The lone exception was eugenol, which was included but could not be refined (compounds 28a and 28b). In most cases, the inclusion of a target guest in both GS hosts was not attempted if successful guest refinement was achieved in one of them (Table S3). The GS inclusion compounds generally afforded better R_1 values, improved Flack parameters where appropriate, and smaller thermal ellipsoids (Tables S3, S4). Inclusion of acetic acid, γ -terpinene, methyl-*L*-pyroglyutamate, *cis*-rose oxide, eucalyptol, and 15-crown-5 in the adamantoid hosts was either not successful, or inclusion was confirmed but satisfactory refinement was not obtained.¹⁷ These guests, however, were included by either G_2 1,5-NDS or GCHMS hosts (compounds 1, 19, 22, 24, 24S, 25, and 31) and satisfactory refinements were obtained for the corresponding inclusion compounds. Data for two inclusion compounds with aniline (8, 8S) and *cis*-rose oxide (24, 24S) guests were

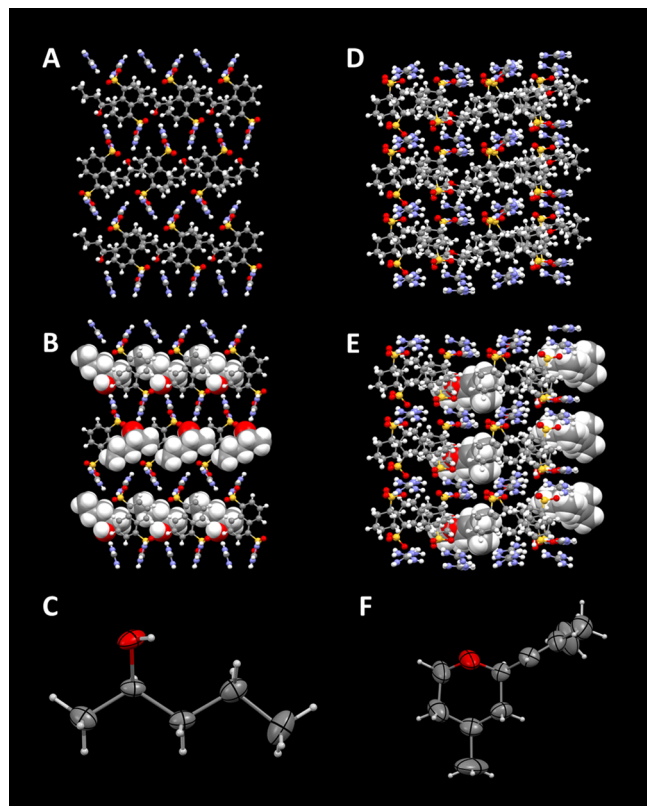


Figure 3. Illustrative crystal structures. (A–C) $(G_{2,1,5}\text{-NDS})_4 \supset (R)\text{-}2\text{-pentanol}$ (**7**) and (D–F) $(\text{GCHMS})_4 \supset \text{cis-rose oxide}$ (**24**), depicted as ball-and-stick (top), target guest molecules as space filling (middle), and guests with ellipsoids at 50% probability (bottom).

collected by using synchrotron radiation as well as on a conventional SCXRD instrument (Table S3). The synchrotron and laboratory data sets both provided low R_1 values and good data quality, demonstrating that access to synchrotron data can improve data quality but the use of a conventional SCXRD instrument is sufficient.

GS hosts have a high density of sulfur atoms, which improves anomalous scattering required for reliable absolute configuration determination. This is illustrated by $G_{2,1,5}\text{-NDS} \supset (R)\text{-}2\text{-pentanol}$ (**7**; Figure 3), for which the Flack parameter was $x = 0.046(14)$. In comparison, the Flack parameter for the adamantoid inclusion compound $\text{TEO} \supset (R)\text{-}2\text{-pentanol}$ (TEO = tetrakis(2,4-diethoxy-phenyl)adamantane; Figure S33), in which oxygen as the strongest scatterer, was $x = -0.6(6)$ (CSD refcode: ZURXIW).¹⁷ One of the three adamantoid chaperones (Figure S33) contains a heavy atom (bromine), but no inclusion compound for $(R)\text{-}2\text{-pentanol}$ was reported for this host, precluding a direct comparison. Of the six reported inclusion compounds using this adamantoid chaperone, only one contained a chiral guest, muscone (CSD refcode: ZURXAO), but the Flack parameter was $x = 0.523(19)$ and absolute configuration could not be assigned.¹⁷

The guests included in the GS frameworks described herein are liquids or oils at room temperature, with the exception of ROY (named for its Red, Orange, and Yellow crystal polymorphs^{35–39}). $\text{GCHMS} \supset \text{ROY}$ (**32**) crystallized as red-orange plates, enabling convenient discrimination of the inclusion compound from guest-free GCHMS crystals. The ROY guest is planar (Figures S37, S38), unlike other GS

inclusion compounds containing ROY.⁴⁰ Moreover, the planar conformation does not exist in any of the 13 polymorphs of ROY for which single crystal structures have been determined, although near-planarity was observed in the “R18” polymorph.^{35–39,41} This example further demonstrates the ability of the GS frameworks to encapsulate solid guest targets, like many others reported previously.^{14,28,42–46}

The complementary nature of the GCHMS and $G_{2,1,5}\text{-NDS}$ hosts can be illustrated with three guest targets (limonene, geraniol, and eugenol). Inclusion of $(S)\text{-}(-)\text{-limonene}$ and $(R)\text{-}(+)\text{-limonene}$ was confirmed in both $G_{2,1,5}\text{-NDS}$ and GCHMS, and satisfactory refinement was achieved for $(S)\text{-}(-)\text{-limonene}$ and $(R)\text{-}(+)\text{-limonene}$ in $G_{2,1,5}\text{-NDS}$ (**17**) and GCHMS (**18**), respectively. Inclusion of geraniol was successful with $G_{2,1,5}\text{-NDS}$, but the guest structure could not be resolved due to substantial positional disorder along a solvent channel. Inclusion and full refinement were achieved, however, by using the GCHMS host (**26**).

Eugenol was included stoichiometrically in both the GCHMS (**28a**) and $G_{2,1,5}\text{-NDS}$ (**28b**) hosts, but its structure could not be resolved due to guest disorder. The stoichiometry (2:1 host:guest in **28a** and 1:1 in **28b**) was assigned based on the electron density of the included guest. This type of disorder was not entirely unexpected, as it has been observed previously for linear triglyme guests in the channels of the $G_{2,1,5}\text{-NDS}$ host (CSD refcode: TUQPIE).⁴⁷ These examples illustrate that inclusion and structure refinement of almost all target guests were possible using only the GCHMS and $G_{2,1,5}\text{-NDS}$ hosts. Satisfactory structure determination of 31 of the 32 guests in Figure 2 was achieved with at least one of these two hosts.

The adamantoid and GS hosts each have unique benefits and challenges, making them complementary with respect to inclusion and structure determination. The GS inclusion compounds are grown readily by adding a guest to a solution (typically methanol and/or ethanol) of the GS host, affording versatility with respect to including solid guests as well as liquids. The typical adamantoid host protocol requires a guest to act as the solvent to dissolve the adamantoid chaperone prior to crystallization, precluding the encapsulation of solid guests. Inclusion of a solid guest was achieved by evaporation of solvent containing the chaperone and guest.²⁰ Moreover, heating is required to dissolve the adamantoid chaperone (up to 150 °C), which can be problematic for thermally sensitive targets. The crystallization of the GS inclusion compounds is achieved at room temperature via slow evaporation, which may be essential for thermally sensitive targets. The GS method requires several days for inclusion compound crystallization, whereas the adamantoid chaperones were reported to form inclusion compounds in 16 hours or less.¹⁷ Guests that are sensitive to acidic environments or the crystallization solvent may decompose or transform during the GS protocol. For example, attempts to grow GS inclusion compounds containing $(S)\text{-epichlorohydrin}$ instead produced crystals of $G_{2,1,5}\text{-NDS} \supset (S)\text{-}1\text{-chloro-}3\text{-methoxypropan-}2\text{-ol}$ (**13**) because of reaction with methanol solvent (Scheme S1). In contrast, unreacted $(S)\text{-epichlorohydrin}$ was included by an adamantoid host, and its structure was determined (CSD refcode: ZURROW).¹⁷ GS hosts can form solvates and guest-free phases, which can compete with their crystallization with molecular targets. The adamantoid chaperones also form guest-free crystalline phases,^{17,22,48} which were observed during attempts to grow inclusion compounds of certain

host–guest combinations. Like many GS inclusion compounds, solvate- and guest-free phases of G₂1,5-NDS and GCHMS often have crystal habits distinct from their inclusion compounds, enabling identification of guest-containing crystals. The adamantoid chaperone protocol requires a substantial amount of the guest target molecule (up to 60 mg)¹⁷ to dissolve the chaperone, whereas inclusion in GS hosts can be realized with as little as 1 mg of the target guest,¹⁶ which is critical when guest quantities are limited. The synthesis of the chaperone molecules is more challenging than the synthesis of organosulfonates. Like other GS hosts, G₂1,5-NDS and GCHMS can be prepared from a simple, single-step reaction from affordable and commercially available starting materials. Moreover, the chaperones are expensive (*ca.* US \$1000 for 100 mg, as offered by Bruker AXS⁴⁹), nearly 50 times the cost of the most expensive organosulfonate used (*ca.* \$20 for 100 mg⁵⁰), and the more recently reported anthracene-modified adamantoid chaperone is not commercially available. The combination of synthetic ease, commercial availability, and affordability promises accessibility of the GS hosts to a wide range of users.

In conclusion, two GS hosts, G₂1,5-NDS and GCHMS, were used to encapsulate 32 guest molecules, all but one as a liquid at room temperature, to form crystalline inclusion compounds. X-ray diffraction permits satisfactory refinement of the inclusion compounds and their respective molecular guests with low *R* factors, limited disorder, and Flack parameters suitable for the definitive assignment of stereochemistry for guests with stereogenic centers. The GS sheet is tolerant of guests with hydrogen bond donors and acceptors, and in several examples the guest is anchored to the GS sheet through hydrogen bonding, an additional mechanism for reducing disorder. The GS system exhibited a high success rate 31 of 32 guests attempted, 97%, for inclusion and successful structure refinement of the guest molecules despite using only two GS hosts. Of the 23 guests in a head-to-head comparison, 17 were included and refined in the adamantoid molecular chaperones, whereas 22 were included and refined in the GS hosts, arguing for the use of both host systems in the arsenal of crystallization methods for structure determination of guest molecules using single crystal X-ray diffraction. Notably, except for eugenol, the two GS hosts outperform the anthracene-modified adamantoid chaperone²⁵ with respect to inclusion and structure refinement for the seven guests common to both. Furthermore, the GS method is characterized by low cost, commercial availability, and facile synthesis of the organosulfonate host components, an absence of host disorder in most inclusion compounds, and manageable guest disorder when it exists. Moreover, more than 100 organosulfonates are readily available for use as hosts, promising to expand the utility of GS hosts even further.

■ ASSOCIATED CONTENT

SI Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acsmaterialslett.4c00400>.

Crystallographic data, X-ray characterization details including the constraint and restraints, experimental procedures, X-ray tables, comparisons to previously published data, crystal structures of inclusion compounds from X-ray data, thermal ellipsoids for refined guests, and crystal images (PDF)

Crystallographic information files (CIF)

Accession Codes

Crystallographic data of these structures, including cif, res, fcf, and hkl files, have been deposited with the Cambridge Crystallographic Data Centre with Numbers 2307188–2307219, 2308623, 2310649, 2312929. Copies of these data can be requested, free of charge, from the CCDC Web site at <https://www.ccdc.cam.ac.uk/structures/>

■ AUTHOR INFORMATION

Corresponding Authors

Alfred Y. Lee – Analytical Research and Development, Merck & Co., Inc., Rahway, New Jersey 07065, United States; orcid.org/0000-0003-3684-4101; Email: alfred.lee@merck.com

Michael D. Ward – Department of Chemistry and Molecular Design Institute, New York University, New York City, New York 10003, United States; orcid.org/0000-0002-2090-781X; Email: mdw3@nyu.edu

Authors

Anna Yusov – Department of Chemistry and Molecular Design Institute, New York University, New York City, New York 10003, United States; orcid.org/0000-0002-6880-0421

Alexandra M. Dillon – Department of Chemistry and Molecular Design Institute, New York University, New York City, New York 10003, United States; orcid.org/0000-0003-4680-0284

Mohammad T. Chaudhry – Analytical Research and Development, Merck & Co., Inc., Rahway, New Jersey 07065, United States; orcid.org/0000-0002-1482-388X

Justin A. Newman – Analytical Research and Development, Merck & Co., Inc., Rahway, New Jersey 07065, United States; orcid.org/0000-0002-2498-1259

Complete contact information is available at: <https://pubs.acs.org/10.1021/acsmaterialslett.4c00400>

Author Contributions

CRedit: **Anna Yusov** conceptualization, data curation, formal analysis, investigation, writing-original draft, writing-review & editing; **Alexandra M. Dillon** conceptualization, data curation, formal analysis, investigation, writing-review & editing; **Mohammad T. Chaudhry** data curation, formal analysis, investigation, writing-review & editing; **Justin A. Newman** data curation, formal analysis, funding acquisition, investigation, writing-review & editing; **Alfred Y. Lee** conceptualization, data curation, funding acquisition, investigation, writing-review & editing; **Michael D. Ward** conceptualization, formal analysis, funding acquisition, investigation, methodology, project administration, supervision, writing-original draft, writing-review & editing.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the National Science Foundation Grant Opportunities for Academic Liaison with Industry (GOALI) program through award DMR-2002964 and the NSF Chemistry Research Instrumentation and Facilities Program (CHE-0840277). M.T.C. thanks Merck Research Laboratories for support through the Postdoctoral Fellowship program at Merck & Co., Inc., Rahway, NJ, USA. A.Y. and

A.M.D. were also supported partially by the Margaret Strauss Kramer Fellowship. The authors would like Dr. Chunhua (Tony) Hu for collections and/or refinement for samples 3, 5, 7, 8S, 9, 11–16, 19–21, 23, 24S, 29, and 30. We are grateful to Dr. Lee Daniels at Rigaku and Dr. Yu-Sheng Chen at the University of Chicago and the Advanced Photon Source at Argonne National Laboratory. The authors also are grateful to Dr. Michelle Neary at Hunter College of the City University of New York for collecting diffraction data, made possible through support from the Air Force Office of Scientific Research under award FA9550-20-1-0158. Use of the Advanced Photon Source at Argonne National Laboratory was supported by the U.S. Department of Energy, Office of Science, Office of Basic Energy Sciences, under contract no. DE-AC02-06CH11357.

REFERENCES

- (1) Bragg, W. H. The Reflection of X-Rays by Crystals. (II). *Proc. R. Soc. London Ser. Contain. Pap. Math. Phys. Character* **1913**, 89 (610), 246–248.
- (2) Lonsdale, K.; Whiddington, R. The Structure of the Benzene Ring in C₆ (CH₃)₆. *Proc. R. Soc. London Ser. Contain. Pap. Math. Phys. Character* **1929**, 123 (792), 494–515.
- (3) Bijvoet, J. M.; Peerdeman, A. F.; van Bommel, A. J. Determination of the Absolute Configuration of Optically Active Compounds by Means of X-Rays. *Nature* **1951**, 168 (4268), 271–272.
- (4) Inokuma, Y.; Yoshioka, S.; Ariyoshi, J.; Arai, T.; Hitora, Y.; Takada, K.; Matsunaga, S.; Rissanen, K.; Fujita, M. Erratum: Corrigendum: X-Ray Analysis on the Nanogram to Microgram Scale Using Porous Complexes. *Nature* **2013**, 501 (7466), 262–262.
- (5) Ning, G.-H. H.; Matsumura, K.; Inokuma, Y.; Fujita, M. A Saccharide-Based Crystalline Sponge for Hydrophilic Guests. *Chem. Commun.* **2016**, 52 (43), 7013–7015.
- (6) Yoshioka, S.; Inokuma, Y.; Duplan, V.; Dubey, R.; Fujita, M. X-Ray Structure Analysis of Ozonides by the Crystalline Sponge Method. *J. Am. Chem. Soc.* **2016**, 138 (32), 10140–10142.
- (7) Hoshino, M.; Khutia, A.; Xing, H.; Inokuma, Y.; Fujita, M. The Crystalline Sponge Method Updated. *IUCrJ* **2016**, 3 (2), 139–151.
- (8) Yoshioka, S.; Inokuma, Y.; Hoshino, M.; Sato, T.; Fujita, M. Absolute Structure Determination of Compounds with Axial and Planar Chirality Using the Crystalline Sponge Method. *Chem. Sci.* **2015**, 6 (7), 3765–3768.
- (9) Urban, S.; Brkljača, R.; Hoshino, M.; Lee, S.; Fujita, M. Determination of the Absolute Configuration of the Pseudo-Symmetric Natural Product Elatinyne by the Crystalline Sponge Method. *Angew. Chem., Int. Ed.* **2016**, 55 (8), 2678–2682.
- (10) Inokuma, Y.; Ukegawa, T.; Hoshino, M.; Fujita, M. Structure Determination of Microbial Metabolites by the Crystalline Sponge Method. *Chem. Sci.* **2016**, 7 (6), 3910–3913.
- (11) Jiao, J.; Li, H.; Xie, W.; Zhao, Y.; Lin, C.; Jiang, J.; Wang, L. Host–Guest System of a Phosphorylated Macrocyclic Assisting Structure Determination of Oily Molecules in Single-Crystal Form. *Chem. Sci.* **2023**, 14 (41), 11402–11409.
- (12) Pei, X.; Bürgi, H.-B.; Kapustin, E. A.; Liu, Y.; Yaghi, O. M. Coordinative Alignment in the Pores of MOFs for the Structural Determination of N-, S-, and P-Containing Organic Compounds Including Complex Chiral Molecules. *J. Am. Chem. Soc.* **2019**, 141 (47), 18862–18869.
- (13) Brummel, B. R.; Lee, K. G.; McMillen, C. D.; Kolis, J. W.; Whitehead, D. C. One-Pot Absolute Stereochemical Identification of Alcohols via Guanidinium Sulfate Crystallization. *Org. Lett.* **2019**, 21 (23), 9622–9627.
- (14) Li, Y.; Tang, S.; Yusov, A.; Rose, J.; Borrfors, A. N.; Hu, C. T.; Ward, M. D. Hydrogen-Bonded Frameworks for Molecular Structure Determination. *Nat. Commun.* **2019**, 10 (1), 4477.
- (15) Potter, T. J.; Li, Y.; Ward, M. D.; Ellman, J. A. RhIII-Catalyzed Synthesis of Isoquinolones and 2-Pyridones by Annulation of N-Methoxyamides and Nitroalkenes. *Eur. J. Org. Chem.* **2018**, 2018 (32), 4381–4388.
- (16) Bartolo, N. D.; Demkiw, K. M.; Read, J. A.; Valentin, E. M.; Yang, Y.; Dillon, A. M.; Hu, C. T.; Ward, M. D.; Woerpel, K. A. Conformationally Biased Ketones React Diastereoselectively with Allylmagnesium Halides. *J. Org. Chem.* **2022**, 87 (5), 3042–3065.
- (17) Krupp, F.; Frey, W.; Richert, C. Absolute Configuration of Small Molecules by Co-Crystallization. *Angew. Chem., Int. Ed.* **2020**, 59 (37), 15875–15879.
- (18) Schwenger, A.; Frey, W.; Richert, C. Reagents with a Crystalline Coat. *Angew. Chem., Int. Ed.* **2016**, 55 (44), 13706–13709.
- (19) Krupp, F.; Picher, M.-I.; Frey, W.; Plietker, B.; Richert, C. Determining the Relative Configuration of Propargyl Cyclopropanes by Co-Crystallization. *Synlett* **2021**, 32 (04), 350–353.
- (20) Rami, F.; Nowak, J.; Krupp, F.; Frey, W.; Richert, C. Co-Crystallization of an Organic Solid and a Tetraaryladamantane at Room Temperature. *Beilstein J. Org. Chem.* **2021**, 17, 1476–1480.
- (21) Ou, G.-C.; Chen, H.-Y.; Wang, Q.; Zhou, Q.; Zeng, F. Structure and Absolute Configuration of Liquid Molecules Based on Adamantane Derivative Cocrystallization. *RSC Adv.* **2022**, 12 (11), 6459–6462.
- (22) Schwenger, A.; Frey, W.; Richert, C. Tetrakis-(Dimethoxyphenyl)Adamantane (TDA) and Its Inclusion Complexes in the Crystalline State: A Versatile Carrier for Small Molecules. *Chem.—Eur. J.* **2015**, 21 (24), 8781–8789.
- (23) Qin, S.-Q.; Xu, W.; Ye, W.-C.; Jiang, R.-W. Structure Determination of Liquid Molecules by Encapsulation in an Aromatic Cavity with Hydrogen Bonding and Enhanced C–H... π Interactions. *CrystEngComm* **2022**, 24 (46), 8060–8069.
- (24) Qin, S.-Q.; Gan, Q.-Y.; Xu, W.; Jiang, R.-W. Hybrid Interaction Network of Guanidinium–Biphenyldisulfonic Acid for the Structure Determination of Liquid Molecules. *CrystEngComm* **2022**, 24 (22), 4144–4154.
- (25) Li, H.; Jiao, J.; Xie, W.; Zhao, Y.; Lin, C.; Jiang, J.; Wang, L. The Structure Determination of Organic Molecules by Co-Crystallization of Anthracene-Based Crystallization Chaperone. *ACS Mater. Lett.* **2023**, 5 (10), 2673–2682.
- (26) Russell, V. A.; Evans, C. C.; Li, W.; Ward, M. D. Nanoporous Molecular Sandwiches: Pillared Two-Dimensional Hydrogen-Bonded Networks with Adjustable Porosity. *Science* **1997**, 276 (5312), 575–579.
- (27) Horner, M. J.; Holman, K. T.; Ward, M. D. Architectural Diversity and Elastic Networks in Hydrogen-Bonded Host Frameworks: From Molecular Jaws to Cylinders. *J. Am. Chem. Soc.* **2007**, 129 (47), 14640–14660.
- (28) Holman, K. T.; Pivovar, A. M.; Swift, J. A.; Ward, M. D. Metric Engineering of Soft Molecular Host Frameworks. *Acc. Chem. Res.* **2001**, 34 (2), 107–118.
- (29) Yusov, A.; Dillon, A. M.; Ward, M. D. Hydrogen Bonded Frameworks: Smart Materials Used Smartly. *Mol. Syst. Des. Eng.* **2021**, 6 (10), 756–778.
- (30) Horner, M. J.; Holman, K. T.; Ward, M. D. Lamellae–Nanotube Isomerism in Hydrogen-Bonded Host Frameworks. *Angew. Chem., Int. Ed.* **2001**, 40 (21), 4045.
- (31) Liu, Y.; Hu, C.; Comotti, A.; Ward, M. D. Supramolecular Archimedean Cages Assembled with 72 Hydrogen Bonds. *Science* **2011**, 333 (6041), 436–440.
- (32) Adachi, T.; Ward, M. D. Versatile and Resilient Hydrogen-Bonded Host Frameworks. *Acc. Chem. Res.* **2016**, 49 (12), 2669–2679.
- (33) Groom, C. R.; Bruno, I. J.; Lightfoot, M. P.; Ward, S. C. The Cambridge Structural Database. *Acta Crystallogr. Sect. B* **2016**, 72 (2), 171–179.
- (34) Zhao, Y. H.; Abraham, M. H.; Zissimos, A. M. Fast Calculation of van Der Waals Volume as a Sum of Atomic and Bond Contributions and Its Application to Drug Compounds. *J. Org. Chem.* **2003**, 68 (19), 7368–7373.

- (35) Beran, G. J. O.; Sugden, I. J.; Greenwell, C.; Bowskill, D. H.; Pantelides, C. C.; Adjiman, C. S. How Many More Polymorphs of ROY Remain Undiscovered. *Chem. Sci.* **2022**, *13* (5), 1288–1297.
- (36) Chen, S.; Guzei, I. A.; Yu, L. New Polymorphs of ROY and New Record for Coexisting Polymorphs of Solved Structures. *J. Am. Chem. Soc.* **2005**, *127* (27), 9881–9885.
- (37) Lévesque, A.; Maris, T.; Wuest, J. D. ROY Reclaims Its Crown: New Ways To Increase Polymorphic Diversity. *J. Am. Chem. Soc.* **2020**, *142* (27), 11873–11883.
- (38) Tan, M.; Shtukenberg, A. G.; Zhu, S.; Xu, W.; Dooryhee, E.; Nichols, S. M.; Ward, M. D.; Kahr, B.; Zhu, Q. ROY Revisited, Again: The Eighth Solved Structure. *Faraday Discuss.* **2018**, *211*, 477–491.
- (39) Li, X.; Ou, X.; Rong, H.; Huang, S.; Nyman, J.; Yu, L.; Lu, M. The Twelfth Solved Structure of ROY: Single Crystals of Y04 Grown from Melt Microdroplets. *Cryst. Growth Des.* **2020**, *20* (11), 7093–7097.
- (40) Tang, S.; Yusov, A.; Li, Y.; Tan, M.; Hao, Y.; Li, Z.; Chen, Y.-S.; Hu, C. T.; Kahr, B.; Ward, M. D. ROY Confined in Hydrogen-Bonded Frameworks: Coercing Conformation of a Chromophore. *Mater. Chem. Front.* **2020**, *4* (8), 2378–2383.
- (41) Tyler, A. R.; Ragbirsingh, R.; McMonagle, C. J.; Waddell, P. G.; Heaps, S. E.; Steed, J. W.; Thaw, P.; Hall, M. J.; Probert, M. R. Encapsulated Nanodroplet Crystallization of Organic-Soluble Small Molecules. *Chem* **2020**, *6* (7), 1755–1765.
- (42) Holman, K. T.; Pivovar, A. M.; Ward, M. D. Engineering Crystal Symmetry and Polar Order in Molecular Host Frameworks. *Science* **2001**, *294* (5548), 1907–1911.
- (43) Swift, J. A.; Pivovar, A. M.; Reynolds, A. M.; Ward, M. D. Template-Directed Architectural Isomerism of Open Molecular Frameworks: Engineering of Crystalline Clathrates. *J. Am. Chem. Soc.* **1998**, *120* (24), 5887–5894.
- (44) Pivovar, A. M.; Holman, K. T.; Ward, M. D. Shape-Selective Separation of Molecular Isomers with Tunable Hydrogen-Bonded Host Frameworks. *Chem. Mater.* **2001**, *13* (9), 3018–3031.
- (45) Swift, J. A.; Ward, M. D. Cooperative Polar Ordering of Acentric Guest Molecules in Topologically Controlled Host Frameworks. *Chem. Mater.* **2000**, *12* (6), 1501–1504.
- (46) Soegiarto, A. C.; Comotti, A.; Ward, M. D. Controlled Orientation of Polyconjugated Guest Molecules in Tunable Host Cavities. *J. Am. Chem. Soc.* **2010**, *132* (41), 14603–14616.
- (47) Russell, V. A.; Evans, C. C.; Li, W.; Ward, M. D. Nanoporous Molecular Sandwiches: Pillared Two-Dimensional Hydrogen-Bonded Networks with Adjustable Porosity. *Science*. **1997**, *276* (5312), 575–579.
- (48) Alexandre, P.-E.; Schwenger, A.; Frey, W.; Richert, C. High-Loading Crystals of Tetraaryladamantanes and the Uptake and Release of Aromatic Hydrocarbons from the Gas Phase. *Chem.—Eur. J.* **2017**, *23* (38), 9018–9021.
- (49) Bruker. Chaperone compounds | Bruker. <https://www.bruker.com/en/products-and-solutions/diffractometers-and-x-ray-microscopes/single-crystal-x-ray-diffractometers/sc-xrd-components/chaperone-compounds.html> (accessed April 9, 2024).
- (50) Sigma Aldrich. Cyclohexanesulfonic Acid Aldrich CPR 28100-07-4. <https://www.sigmaaldrich.com/US/en/product/aldrich/ph018131> (accessed May 26, 2022).