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Mapping the structural boundaries of quasiracemate fractional crystallization using 2-substituted diarylamides†

Ian C. Tinsley, Jacqueline M. Spaniol and Kraig A. Wheeler *

Video-assisted hot stage polarized light microscopy of 55 quasie-nantiomeric pairs, constructed from 22 chiral diarylamides that systematically differ in topology, reveals the structural boundaries of molecular shape to supramolecular assembly.

The manner in which molecules recognize each other holds critical importance to nearly every area of science.^{1–3} This significance stems from the key underpinning of molecular assembly to our most basic understanding of chemical processes. Whether these interactions relate to small-molecule catalytic transformations or complex physiological processes, the structural features responsible for molecular association play into the well-known adage that *form follows function* where material property arises from the collective structural features of the molecular components.^{4,5} Because the *form* of chemical systems is derived from a complex blend of covalent and non-bonded contacts, codifying each contributor has become essential for recognizing the functions and potential applications of materials.^{6–8} While considerable progress in this area has been realized by isolating and identifying molecular contacts and the structural details of their conditional exceptions, insight to the entire landscape of molecular associations remains an ongoing effort. Some of this challenge rests with chemical features that produce less manageable motifs *via* ill-defined or weak contacts. Molecular shape is one such feature. Although generally recognized as an important contributor to molecular assembly, the systematic use of topological features as a design element for supramolecular synthesis remains a relatively unexplored area.^{9–11} The lack of direct attention to molecular shape largely relates to the intractable

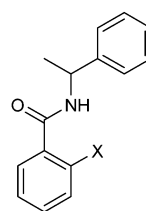
nature of this structural feature. To date, virtual screening based on molecular shape similarity has been widely used in drug discovery;¹² however, surprisingly, no practically useful set of parameters or experiments for probing supramolecular synthesis *via* topological features exist.

Here we report the systematic investigation of the relationship between molecular shape and molecular recognition. We find that an understanding can be effectively achieved by mapping the shape space of quasiracemate fractional crystallization using structurally simple chiral diarylamides precursors (Scheme 1). Quasiracemates – pairs of chemically distinct molecules of opposite handedness [*e.g.*, (*R*)-X and (*S*)-X' (ref. 13)] – without exception, cocrystallize with component alignment that mimic the centrosymmetric patterns observed in their analogous racemic counterparts.^{9,10,14} This thermodynamic preference provides a key entry point for the study since the complementary shapes of the quasienantiomeric building blocks serve as the primary driving force for these assemblies. Such a notion is supported by the diversity of molecular architectures and functional groups represented by the collection of racemic and quasiracemic crystal structures. It should also be noted that non-bonded contacts (*e.g.*, hydrogen bonds), while often important to the overall molecular recognition process, cannot explain the crystal growth events of racemates or quasiracemates since comparable stabilization may be achieved from homomeric [(*R*)-X ··· (*R*)-X] or heteromeric [(*S*)-X ··· (*R*)-X or (*S*)-X ··· (*R*)-X'] contacts.

Department of Chemistry, Eastern Illinois University, 600 Lincoln Avenue, Charleston, Illinois, 61910, USA. E-mail: kawheeler@eiu.edu

† Electronic supplementary information (ESI) available: Synthetic procedures, hot stage micrographs, X-ray powder and NMR spectroscopic data for Cl/Br, CH₃/CF₃, Br/CF₃, and Cl/I pairs, and full crystal structure and hydrogen bond tables for quasiracemates H/F, NO₂/CF₃, NO₂/Br, CH₃/CF₃, and CF₃/I, and group/framework volume and surface area comparisons. CCDC 1534589–1534594. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c7cc01638g

X =	Group	Group Surface
	Volume (Å ³)	Area (Å ²)
H	5.9	6.8
F	7.8	12.1
Cl	19.6	29.0
CN	21.0	32.2
CH ₃	22.3	33.4
NO ₂	23.2	37.0
Br	27.6	37.1
CF ₃	28.9	37.3
OCH ₃	32.6	40.1
I	34.6	45.0
C ₆ H ₅	82.9	94.9



Scheme 1 Chiral diarylamides used in the present study.

Moving beyond the current collection of known quasiracemic systems where component selection often follows pairs of closely related quasienantiomers, our investigation examined a topologically diverse set of related compounds to understand the structural boundaries of quasiracemate formation. A homologous family of *R* and *S* diarylamides that differ incrementally in the size and shape of the pendant substituents was selected for this study – a total of 22 compounds (Scheme 1). The collection of 2-substituted components range from $X = H$ to C_6H_5 with the topological features of these groups approximated using their volumes and surface areas.^{15,16} To exclude the challenges that arise from solvent-assisted crystal growth processes, cocrystallization of pairs of quasienantiomers was pursued from the melt using the Kofler contact fusion method.^{17–19} A utility of this technique draws attention to the formation of new crystalline phases during the heating cycle as indicated by the emergence of melting regions (eutectic regions) in the viewing area. In the case of racemic and quasiracemic mixtures, distinguishing between the various modes of crystallization (*i.e.*, racemic/quasiracemic compounds, conglomerates, and solid solutions) is possible given the unique thermal signature of each phase (Fig. 1). Fig. 2A demonstrates proof-of-concept as applied to the $(\pm)$ -*N*-(2-bromobenzoyl)methylbenzylamine system. The first snapshot indicates the two racemic components [(*S*)-Br (left), (*R*)-Br (right)] with a

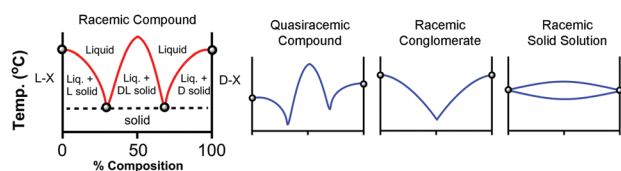


Fig. 1 Melting point phase diagrams of idealized racemic and quasiracemic mixtures.

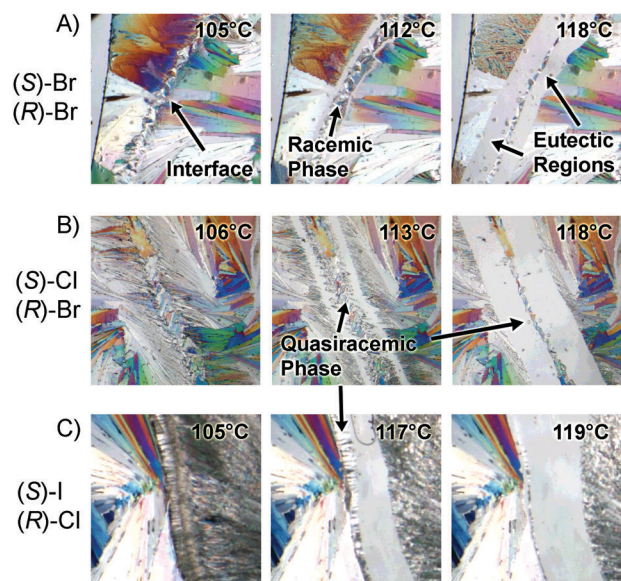


Fig. 2 Hot stage polarized light microscopy using the (A) (*S*)-Br (left) and (*R*)-Br (right), (B) (*S*)-Cl and (*R*)-Br and (C) (*S*)-I and (*R*)-Br pairs showing the emergence of new racemic and quasiracemic crystalline phases.

distinct interface between the crystalline phases. Video recording with increasing temperature provided an opportunity to view the thermal behavior of cocrystallization in real-time. The onset of melting of the (*S*)-Br and (*R*)-Br adducts occurs at 112 °C with the emergence of the racemic phase at the component interface (Fig. 2A, center and right micrographs). The identity of this racemic phase was further supported by comparing its X-ray powder pattern to those calculated from the known crystal structures of (*S*)-Br and $(\pm)$ -Br (ESI[†]).²⁰

The success of this method as applied to racemic Br suggests that the strategy could also be amenable to probing the molecular recognition profiles of quasiracemic systems. Similar to enantiomers (*S*)-Br and (*R*)-Br, quasienantiomers (*S*)-Cl and (*R*)-Br were thermally processed with video capture using the hot stage technique. Several micrographs of this process are provided in Fig. 2B with results showing the onset of melting near 113 °C for both the (*S*)-Cl (left) and (*R*)-Br (right) components. The complete thermal signature of this process offers an important glimpse into the molecular assembly of this material and highlights the formation of the (*S*)-Cl/(*R*)-Br quasiracemic phase at the interface region.

The appearance of the Cl/Br diarylamide quasiracemic phase was largely anticipated given the crystal structure was previously reported.²⁰ Furthermore, combining quasienantiomers that differ in Cl and Br substitutions has provided a common theme for other quasiracemate studies.^{9,21,22} Though similar in topological features (spherical), a change from Cl to Br represents a 41% increase in substituent volume and an overall increase in diarylamide framework volume of 3%. Evidently, the structural difference imposed by the Cl and Br substituents does not present a sufficient deterrent to quasiracemate formation. Even so, we wondered if expanding the margin of shape space using the Cl/I pair would also achieve similar molecular recognition. The absence of reports featuring Cl/I quasiracemates, significantly different volumes (77% increase for Cl/I and 6% when considering the entire diarylamide framework), and our lack of success with growing single crystals of (*S*)-I/(*R*)-Cl *via* solution methods initially suggested that the spatial difference of this substituent pair was beyond the structural boundary for quasiracemate formation. However, pursuing recognition behavior of the (*S*)-I/(*R*)-Cl quasienantiomeric pair from the melt yielded key insight to the recognition profile of this system. Inspection of Fig. 2C reveals a small, but distinct quasiracemic phase appearing at the boundary of the starting materials. This result, like that for the (*S*)-Cl/(*R*)-Br quasiracemic phase, underscores the importance of the recognition profile of quasienantiomers in forming quasiracemates from the melt.

Considering the success of the (*S*)-Cl/(*R*)-Br and (*S*)-I/(*R*)-Cl systems, could our hot stage approach be broadly applied as a diagnostic tool for mapping the shape space of quasiracemate assemblies? The collection of diarylamides selected for this study differ incrementally in size and shape and provided 55 unique bimolecular combinations (Scheme 1 and Fig. 3A). Thermally processing all possible sets as before and tabulating these results provided a comprehensive view of the topological landscape for this diarylamide family. It is initially worth noting that heating each enantiomeric pair resulted in, without exception,

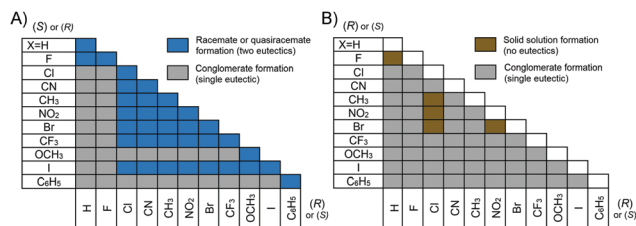


Fig. 3 Hot stage microscopy results from combining diarylamide (A) quasienantiomers and (B) molecular pairs with the same chirality [e.g. (*R*)-X and (*R*)-X'].

the growth of racemic phases where similar shapes of opposing chirality influence crystal formation. Such a structural bias during the heating stage is significant and indicates the relative thermodynamic stability of the racemic phase compared to that of the starting components. This same structural preference should also apply to the formation of the diarylamide quasiracemates. The remaining entries in Fig. 3A correspond to the thermal signatures of each quasienantiomeric pair. This data offers critical insight to those systems where a quasiracemic phase forms, but also highlights instances where quasiracemates fail to form as indicated by the appearance of a single eutectic region. Several important trends emerge from this data. Combining (*S*)-H and (*R*)-F diarylamides produced a quasiracemic phase, but conglomerates formed upon thermal processing using the other building blocks in the series, presumably owing to a greater difference in functional group/molecular shape profiles. It is not surprising the Cl/Br, Cl/CH₃, Br/CH₃, NO₂/CH₃ pairs gave new quasiracemic phases since these sets are topologically similar and have been successfully used with other quasiracemic systems.^{9,20,21,23,24} Of interest are also pairs that result in quasiracemates, but are less prevalent in the literature or consist of significantly different shape spaces (e.g. Cl/I, CN/CF₃).

One outlier in this study is the OCH₃ entry where molecular assembly with the second component only occurs with its enantiomer. This distinct hot stage behavior is consistent with the unique conformational topology of the OCH₃ adduct. Unlike other crystal structures of 2-substituted diarylamides, the structure of (*S*)-OCH₃ shows an intramolecular N-H...OCH₃ contact (N...O, 2.669(3) Å; N-H...O, 139(3)°). This interaction controls the conformation, and thus topological features of (*S*)-OCH₃ as indicated by a significantly smaller N-C(=O)-C_{Ar}-C_{Ar} torsion angle (18.4°) compared to other 2-substituted diarylamides (47.5–79.9°).[‡]

Since the formation of new crystalline phases does not necessarily signify quasiracemate formation, additional information was also retrieved for several sets of these thermally processed systems (ESI[†]). Both NMR and powder X-ray diffraction (PXRD) data were collected for the Cl/Br, CH₃/CF₃, NO₂/CF₃, Br/CF₃, and Cl/I pairs and crystal structures were determined or retrieved from the extant database for the H/F, Cl/Br, NO₂/CF₃, NO₂/Br, CH₃/CF₃, and CF₃/I quasiracemates. This collective information offers key support for the assignment of the quasiracemic phases generated from these hot stage experiments. Additionally, the crystal structures confirmed the role of

approximate inversion symmetry in these systems and in several cases provided calculated PXRD patterns for comparison with the hot stage samples.

As shown, the attraction between pairs of quasienantiomers results from their complementary topologies and the thermodynamic consequence of constructing approximate inversion related motifs. Close-packing arrangements achieved from these near symmetry motifs are significant and provide sufficient incentive for quasiracemate formation. Even so, what would be the impact by exchanging the handedness of one component of a quasiracemate to give (*R*)-X and (*R*)-X' pair [or (*S*)-X and (*S*)-X'] and then assessed using the hot stage method? If the pairs were altogether incompatible, then a thermal signature corresponding to a conglomerate should result. However, if comparable affinities of the (*R*)-X or (*R*)-X' molecules exist for the same compound and the other component then the hot stage event will reflect that of a solid solution. Fig. 4 shows the results from thermally processing the (*R*)-Cl/(*R*)-Br and (*R*)-I/(*R*)-Cl systems. The lack of eutectic region for (*R*)-Cl/(*R*)-Br (Fig. 4A, solid solution), but its presence in (*R*)-I/(*R*)-Cl (Fig. 4B, conglomerate) clearly shows the variation with these thermal signatures. Fig. 3B provides the hot stage results from processing the entire diarylamide family using pairs of components of the same chirality. Interestingly, only five of these entries – H/F, Cl/CH₃, Cl/NO₂, Cl/Br, and NO₂/Br – exhibit solid solution behavior. Because the structural principles that govern quasiracemic materials do not apply with these systems, hot stage results from (*R*)-X/(*R*)-X' binary mixtures offer a more subtle assessment tool of molecular topology.

In summary, we have developed experimental methods for assessing the structural boundary of molecular shape to molecular recognition. This strategy probes the complementary spatial features for a sizable family of diarylamide (*R*)-X/(*S*)-X' and (*R*)-X/(*R*)-X' pairs *via* hot stage microscopy. Without access to effective methods for evaluating molecular shape, this study represents a step forward in determining the role of topology features to molecules assembly.

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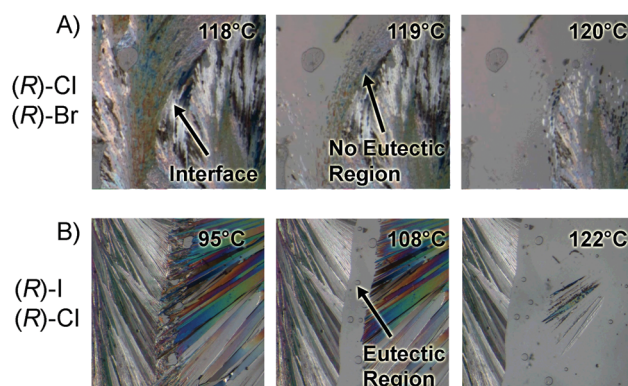


Fig. 4 Hot stage polarized light microscopy using the (A) (*R*)-Cl (left) and (*R*)-Br (right) and (B) (*R*)-I/(*R*)-Br pairs and showing the characteristics of solid solution and conglomerate crystalline phase formation.

Notes and references

‡ N–C(=O)–C_{Ar}–C_{Ar} torsion angles were retrieved from the CSD entries LUNPOZ, LUNPOZ01, LUNPUF, LUNQAM, LUNQEQ, and LUNQIU and crystal structures of quasiracemates H/F, NO₂/CF₃, NO₂/Br, CH₃/CF₃, and CF₃/I determined for this study.

- 1 E. Persch, O. Dumele and F. Diederich, *Angew. Chem., Int. Ed.*, 2015, **54**, 3290.
- 2 E. Mattia and S. Otto, *Nat. Nanotechnol.*, 2015, **10**, 111–119.
- 3 J.-M. Lehn, *Angew. Chem., Int. Ed.*, 2013, **52**, 2836.
- 4 R. Merindola and A. Walther, *Chem. Soc. Rev.*, 2017, DOI: 10.1039/C6CS00738D.
- 5 J.-M. Lehn, *Angew. Chem., Int. Ed.*, 1990, **29**, 1304.
- 6 T. S. Thakur, R. Dubey and G. R. Desiraju, *IUCrJ*, 2015, **2**, 159.
- 7 G. R. Desiraju, *J. Am. Chem. Soc.*, 2013, **135**, 9952.
- 8 D. B. Varshey, J. R. G. Sander, T. Friščić and L. R. MacGillivray in *Supramolecular Chemistry: From Molecules to Nanomaterials*, ed. J. W. Steed and P. A. Gale, John Wiley & Sons, Chichester, 2012, vol. 1, pp. 10–24.
- 9 J. M. Spaniol and K. A. Wheeler, *RSC Adv.*, 2016, **6**, 64921.
- 10 Q. Zhang and D. P. Curran, *Chem. – Eur. J.*, 2005, **11**, 4866.
- 11 R. E. Davis, J. K. Whitesell, M.-S. Wong and N.-L. Chang, in *Perspectives in Supramolecular Chemistry: The Crystal as a Supramolecular Entity*, ed. G. R. Desiraju, John Wiley & Sons, Chichester, 1996, ch. 3, vol. 2.
- 12 A. Nicholls, G. B. McGaughey, R. P. Sheridan, A. C. Good, G. Warren, M. Mathieu, S. W. Muchmore, S. P. Brown, J. A. Grant, J. A. Haigh, N. Nevins, A. N. Jain and B. Kelley, *J. Med. Chem.*, 2010, **53**, 3862.
- 13 A. Fredga, *Bull. Soc. Chim. Fr.*, 1973, **1**, 173.
- 14 S. P. Kelley, L. Fábán and C. P. Brock, *Acta Crystallogr., Sect. B: Struct. Sci.*, 2011, **B67**, 79.
- 15 A. Gavezzotti, *J. Am. Chem. Soc.*, 1985, **107**, 962.
- 16 A. Gavezzotti, *J. Am. Chem. Soc.*, 1983, **105**, 5220.
- 17 A. Lemmerer, J. Bernstein, U. J. Griesser, V. Kahlenberg, D. M. Tobbens, S. H. Lapidus, P. W. Stephens and C. Esterhuysen, *Chem. – Eur. J.*, 2011, **17**, 13445.
- 18 D. J. Berry, C. C. Seaton, W. Clegg, R. W. Harrington, S. J. Coles, P. N. Horton, M. B. Hursthouse, R. Storey, W. Jones, T. Friščić and N. Blagden, *Cryst. Growth Des.*, 2008, **8**, 1697.
- 19 L. Kofler and A. Kofler, *Thermal Micromethods for the Study of Organic Compounds and Their Mixtures*, Wagner, Innsbruck, 1952; translated by McCrone, W. C. McCrone Research Institute, Chicago, 1980.
- 20 S. L. Fomulu, M. S. Hendi, R. E. Davis and K. A. Wheeler, *Cryst. Growth Des.*, 2005, **5**, 727.
- 21 A. M. Lineberry, E. T. Benjamin, R. E. Davis, W. S. Kassel and K. A. Wheeler, *Cryst. Growth Des.*, 2008, **8**, 612.
- 22 F. Toda, K. Tanaka, H. Miyamoto, H. Koshima, I. Miyahara and K. Hirotsu, *J. Chem. Soc., Perkin Trans. 2*, 1997, 1877.
- 23 M. S. Hendi, P. Hooter, R. E. Davis, V. M. Lynch and K. A. Wheeler, *Cryst. Growth Des.*, 2004, **4**, 95.
- 24 J. T. Cross, N. A. Rossi, M. Serafin and K. A. Wheeler, *CrystEngComm*, 2014, **16**, 7251.