

Unraveling Chiral Selection in the Self-assembly of Chiral Fullerene Macroions: Effects of Small Chiral Components Including Counterions, Co-ions, or Neutral Molecules

Jiancheng Luo, Songtao Ye, Putu Ustriyana, Benqian Wei, Jiahui Chen, Ehsan Raee, Yinghe Hu, Yuqing Yang, Yifan Zhou, Chrys Wesdemiotis, Nita Sahai, and Tianbo Liu*



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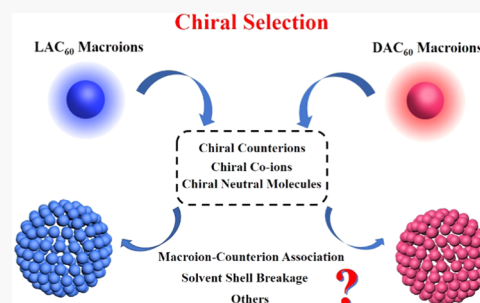


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ABSTRACT: Lactic acid-functionalized chiral fullerene (C_{60}) molecules are used as models to understand chiral selection in macroionic solutions involving chiral macroions, chiral counterions, and/or chiral co-ions. With the addition of Zn^{2+} cations, the C_{60} macroions exhibit slow self-assembly behavior into hollow, spherical, blackberry-type structures, as confirmed by laser light scattering (LLS), transmission electron microscopy (TEM), and atomic force microscopy (AFM) techniques. Chiral counterions with high charge density show no selection to the chirality of AC_{60} macroions (LAC_{60} and DAC_{60}) during their self-assembly process, while obvious chiral discrimination between the assemblies of LAC_{60} and DAC_{60} is observed when chiral counterions with low charge density are present. Compared with chiral counterions, chiral co-ions show weaker effects on chiral selection with larger amounts needed to trigger the chiral discrimination between LAC_{60} and DAC_{60} . However, they can induce a higher degree of discrimination when abundant chiral co-ions are present in solution. Furthermore, the self-assembly of chiral AC_{60} macroions is fully suppressed by adding significant amounts of neutral molecules with opposite chirality. Thermodynamic parameters from isothermal titration calorimetry (ITC) reveal that chiral selection is controlled by the ion pairing and the destruction of solvent shells between ions, and meanwhile originates from the delicate balance between electrostatic interaction and molecular chirality.



INTRODUCTION

Since Pasteur's discovery of molecular chirality,^{1–3} homochiral self-sorting phenomena have been extensively documented in solid state, especially crystallization processes,^{4–6} and later extended to the aggregation of amino acids in gas phase,^{7–9} molecular interaction at the interface,^{10,11} chemical reactions,^{12–15} and supramolecular assemblies.^{16–24} Despite the great efforts invested to understand the significance of homochirality in living systems (e.g., L-amino acids and D-sugars during the evolution of life^{25–27}), the origin of homochirality is still a matter of debate today.²⁸ How the tiny difference from molecular chirality is transmitted and amplified, and consequently initiates recognition or selection phenomena during supramolecular self-assembly, is still an intriguing question. As the formation of supramolecular complexes is driven by noncovalent interactions, some studies attempted to explore chiral recognition or selection by using such interactions, including hydrogen bonding,^{29–31} π interactions,^{32,33} host–guest interaction,^{34,35} electrostatic interaction,³⁶ etc. While these explorations mainly focus on different supramolecular structures achieved by chiral recognition/selection, a molecular-level understanding of chiral selection during supramolecular formation is still rare.

Biomacromolecules (e.g., proteins) are often charged, i.e., macroions.^{37–39} In solution, three components are often

essential for the behavior of macroions: counterions, co-ions, and neutral molecules such as solvents.^{40–42} Since biomacromolecules possess complicate molecular structures and various conformations in response to the solution conditions,^{43,44} some nanoscale molecules with a well-defined structure, size, and charge could be a valuable model to understand the origin of homochirality in nature. We previously reported that soluble ions with nanometer size (macroions), represented by polyoxometalates,⁴⁵ metal–organic nanocages,⁴⁶ and functional fullerenes (C_{60}),⁴⁷ can spontaneously self-assemble into single-layered, hollow, spherical supramolecular structures (blackberry-type) in solution. The kinetics of self-assembly process, as well as the final supramolecular structures, exhibits similarity to some bioprocesses such as virus capsid formation.⁴⁸ Moreover, the blackberry-type structures are highly sensitive to solution conditions^{47,49–51} (e.g., the type of counterions, co-ions, solvent polarity, and temperature),

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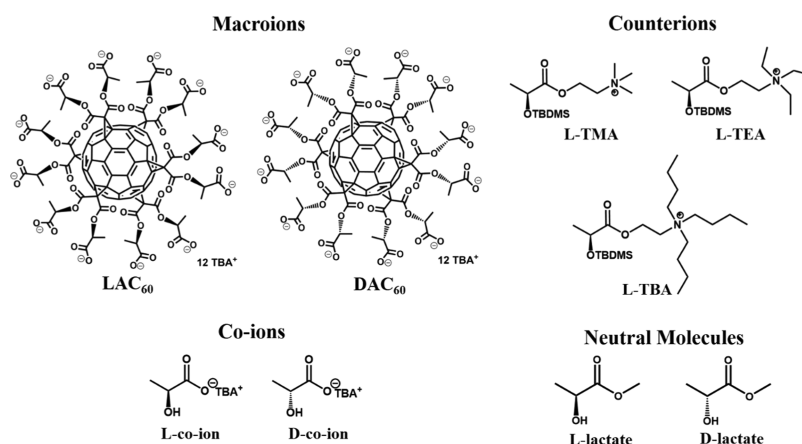


Figure 1. Molecular structures of chiral AC_{60} macroions, counterions, co-ions, and neutral molecules used in this study.

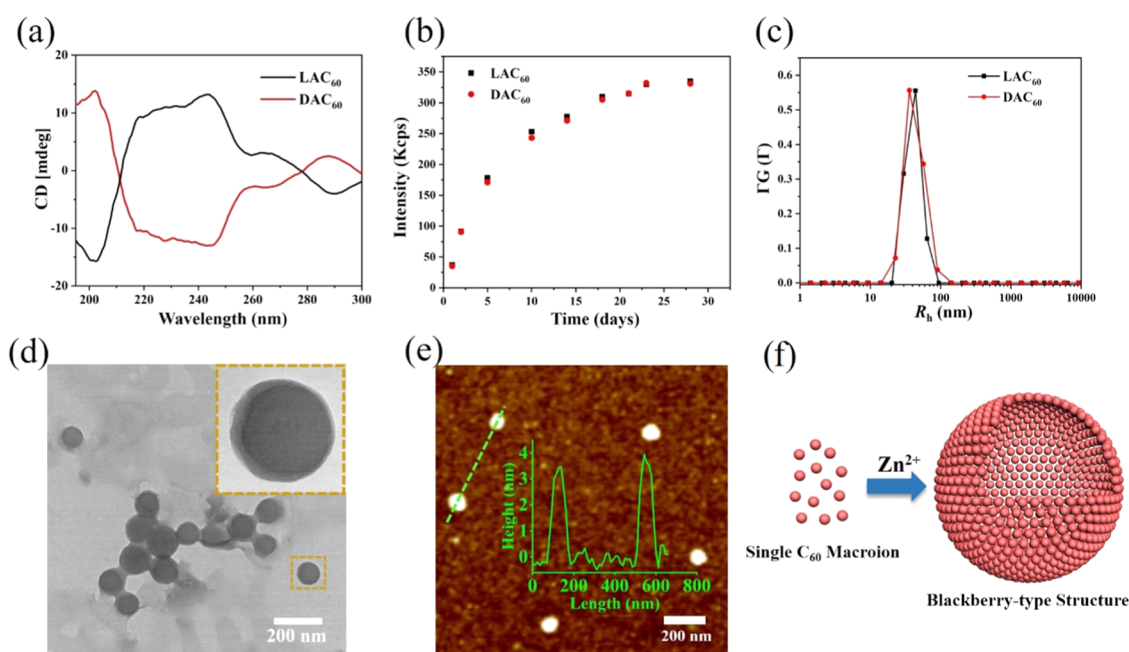


Figure 2. (a) CD spectra of LAC_{60} and DAC_{60} at the same solution concentration of 0.4 mg mL^{-1} . (b) Scattered intensities measured from 0.2 mg mL^{-1} LAC_{60} and DAC_{60} solutions with the addition of 10 equiv amounts of Zn^{2+} each. (c) CONTIN analysis of 0.2 mg mL^{-1} LAC_{60} and DAC_{60} solutions on the 23rd day. (d) TEM images of spherical assemblies. (e) AFM measurements of collapsed blackberries. (f) Schematic illustration of blackberry-type structures formed by chiral AC_{60} macroions.

making them good models to explore the interactions between macroions and other species in solution. Recently, we observed that two macroionic enantiomers tended to assemble into two types of chiral blackberries instead of mixed ones in their mixed solution, indicating an impressive chiral selection process that transmits the homochirality from molecular to supramolecular level.³⁶ The long-range electrostatic interaction is expected to play important roles behind this chiral recognition.

The next and more important question is how do these chiral macroions behave when they are in a chiral environment, *i.e.*, with other chiral components around them, such as chiral counterions, co-ions, or neutral molecules? Will these small chiral components have the same effect (identical interaction) on two macroionic enantiomers? If not, how significant can the difference be? We try to address these fundamental questions in this work, by using buckminsterfullerene (C_{60})^{52–55} functionalized with chiral lactic acids (AC_{60}) on the surface.

The anchored carboxylic acids make C_{60} fully hydrophilic, charged, and chiral. Two enantiomeric C_{60} macroions with identical chemical structure, size, and shape but opposite chirality (LAC_{60} and DAC_{60} in Figure 1) were synthesized, and they share similar features as macroions in polar solvents, as previously reported.³⁹ They are good models to explore interactions with small chiral species, including counterions, co-ions, and neutral molecules in solution, and consequently understand the effects of these small chiral components on chiral selection phenomena during supramolecular structure formation.

RESULTS AND DISCUSSION

Synthesis and Molecular Structure. The LAC_{60} and DAC_{60} macroions were prepared through the Bingel–Hirsch cyclopropanation reaction.^{56–59} Each C_{60} was functionalized with 12 lactic acids and fully characterized by ^1H NMR, ^{13}C NMR, matrix-assisted laser desorption/ionization time-of-flight

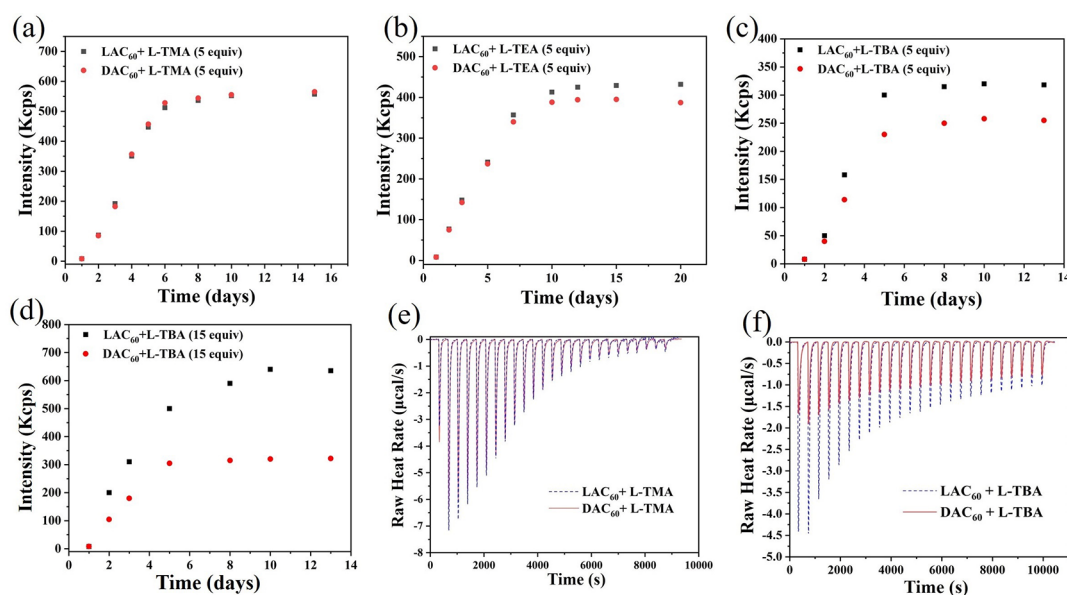


Figure 3. SLS measurements of LAC₆₀ and DAC₆₀ solutions when adding 5 equiv amounts of (a) L-TMA, (b) L-TEA, and (c) L-TBA, and (d) 15 equiv amounts of L-TBA. ITC titration curves of (e) L-TMA and (f) L-TBA into LAC₆₀ and DAC₆₀ solutions.

mass spectrometry (MALDI-TOF MS), and ultraviolet–visible (UV–vis) in Figures S1–S20. The chemical structures of chiral counterions, co-ions, and neutral molecules are shown in Figure 1 (detailed synthetic procedures and characterizations in Figures S21–S45).

Self-assembly of Chiral AC₆₀ Macroions in Solution.

The LAC₆₀ and DAC₆₀ have identical chemical composition, size, and charge number, with the only difference being chirality, as confirmed by circular dichroism (CD) measurements (Figure 2a). The AC₆₀ with COOH groups (AC₆₀–COOH in Figure S19) has very limited solubility in water unless increasing the solution pH to 12. Therefore, acetonitrile is used for this study, in which the AC₆₀ is quite soluble. Previously, we reported that the counterion-mediated attraction was an important driving force for the self-assembly of macroions.⁶⁰ To enhance the strength of the counterion-mediated attraction, the COOH groups are neutralized with tetrabutylammonium hydroxide (TBAOH; detailed procedure in the Supporting Information). In addition to the increase in charge density on the AC₆₀ surface, extra divalent cations with strong binding with AC₆₀ are added to enhance the macroion–counterion-mediated attraction. ZnCl₂ is chosen for this study due to its good solubility in acetonitrile. As monitored by static light scattering (SLS), the scattered intensities of 0.2 mg mL^{−1} LAC₆₀ or DAC₆₀ in MeCN slowly and continuously increase and become stable after a long time period (Figure 2b), indicating the formation of large supramolecular structures. The slow self-assembly kinetics of macroions, which usually takes several weeks or even months, has also been reported in our previous studies.^{45,47} From the final scattered intensity, LAC₆₀ and DAC₆₀ solutions show no obvious difference. Moreover, the CONTIN analysis⁶¹ of dynamic light scattering (DLS) measurements demonstrates that the hydrodynamic radii (R_h) of assemblies formed by LAC₆₀ and DAC₆₀ are identical (46 nm in Figure 2c), indicating that they have no difference when interacting with Zn²⁺. The average radius of the spherical assemblies from transmission electron microscopy (TEM) measurements (51 ± 8 nm in Figure 2d) is consistent with that of DLS measurements. Furthermore, the

radius of gyration (R_g) of the assemblies obtained from SLS measurements is 48 ± 3 nm (Figure S46), leading to the R_g/R_h ratio of 1.04, matching the theoretical value for a hollow sphere model (1.00).⁶² Therefore, the hollow spheres have either a single layer or a few layers of AC₆₀ molecules on their surface. The results from atomic force microscopy (AFM) measurements (Figure 2e) further confirm the single-layered model. The average height of the collapsed spheres after drying is 3.7 ± 0.3 nm (detailed analysis in Figures S47 and S48), which is close to two layers of AC₆₀ macroions (diameter ~1.5 nm), suggesting that the hollow spheres are likely to contain only one layer of AC₆₀ on the surface. The combined results from light scattering, TEM, and AFM confirm that single-layered, hollow, spherical assemblies (blackberry-type structures) are formed in solution.

Effects of Counterions on the Chiral Selection of AC₆₀ Macroions. The addition of Zn²⁺ cations leads to the formation of identical blackberry-type assemblies by LAC₆₀ and DAC₆₀. The next question is the effects of chiral counterions. Figure 1 shows monovalent chiral counterions with increasing sizes from L-TMA to L-TEA and then to L-TBA, *i.e.*, decreasing charge density. For a typical experiment, two enantiomeric solutions (0.2 mg mL^{−1} LAC₆₀ and DAC₆₀, each with 10 equiv of Zn²⁺) were prepared, and additional chiral counterions (L-TMA, L-TEA, or L-TBA) were added into the solutions. For L-TMA (Figure 3a), LAC₆₀ and DAC₆₀ solutions have almost the same scattered intensity at equilibrium, indicating that L-TMA cannot induce chiral selection during the self-assembly of AC₆₀ macroions. When larger counterions (L-TEA) are used, the final scattered intensity from the LAC₆₀ solution is slightly higher than that from the DAC₆₀ solution (Figure 3b). Moreover, the difference between LAC₆₀ and DAC₆₀ solutions is further magnified when even bulkier L-TBA counterions are applied (Figure 3c). DLS measurements show that the assembly sizes in LAC₆₀ and DAC₆₀ solutions are nearly identical with the presence of chiral counterions (Figures S49–S51), suggesting that the higher scattered intensity of LAC₆₀ solutions is due to the higher number of assemblies in solution,⁶² *i.e.*, LAC₆₀ has a higher

Table 1. Thermodynamic Parameters Fitted from ITC Titrations of Chiral Counterions into LAC₆₀/DAC₆₀ Solutions

	<i>n</i>	ΔH (kJ mol ⁻¹)	$-T\Delta S$ (kJ mol ⁻¹)	ΔG (kJ mol ⁻¹)	K_a (M ⁻¹)
LAC ₆₀ + L-TMA	10.1 ± 0.5	-5.86 ± 0.24	-15.89 ± 0.37	-21.75 ± 0.12	(7.49 ± 0.36) × 10 ³
DAC ₆₀ + L-TMA	10.8 ± 0.3	-3.83 ± 0.15	-17.79 ± 0.42	-21.62 ± 0.17	(7.12 ± 0.50) × 10 ³
LAC ₆₀ + L-TBA	5.6 ± 0.8	-11.25 ± 0.48	-4.51 ± 0.13	-15.76 ± 0.21	(6.42 ± 0.54) × 10 ²
DAC ₆₀ + L-TBA	4.7 ± 0.5	-3.44 ± 0.31	-10.45 ± 0.62	-13.89 ± 0.40	(2.98 ± 0.48) × 10 ²

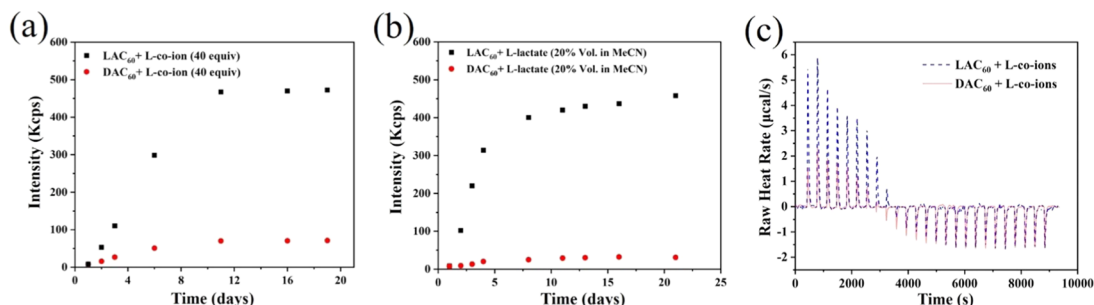


Figure 4. (a) SLS measurements of 0.2 mg mL⁻¹ LAC₆₀ and DAC₆₀ solutions (MeCN, 10 equiv of Zn²⁺) when adding 40 equiv of L-co-ions. (b) SLS measurements of 0.2 mg mL⁻¹ LAC₆₀ and DAC₆₀ solutions (10 equiv of Zn²⁺) with a solution condition of 20 vol % L-lactate in MeCN. (c) ITC titration curves of L-co-ions into LAC₆₀ and DAC₆₀ solutions.

tendency to form supramolecular structures with the help of L-counterions. Increasing L-TBA concentration further magnified the difference (Figure 3d).

It is intriguing that some chiral counterions can induce discrimination between the assemblies of two enantiomeric AC₆₀, while others cannot. To further understand this observation, isothermal titration calorimetry (ITC) is applied to determine the binding affinity (K_a) and other thermodynamic parameters such as enthalpy (ΔH) and entropy (ΔS) during the macroion-counterion interaction.^{63,64} During the binding process, the macroion-counterion ion pairing leads to a thermodynamic change of $\Delta H < 0$ and $\Delta S < 0$, while the breakage of their solvent shells is a process with $\Delta H > 0$ and $\Delta S > 0$.^{65–67} From ITC titration curves of L-counterions (L-TMA and L-TBA in Figure 3d,e, respectively), the macroion-counterion interaction shows exothermic peaks, suggesting that the ion pairing is dominant over the breakage of solvent shells due to the strong electrostatic interaction (macroion-counterion association). From Figure 3d, the heat releases between LAC₆₀ + L-TMA and DAC₆₀ + L-TMA titrations exhibit no significant difference, consistent with the SLS results that LAC₆₀ and DAC₆₀ assemble almost identically in the presence of L-TMA. The binding numbers (n) of two titrations (10.1 and 10.8 in Table 1) are close to the charge ratio of AC₆₀/L-TMA (12), indicating that L-TMA interacts strongly with chiral AC₆₀ macroions and consequently can effectively replace the original counterions. In comparison, the titrations of L-TBA show that the heat release of LAC₆₀ + L-TBA is higher than that of DAC₆₀ + L-TBA, i.e., stronger interaction between L-TBA and LAC₆₀. The binding numbers (n) from L-TBA titrations are less than those from L-TMA titrations due to the lower charge density of L-TBA (Table 1), which accordingly weakens their interactions with macroions and leads to partial replacement of the original counterions.

Interestingly, although the free energies ΔG of the two L-TMA titrations (LAC₆₀ + L-TMA and DAC₆₀ + L-TMA in Table 1) are very close, the contributions from entropy and enthalpy are quite different. Compared with DAC₆₀, the interaction between LAC₆₀ and L-TMA has smaller ΔH to favor the lower ΔG . However, the interaction of LAC₆₀ + L-

TMA is entropically unfavored (larger ΔS). The enthalpy-entropy compensation leads to a similar level of ΔG between two L-TMA titrations. Therefore, L-TMA exhibits the same tendency to interact with two chiral AC₆₀ macroions, regardless of their opposite chirality. When counterions with lower charge density are used (L-TBA), the enthalpy/entropy differences between LAC₆₀ + L-TBA and DAC₆₀ + L-TBA titrations are further magnified (Table 1). Moreover, the enthalpic advantage of LAC₆₀ + L-TBA titration is dominant over its entropic disadvantage compared with DAC₆₀ + L-TBA titration; consequently, the ΔG of LAC₆₀ + L-TBA titration is lower than that of DAC₆₀ + L-TBA titration, making the interaction between L-TBA and LAC₆₀ more preferred—also matching our SLS observations that the final scattered intensity of LAC₆₀ + L-TBA solution is higher than that of DAC₆₀ + L-TBA (Figure 3c,d). For molecules with special shapes such as helices or macrocycles,^{68–70} the entropic advantages, originated from a more condensed packing of one enantiomer over the other, are widely reported as an important reason for the chiral selection. However, the chiral AC₆₀ is spherical. Meanwhile, the preferred interaction of LAC₆₀ + L-TBA is largely due to enthalpy⁶⁶ (from macroion-counterion association; Figure 5a), as confirmed by the ITC, suggesting that the chiral selection here is quite different from the geometry-induced ones reported earlier. Therefore, the chiral AC₆₀ is a good model to understand the chiral selection process controlled by the electrostatic interaction.

Effect of Co-ions on the Chiral Selection of AC₆₀ Macroions. In solution, co-ions have the same type of charge as macroions. The electrostatic repulsion forces them away from the central macroions, and they are expected to have less impact on the solution behavior of macroions. A common effect of co-ions is to stabilize single macroions by forming an external layer outside the layer of associated counterions.^{71–73} However, co-ion effects are ubiquitous in various systems such as chemistry and biology.^{74–77} Our group also reported strong co-ion effects on the self-assembly of charged metal-organic macrocycles⁷⁸ and chiral polyoxometalates.³⁶ Therefore, it is interesting to explore co-ion effects on chiral selection.

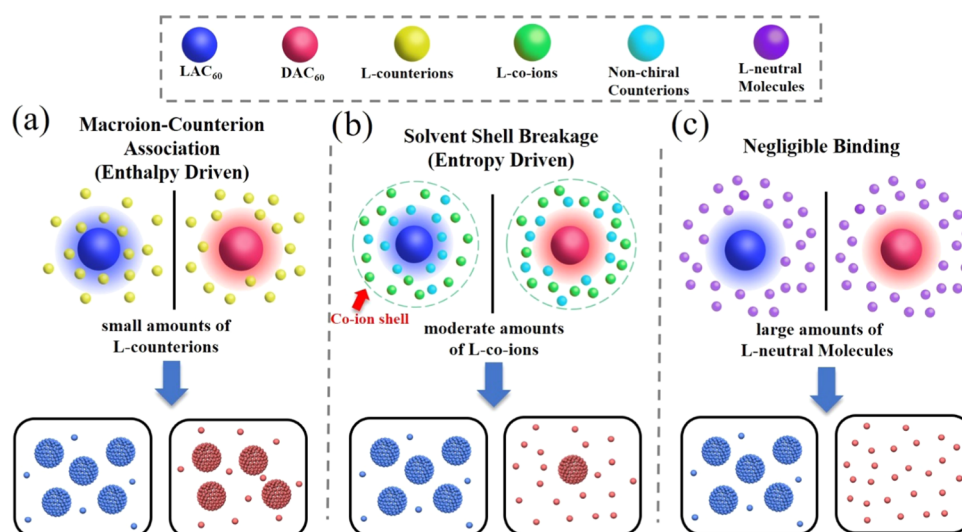


Figure 5. (a) Schematic illustration showing the effects of chiral counterions (a), chiral co-ions (b), and chiral neutral molecules (c) on the self-assembly and chiral selection during the blackberry formation of LAC₆₀ and DAC₆₀. In counterion case (a), the preferred interaction between LAC₆₀ and L-counterions attracts more counterions closely associated with LAC₆₀ macroions. In the co-ion case (b), the stronger interaction between L-co-ions and DAC₆₀—counterion system leads to less solvent shell breakages of macroions by attracting more counterion away from the central macroions and therefore suppresses the self-assembly of DAC₆₀. While in the neutral molecule case (c), the binding between chiral C₆₀ macroions and chiral neutral molecules is negligible. In each figure, the rest of counterions, co-ions, or neutral molecules are omitted for clarity.

Table 2. Thermodynamic Parameters Fitted from ITC Titrations of Chiral Co-ions into LAC₆₀/DAC₆₀ Solutions

	<i>n</i>	ΔH (kJ mol ^{−1})	$-T\Delta S$ (kJ mol ^{−1})	ΔG (kJ mol ^{−1})	K_s (M ^{−1})
LAC ₆₀ + L-co-ion	9.1 ± 0.5	3.70 ± 0.30	−28.70 ± 0.71	−25.00 ± 0.45	(2.85 ± 0.52) × 10 ⁴
DAC ₆₀ + L-co-ion	8.6 ± 0.6	1.99 ± 0.13	−25.42 ± 0.56	−23.43 ± 0.46	(1.49 ± 0.28) × 10 ⁴

For counterions (L-TBA in Figure 3c), the obvious difference between LAC₆₀ and DAC₆₀ solutions can be observed when small amounts of L-TBA counterions (5 equiv) are added. In the case of co-ions, the amount needed to trigger a noticeable difference between LAC₆₀ and DAC₆₀ is larger (20 equiv, Figure S52), indicating that chiral co-ions have weaker effects. By adding 40 equiv of L-co-ions into LAC₆₀ and DAC₆₀ solutions, respectively, LAC₆₀ solutions show faster self-assembly rate with higher scattered intensity at equilibrium, while the self-assembly of DAC₆₀ is significantly suppressed (Figure 4a). When replacing L-co-ions with D-co-ions, the self-assembly of DAC₆₀ is promoted and LAC₆₀ solutions show lower scattered intensity (Figure S53). Surprisingly, although the effects of chiral co-ions are weaker than chiral counterions in terms of the concentration needed to initiate a noticeable difference between LAC₆₀ and DAC₆₀ solutions, chiral co-ions can induce a more significant difference when abundant co-ions are present. For example, the maximum difference in the amount of final assemblies (LAC₆₀/DAC₆₀) achieved by chiral counterions is 2.0 (15 equiv of L-TBA, Figure 3d), while the maximum difference (LAC₆₀/DAC₆₀) in the case of chiral co-ions is 6.6 when 40 equiv of L-co-ions is added (Figure 4a). With the further addition of chiral counterions or chiral co-ions, the blackberry-type structures start to become unstable due to the high ionic strength.⁴⁹ This result suggests that co-ions can induce stronger chiral selection than counterions. When the interactions between macroions and nearby molecules are too strong, it considerably eliminates the difference (D and L) originated from molecular chirality. Observations from the chiral counterion experiments also support this speculation. Among the three counterions (L-TMA, L-TEA, and L-TBA),

L-TMA has the strongest electrostatic interaction with chiral AC₆₀ macroions; as a result, LAC₆₀ and DAC₆₀ solutions show almost no difference in response to L-TMA.

ITC studies are further applied to understand the effect of co-ions by exploring how the presence of chiral co-ions impacts the macroion–counterion interaction during ITC titration. Unlike exothermic peaks observed from the titrations of different chiral counterions, the titrations of salts involving chiral co-ions show overall endothermic processes (Figure 4c), indicating that the breakage of solvent shells ($\Delta H > 0$) is dominant over the ion pairing ($\Delta H < 0$).⁶⁶ The co-ions are usually believed to stay outside the counterion layer, which is associated with a central macroion, and provide an additional shell to further stabilize the individual macroion (Figure 5b),^{72,79} making the macroion–macroion attraction (and their self-assembly) more difficult. If the co-ions tend to interact with the counterion–macroion system stronger, their presence tends to attract the counterions slightly away from the macroions, leading to a less degree of solvent shell breakage of macroions. ITC titration curves show that the L-co-ions + LAC₆₀ interaction can absorb more energy than the L-co-ions + DAC₆₀ interaction (Figure 4c), suggesting less effective destruction of solvent shells in DAC₆₀ solutions. Fitting the ITC data reveals that the enthalpy of DAC₆₀ + L-co-ion titration is lower than that of LAC₆₀ + L-co-ion titration (Table 2), which again confirms a less degree of solvent shell breakage of DAC₆₀. That is, the L-co-ions tend to interact with the counterion–DAC₆₀ system stronger and consequently stabilize the single DAC₆₀ more effectively. This is consistent with the SLS studies that the self-assembly in L-co-ions + DAC₆₀ solution has been suppressed significantly compared with that in L-co-ions + LAC₆₀ solution. Interestingly, although the

interaction between LAC₆₀ and L-co-ions is energetically unfavored (higher ΔH) compared with that of DAC₆₀ + L-co-ions, the entropic gain of LAC₆₀ + L-co-ion titration is much higher and eventually overcomes its disadvantage in enthalpy. As a result, the free energy ΔG of LAC₆₀ + L-co-ion titration is lower than that of DAC₆₀ + L-co-ion titration, making the interaction between L-co-ions and LAC₆₀ preferred over DAC₆₀. Therefore, the chiral selection induced by chiral co-ions is controlled by the entropic gain (related to the solvent shell breakage, shown in Figure 5b), which is completely different from the chiral counterions that the chiral selection is mainly attributed to the difference in enthalpy (related to macroion–counterion association, shown in Figure 5a).

Effects of Neutral Molecules on the Chiral Selection of AC₆₀ Macroions. Chiral methyl lactates (L-lactate and D-lactate in Figure 1) are used to explore whether chiral neutral molecules can impact the self-assembly of LAC₆₀ and DAC₆₀. Without charge, their interactions with macroions are supposed to be negligible (Figure 5c). Indeed, ITC titrations of lactates into chiral AC₆₀ solutions (Figure S54) show that the energy levels are close to background titrations (lactates into solvent), suggesting a very weak interaction between lactates and AC₆₀. From SLS measurements, LAC₆₀ and DAC₆₀ solutions show almost identical self-assembly rate even with the addition of 100 equiv of L-lactate (~0.3 vol % in MeCN; Figure S55), again confirming the very weak effect of lactates. Interestingly, when the added lactates (e.g., L-lactate) further increase to extremely large amounts (5 vol % in MeCN, ~1600 equiv), LAC₆₀ and DAC₆₀ solutions start to exhibit different self-assembly rates, as well as scattered intensity at equilibrium (Figure S56). By further increasing the amounts of L-lactate to 20 vol % in MeCN, the difference becomes more significant, and the self-assembly of DAC₆₀ is fully suppressed (Figure 4b). Unlike counterions and co-ions, which can bind to macroions within a certain length scale (electric double layer^{80,81}), the neutral molecules are evenly distributed in solution because they almost do not interact with macroions. Therefore, the amounts of neutral molecules to trigger chiral selection should be considerably higher than those of counterions/co-ions. However, with the absence of electrostatic interaction, the difference (D and L) from molecular chirality will play the major roles. Moreover, the macroions can stay stable with very large amounts of neutral molecules; eventually, in solution with concentrated chiral neutral molecules, the degree of chiral selection (14.9 in Figure 4b) is observed to be higher than the values from chiral counterions (2.0 in Figure 3c) and co-ions (6.6 in Figure 4a).

CONCLUSIONS

The self-assembly of two C₆₀-based chiral macroions into blackberry-type supramolecular structures is studied in the presence of chiral counterions, chiral co-ions, and chiral neutral molecules, respectively, aiming to understand their effects on inducing the chiral selection during the supramolecular structure formation. High-charge-density chiral counterions (L-TMA) do not show chiral selection feature, while low-charge-density chiral counterions (L-TBA) show obvious discrimination between LAC₆₀ and DAC₆₀ (favoring LAC₆₀). Chiral co-ions can also demonstrate the chiral selection phenomenon, but larger amounts are needed; however, they can induce a higher degree of selection than counterions. ITC measurements reveal that the chiral selection induced by counterions is mainly controlled by enthalpic advantages

originating from the macroion–counterion ion pairing, while entropic advantages from the solvent shell breakage of macroions are responsible for the chiral selection in the case of co-ions. Chiral neutral molecules do not interact electrostatically with macroions; therefore, their impact on the chiral selection of macroions requires a very high concentration of chiral neutral molecules, and the macroions can stay stable under such condition. A very high degree of chiral selection can be achieved with the abundant chiral neutral molecule solution. This study unveils different reasons and impacts of chiral counterions, chiral co-ions, and chiral neutral molecules on the chiral selection in macroionic solutions. In the future, other chiral macroions, which are suitable for the studies in aqueous solution, will be explored.

EXPERIMENTAL SECTION

Dynamic Light Scattering (DLS) and Static Light Scattering (SLS). Both DLS and SLS measurements were performed on a Brookhaven Instruments light scattering spectrometer equipped with a diode-pumped solid-state (DPSS) laser operating at 532 nm and a BI-9000AT multichannel digital correlator. The SLS was performed over a broad range of scattered angles from 40 to 90°, with 2° interval. The radius of gyration (R_g) was calculated by using a partial Zimm plot derived from the Rayleigh–Gans–Debye equation. The partial Zimm plot was obtained from the following approximate formula: $1/I = C(1 + R_g^2 q^2/3)$. The R_g was determined from the slope and intercept of a plot of $1/I$ vs q^2 . For DLS measurements, the intensity–intensity time correlation functions were analyzed by the constrained regularized (CONTIN) method. The average apparent translational diffusion coefficient, D_{app} , was determined from the normalized distribution function of the characteristic line width, $\Gamma(G)$. The hydrodynamic radius (R_h) was converted from D through the Stokes–Einstein equation: $R_h = KT/6\pi\eta D$, where K is the Boltzmann constant and η is the viscosity of the solvent at temperature T .

Nuclear Magnetic Resonance (NMR). Both ¹H NMR and ¹³C NMR were measured on a Varian NMRS 500 spectrometer equipped with a 5 mm dual-broad-band probe. Noise reduction was performed when appropriate.

Transmission Electron Microscopy (TEM). TEM images were taken on a JEOL JEM-1230 electron microscope operated at 120 kV. Samples for TEM analysis were prepared by dropping a small volume of solution on the copper grid and drying under an oil pump; the average radius of assemblies was calculated based on the measured size of spheres in the TEM image.

Matrix-Assisted Laser Desorption/Ionization Time-of-Flight (MALDI-TOF) Mass Spectroscopy. MALDI-TOF mass spectra were measured on a Bruker Ultraflex III TOF/TOF mass spectrometer (Bruker Daltonics). Trans-2-[3-(4-*tert*-butylphenyl)-2-methyl-2-propenylidene] malononitrile (DCTB) was used as the matrix compound. The sample was prepared by depositing a 0.5 μ L matrix solution on the wells of a 384-well ground-steel plate and depositing 0.5 μ L of the sample solution on a spot of dried matrix and then adding another 0.5 μ L matrix solution on top of the dried sample. Mass spectra were measured in the reflection mode, and the mass scale was calibrated externally with PS standards with similar molecular weights to those of the samples under consideration. Data analyses were conducted with Bruker's Flex Analysis software.

Isothermal Titration Calorimetry (ITC). The ITC measurements were conducted on a commercial TA Instruments Nano ITC system. The instrument was equipped with a 1.0 mL sample cell and an identical reference cell with an adiabatic shield in a vacuum-tight chamber. For a typical experiment, 1.0 mL LAC₆₀ or DAC₆₀ acetonitrile solutions were loaded into the sample cell, and the reference cell was filled with 1.0 mL acetonitrile. Chiral counterion, co-ion, or neutral molecule solutions (MeCN) were loaded into a 250 μ L titration syringe and titrated into the sample cell with 10 μ L as the interval. The background heat was subtracted by titrating the same concentration of counterion, co-ion, or neutral molecule solutions

into acetonitrile. All thermodynamic parameters were fitted by the independence model. The error bars were calculated based on the fitting curves (with a 95% confidence level) by using NanoAnalyze software.

Circular Dichroism (CD). The CD measurements were performed on a Jasco J-1500 Series circular dichroism spectropolarimeter in a 1 mm cuvette (J/05S6, Jasco). The range of measurement was set as 195–300 nm, and the LAC₆₀ or DAC₆₀ solution was prepared in acetonitrile at a concentration of 0.4 mg mL⁻¹. Each measurement was conducted at 25 °C using a data pitch of 0.2 nm, a 2 nm bandwidth, a response time of 4 s, and a scan speed of 50 nm min⁻¹. Six accumulations were averaged for each measurement.

Ultraviolet–Visible Spectroscopy (UV–Vis). UV–vis experiments were performed on an Agilent Technologies 8453 UV–vis spectrophotometer and analyzed by UV–vis ChemStation Software.

Atomic Force Microscope (AFM). AFM measurements were performed on a Dimension Icon AFM (Bruker AXS). Samples were prepared by drop-casting the solution onto silica substrates. Tapping mode and a Bruker AFM tip (RTESPA-150) were used.

Sample Preparation. The preparation of LAC₆₀ and DAC₆₀ can be found in the Supporting Information. Since the AC₆₀ can only be dissolved in high pH water (pH > 12), and meanwhile the divalent or trivalent cations will precipitate in such a high pH solution, acetonitrile is used instead of water. Typically, LAC₆₀ or DAC₆₀ was dissolved in acetonitrile, and then the solutions were filtered through a PTFE syringe filter with a 200 nm pore size. The filtered solutions were loaded into a 20 mL vial, and additional ZnCl₂/small chiral molecule solutions (MeCN, prefiltered) were added accordingly.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acs.langmuir.0c00611>.

Sample preparations, detailed synthetic procedures and characterizations of chiral AC₆₀ macroions, counterions, and co-ions, ITC fitting curves, AFM analysis, and other SLS/DLS results (PDF)

■ AUTHOR INFORMATION

Corresponding Author

Tianbo Liu — Department of Polymer Science, The University of Akron, Akron, Ohio 44325, United States; orcid.org/0000-0002-8181-1790; Email: tliu@uakron.edu

Authors

Jiancheng Luo — Department of Polymer Science, The University of Akron, Akron, Ohio 44325, United States; orcid.org/0000-0002-3766-4922

Songtao Ye — Department of Polymer Science, The University of Akron, Akron, Ohio 44325, United States

Putu Ustriyana — Department of Polymer Science, The University of Akron, Akron, Ohio 44325, United States; orcid.org/0000-0001-9804-3081

Benqian Wei — Department of Polymer Science, The University of Akron, Akron, Ohio 44325, United States

Jiahui Chen — Department of Polymer Science, The University of Akron, Akron, Ohio 44325, United States; orcid.org/0000-0002-3861-146X

Ehsan Raee — Department of Polymer Science, The University of Akron, Akron, Ohio 44325, United States

Yinghe Hu — Department of Polymer Science, The University of Akron, Akron, Ohio 44325, United States

Yuqing Yang — Department of Polymer Science, The University of Akron, Akron, Ohio 44325, United States; orcid.org/0000-0002-5407-5740

Yifan Zhou — Department of Polymer Science, The University of Akron, Akron, Ohio 44325, United States

Chrys Wesdemiotis — Department of Polymer Science and Department of Chemistry, The University of Akron, Akron, Ohio 44325, United States

Nita Sahai — Department of Polymer Science, The University of Akron, Akron, Ohio 44325, United States; orcid.org/0000-0003-3852-0557

Complete contact information is available at:

<https://pubs.acs.org/10.1021/acs.langmuir.0c00611>

Notes

The authors declare no competing financial interest.

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