Rapid Dissolution of BaSO₄ by Macropa, an 18-Membered Macrocycle with High Affinity for Ba²⁺

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Supporting Information

ABSTRACT: Insoluble BaSO₄ scale is a costly and time-consuming problem in the petroleum industry. Clearance of BaSO₄-impeded pipelines requires chelating agents that can efficiently bind Ba²⁺, the largest nonradioactive +2 metal ion. Due to the poor affinity of currently available chelating agents for Ba²⁺, however, the dissolution of BaSO₄ remains inefficient, requiring very basic solutions of ligands. In this study, we investigated three diaza-18-crown-6 macrocycles bearing different pendent arms for the chelation of Ba²⁺ and assessed their potential for dissolving BaSO₄ scale. Remarkably, the bis-picolinate ligand macropa exhibits the highest affinity reported to date for Ba²⁺ at pH 7.4 (log K°′ = 10.74), forming a complex of significant kinetic stability with this large metal ion. Furthermore, the BaSO₄ dissolution properties of macropa dramatically surpass those of the state-of-the-art ligands DTPA and DOTA. Using macropa, complete dissolution of a molar equivalent of BaSO₄ is reached within 30 min at room temperature in pH 8 buffer, conditions under which DTPA and DOTA only achieve 40% dissolution of BaSO₄. When further applied for the dissolution of natural barite, macropa also outperforms DTPA, showing that this ligand is potentially valuable for industrial processes. Collectively, this work demonstrates that macropa is a highly effective chelator for Ba²⁺ that can be applied for the remediation of BaSO₄ scale.

INTRODUCTION

Barium, the 14th most abundant element in the earth’s crust, is the heaviest and largest nonradioactive alkaline earth (AE) metal.² Administered as a suspension of BaSO₄, this element has been employed for over a century as a contrast agent for X-ray imaging of the gastrointestinal tract.³ The insolubility of BaSO₄ (Ksp = 1.08 × 10⁻¹⁰)³ is essential for its use in medicine because it prevents this toxic heavy metal from being absorbed into the body. This same physical property, however, presents a serious problem in the industrial sector. Precipitation of BaSO₄ occurs frequently in oil field and gas production operations. When Ba²⁺-rich formation waters mix with SO₄²⁻-rich seawater, an intractable scale of BaSO₄ is deposited, obstructing downhole pipes and surface equipment.⁵ As such, BaSO₄ scale is a major economic burden to the petroleum industry that slows or halts production and requires costly scale removal efforts.⁶,⁷ In addition, the scale poses a significant health hazard to petroleum workers. Naturally occurring radioactive material (NORM), particularly long-lived bone-seeking Ba²⁺ ions, is readily incorporated into BaSO₄ and is mobilized during scale remediation, exposing humans to toxic levels of radioactivity.⁸,⁹ Hence, the efficient and safe removal of BaSO₄ scale is of global significance.

The elimination of BaSO₄ scale is achieved by solubilization using chelating agents.¹⁰⁻¹⁴ One of the most commonly used chelators is the acyclic ligand DTPA (Chart 1).¹² The thermodynamic stabilities of DTPA complexes of the AEs, however, decrease with increasing ionic radius of the metal ion, rendering DTPA a relatively low-affinity ligand for Ba²⁺ (log KBaL = 8.78).¹⁵ Extreme conditions of high pH (pH > 11) and heat are required to efficiently remove scale using DTPA,¹⁶ reflecting the fact that this ligand is not optimal for the chelation of Ba²⁺. The tetraaza macrocycle DOTA (Chart 1) has also been investigated for the dissolution of BaSO₄.¹² Despite having the highest reported thermodynamic affinity for Ba²⁺ in aqueous solution (log KBaL = 11.75),¹⁸⁻²¹ DOTA dissolves BaSO₄ less efficiently than DTPA,²² reflecting the slow metal-binding kinetics of this macrocycle. Collectively, these limitations underscore the necessity to develop new ligands for Ba²⁺.

Despite the need for new, more effective Ba²⁺ chelators for the removal of BaSO₄ scale, few efforts to date have been directed toward this objective.²³⁻²⁵ The development of improved chelators for Ba²⁺ has further been hindered by the lack of fundamental coordination chemistry studies of this ion.²⁶ A key challenge for the chelation of Ba²⁺ arises from the fact that the large AEs engage primarily in ionic, rather than covalent, binding interactions with ligands. The strength of these ionic bonds is proportional to the charge-to-size ratio of the metal center, with smaller ratios giving rise to weaker electrostatic interactions. As the largest nonradioactive +2 ion...
in the Periodic Table (6-coordinate ionic radius = 1.35 Å),² Ba⁶⁺ has a low charge density, resulting in coordination complexes of lower stability compared to the smaller AEs. As a result, the selective, rapid, and stable chelation of Ba⁶⁺ has remained elusive.

Based on our success in using the expanded 18-membered macrocycle macropa (Chart 1) for the chelation of the largest +3 ion, actinium (6-coordinate ionic radius = 1.12 Å),²⁷−²⁹ we investigated the suitability of this ligand for the large Ba⁶⁺ ion. Additionally, two novel ligands, macropaquin and macroquin−SO₃ (Chart 1), were evaluated to systematically probe the influence of varying the metal-binding pendent arms on Ba⁶⁺ coordination. Our studies show that macropa has the highest affinity for Ba⁶⁺ at pH 7.4 reported to date, to the best of our knowledge. This ligand also possesses excellent selectivity for large over small AEs, a feature that is not observed for conventional ligands such as DTPA and DOTA. Furthermore, macropa exhibits superior BaSO₄ dissolution properties relative to DTPA and DOTA, rapidly solubilizing BaSO₄ under mild conditions. These results reveal macropa to be an exceptional chelator for the large Ba⁶⁺ ion and establish proof-of-concept for its industrial application as a scale dissolver, demonstrating that fundamental coordination chemistry principles can be applied to satisfy unmet societal needs.

### RESULTS AND DISCUSSION

Previous studies have shown that macropa selectively binds large over small metal ions;²⁷,³⁰,³¹ notably, the affinity of macropa for Sr⁰ (log Kₘ₅ = 9.57) is 4 orders of magnitude higher than for the smaller Ca⁰ ion (log Kₘ₅ = 5.25).³² Based on these findings, we hypothesized that macropa may possess even higher affinity for Ba⁶⁺. Macroquin, a ligand in which the picolinate pendant arms of macropa are replaced with 8-hydroxyquinoline groups, has also been investigated.³³ Ligands of this class are highly selective for Ba⁶⁺ over smaller AEs, although this selectivity has only been demonstrated in organic solvents owing to the poor aqueous solubility of these ligands.³³−³⁵ To increase aqueous solubility, we installed sulfonate groups onto the 8-hydroxyquinoline arms of the macrocycle, generating macroquin−SO₃. Finally, to investigate potential metal-binding synergy between the two types of pendent arms, the mixed variant, macropaquin, was synthesized by the stepwise installation of one picolinate group and one 8-hydroxyquinoline group onto the diaza-18-crown-6 backbone. Details of the synthesis and characterization of the ligands are provided in the Supporting Information, (Figures S1−S4, S9−S12).

To probe the fundamental coordination chemistry of these ligands with Ba⁶⁺, their complexes with this ion were prepared (Figures S5−S8, S13, S14) and analyzed by X-ray crystallography to elucidate their solid-state structures (Figure 1, Tables S1−S4). In each complex, the Ba⁶⁺ ion is situated slightly above the diaza-18-crown-6 ring, and the two pendent arms are oriented on the same side of the macrocycle. The coordination sphere of the Ba⁶⁺ ion comprises all 10 donor atoms of each ligand (N₄O₆), together with an oxygen atom from a coordinated solvent molecule that penetrates each macrocycle from the opposite face. Similar 11-coordinate arrangements were observed for the Ba⁶⁺ complexes of BHEE-18-aneN₂O₄, a diaza-18-crown-6 macrocycle bearing two pendant −CH₂CH₂OCH₂CH₂OH arms,³⁶,³⁷ and macroquin−Cl, in which the sulfonate groups of macroquin−SO₃ are replaced by chlorine atoms.

The ligand conformation, which can be denoted with Δ or Λ to indicate the pendent arm helical twist and δ or ω to indicate the tilt of each five-membered chelate ring,³⁶ is identical for the three complexes. Each ligand attains the δ(δδδ)(δδδ) conformation, present in equal amounts with its enantiomer. For complexes of macropa with other large metal ions, this conformation is also the most stable.³⁰,³² Protonation of one picolinate arm of macropa and the 8-hydroxyquinoline arm of macroquin gives rise to complexes of the cationic formulas [Ba(Hmacropa)(DMF)]⁺ and [Ba(Hmacropuquin)(DMF)]⁺, respectively. By contrast, macroquin−SO₃ forms a neutral complex with Ba⁶⁺, [Ba(H₂macroquin−SO₃)(H₂O)]. In this case, both phenolates are protonated to form neutral donors, but the sulfonic acid groups exist in the deprotonated anionic form. As reflected by the similar distances between Ba⁶⁺ and the two nitrogen atoms of each macrocycle, the Ba⁶⁺ ion is situated symmetrically within the macrocycle of each complex. Collectively, the structural features of these complexes suggest that macropa, macroquin, and macroquin−SO₃ can optimally accommodate the large Ba⁶⁺ ion.

To further evaluate the coordination properties of the ligands with the AEs, their protonation constants and the stability constants of their Ca⁰, Sr⁰, and Ba⁶⁺ complexes were
A comparison of the ligand protonation constants reveals that sequential replacement of each picolinate arm of macropa by 8-hydroxyquinoline-based binding groups significantly decreases the basicity of the nitrogen atoms of the macrocyclic core to which they are attached. This trend is evidenced by the lower amine protonation constants of 7.15 (log \( K_{a1} \)) and 6.97 (log \( K_{a2} \)) for macropaquin and 6.75 (log \( K_{a3} \)) and 6.62 (log \( K_{a4} \)) for macroquin−SO₃ versus 7.41 (log \( K_{a1} \)) and 6.899 (log \( K_{a2} \)) for macropa. A comparison between related ethylenediamine-derived ligands bearing either picolinate or 8-hydroxyquinoline groups also shows that the basicity of the secondary amine is lower when attached to the latter.⁴¹,⁴² The electron-withdrawing sulfonate groups on macroquin−SO₃ give rise to more acidic phenols (log \( K_{a1} = 9.34 \), log \( K_{a2} = 9.43 \)) compared to macropaquin (log \( K_{a1} = 10.33 \)). Notably, the second protonation constant of macroquin−SO₃ is slightly larger than the first protonation constant. This apparent reversal in expected values may be attributed to intramolecular hydrogen bonding that stabilizes the second proton; upon its removal, the hydrogen-bond network is broken, and the final remaining proton becomes more acidic. This phenomenon has been previously reported for other macrocyclic ligands.⁴¹,⁴²

Because protons compete with metal ions for binding sites on ligands, ligand basicity is an important factor that contributes to the affinity of a ligand for a metal ion at a specific pH.⁴³,⁴⁴ The overall basicity of the ligands, taken as the sum of their log \( K_a \) values, follows the order macropa (19.99) < macropaquin (27.69) < macroquin−SO₃ (32.14). The speciation of the ligands reflects these overall basicity values. At pH 7.4, 43% of macroquin is highly deprotonated (\( \text{L}^{2−} \)), consistent with the lower overall basicity of this ligand (Figure S18). By contrast, fully deprotonated macroquin²⁻ and macroquin−SO₃⁴⁻ do not exist in solution below pH 8 (Figures S19 and S20). At pH 7.4, the monoprotonated species of macropaquin, \( \text{HL}^- \), predominates (56%), whereas macroquin−SO₃ is mostly present as \( \text{H}_2\text{L}^{2−} \) (78%). On the basis of these results, macropaquin and macroquin−SO₃ may chelate metal ions less effectively than macropa near neutral pH due to greater competition with protons for binding sites on these ligands.

With the protonation constants in hand, the stability constants of these ligands with Ca²⁺, Sr²⁺, and Ba²⁺ were determined. Remarkably, macropa, macropaquin, and macroquin−SO₃ all exhibit significant thermodynamic preferences for large over small AEs; the measured log \( K_{ML} \) values are highest for complexes of Ba²⁺ and lowest for complexes of Ca²⁺. However, the affinities of the ligands for Ba²⁺ and Sr²⁺ decrease as the picolinate arms on the macrocyclic scaffold are replaced with 8-hydroxyquinoline or 8-hydroxyquinoline-5-sulfonic acid arms. For example, log \( K_{ML} \) values of 11.11, 10.87, and 10.44 were measured for complexes of macropa, macropaquin, and macroquin−SO₃, respectively, containing zero, one, and two 8-hydroxyquinoline-based pendant arms. This trend signifies that 8-hydroxyquinoline-based pendant arms may not be suitable metal-binding groups for the chelation of large metal ions such as Ba²⁺.

Refinement of our potentiometric titration data also revealed the presence of protonated metal complexes, or MHL and MH₂L species, for all three ligands bound to Ca²⁺, Sr²⁺, and Ba²⁺ (Table 1 and Figures S21−S26). The inclusion of these species within our solution phase model is consistent with the results from X-ray crystallography, which also identified them in the solid state (Figure 1). The speciation diagrams for

**Figure 1.** X-ray crystal structures of \([\text{Ba(Hmacropa)(DMF)}]\text{ClO}_4·\text{Et}_2\text{O} \text{ (a,b), [Ba(Hmacropaquin)(DMF)]ClO}_4·\text{DMF} \text{ (c,d), and [Ba(Hmacroquin−SO}_3\text{(H}_2\text{O})\text{]}·4\text{H}_2\text{O} \text{ (e,f). Ellipsoids are drawn at the 50% probability level. Counteranions, nonacidic hydrogen atoms, and outer-sphere solvent molecules are omitted for clarity.}**
solutions of Ba$^{2+}$ and the three ligands, based on the thermodynamic constants in Table 1, are shown in Figure 2. The major species present at pH 7.4 is the ML species for macropa, the MHL species for macroquin, and the MH$_2$L species for macroquin$-$SO$_3$. These data indicate that the 8-hydroxyquinoline donors retain their basicity when bound to the Ba$^{2+}$ ion. The presence of two such donors in macroquin$-$SO$_3$ gives rise to the large prevalence of the protonated L complex, the MHL species for macroquin, and the MH$_2$L species for macroquin$-$SO$_3$, indicating that macropa is a high-affinity ligand for Ba$^{2+}$. A more accurate reflection of thermodynamic affinity in aqueous solution, however, can be expressed using conditional stability constants, which account for the effect of protonation equilibria of the ligands on complex stability. The conditional stability constants (log $K'$) of the AE complexes at pH 7.4 are given in Table 2. The log $K'_{Ba}$ value of 10.74 for macropa is 5−6 orders of magnitude greater than those for DOTA (log $K'_{Ba}$ = 5.72) and DTPA (log $K'_{Ba}$ = 4.63). Macropa also exhibits higher affinity for Ba$^{2+}$ at pH 7.4 than macroquin (log $K'_{Ba}$ = 10.05) and macroquin$-$SO$_3$ (log $K'_{Ba}$ = 8.76). From these values, macropa emerges as remarkably superior to all other ligands for the chelation of Ba$^{2+}$ at neutral pH.

Another measure of conditional thermodynamic affinity of a ligand for a metal ion is provided by pM values (Table 2), which are defined as the negative log of the free metal concentration in a pH 7.4 solution containing 10$^{-6}$ M metal ion and 10$^{-7}$ M ligand. Larger pM values correspond to higher affinity chelators because they indicate that there is a smaller concentration of free metal ion under these conditions at equilibrium. The pBa values of DOTA and DTPA are only 6.76 and 6.15, respectively, reflecting the presence of a significant amount of free Ba$^{2+}$ at pH 7.4 (Figure 2). By contrast, 90% of Ba$^{2+}$ is already bound by macropa at pH 4.0 and 99% is complexed at pH 5.1, consistent with the high pBa value of 11.69 for this ligand. Furthermore, macropa is 1.17-fold and 1.79-fold more selective for Ba$^{2+}$ over Sr$^{2+}$ and Ca$^{2+}$, respectively, as determined by the ratio of the corresponding pM values. By contrast, these selectivity values are <1 for DOTA and DTPA, emphasizing their poor affinities for the large Ba$^{2+}$ ion at pH 7.4.

Having demonstrated that macropa chelates Ba$^{2+}$ with high thermodynamic stability and selectivity, the kinetic inertness of this complex was examined in comparison to that of macroquin$-$SO$_3$ and macroquin$-$SO$_3$. We first challenged the Ba$-$L complexes with 1000 equiv of La$^{3+}$, a metal that forms a complex of high thermodynamic stability with macropa (log $K'_{La}$ = 14.99). The substitution of Ba$^{2+}$ with La$^{3+}$ was monitored at room temperature (RT) and pH 7.3 by UV−vis spectrophotometry (Figures S27−S29). Ba$-$macropa and Ba$-$macropuin exhibited moderate stability, giving rise to similar half-lives of 5.45 ± 0.20 min and 6.07 ± 0.13 min, respectively. By contrast, Ba$-$macroquin$-$SO$_3$ underwent transmetalation with La$^{3+}$ much more rapidly ($t_{1/2}$ = 0.65 ± 0.05 min), indicating that macroquin$-$SO$_3$ cannot adequately retain Ba$^{2+}$ under these conditions.

Because Ba$^{2+}$ possesses bone-seeking properties, the stability of the Ba$^{2+}$ complexes in the presence of hydroxyapatite (Ca$_3$(PO$_4$)$_2$(OH), HAP), the predominant mineral that comprises bone, was also evaluated. HAP was suspended in solutions containing the complexes formed in situ (1.1 equiv L, 1.0 equiv Ba$^{2+}$) in pH 7.6 buffer, and the amount of Ba$^{2+}$ remaining in the liquid phase, reflecting intact Ba$-$L complex, was determined by graphite furnace atomic absorption spectroscopy (GFAAS) (Figure S30). Whereas free Ba$^{2+}$ is adsorbed by HAP in <10 min, Ba$-$macropa and Ba$-$macropuin, respectively, retained 82% and 68% of this ion after 20 h. Ba$-$macroquin$-$SO$_3$ displayed the least stability in the presence of HAP, with only 17% of the complex remaining intact after 20 h. Taken together, the results of these challenges demonstrate that Ba$-$macropa and Ba$-$macropuin are considerably more stable than Ba$-$macroquin$-$SO$_3$ under extreme conditions of large excesses of competing metal ions. This feature may be important for Ba$^{2+}$ chelation in industrial applications, such as scale dissolution, because numerous other metal ions are present during these processes. The inferior kinetic stability of Ba$-$macroquin$-$SO$_3$ relative to the other two complexes correlates with the lower thermodynamic affinity of this ligand for Ba$^{2+}$ and is most likely a consequence of the fact that the diprotonated Ba$^{2+}$ complex of macroquin$-$SO$_3$ is the major species at pH 7.4 (Figure 2).

<table>
<thead>
<tr>
<th></th>
<th>macropa$^{2-}$</th>
<th>macroquin$^{2-}$</th>
<th>macroquin$-$SO$_3$$^{4-}$</th>
<th>DOTA$^{4-}$</th>
<th>DTPA$^{4-}$</th>
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<tr>
<td>log $K_{Ba}$</td>
<td>7.41(1), 7.41</td>
<td>10.33(4)</td>
<td>9.34(4)</td>
<td>11.14</td>
<td>10.34</td>
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<td>log $K_{La}$</td>
<td>6.899(3), 6.85</td>
<td>7.15(3)</td>
<td>9.43(1)</td>
<td>9.69</td>
<td>8.59</td>
</tr>
<tr>
<td>log $K_{Sr}$</td>
<td>3.23(1), 3.32</td>
<td>6.97(2)</td>
<td>6.75(4)</td>
<td>4.85</td>
<td>4.25</td>
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<td>log $K_{Ca}$</td>
<td>2.45(5), 2.36</td>
<td>3.24(4)</td>
<td>6.62(4)</td>
<td>3.95</td>
<td>2.71</td>
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<tr>
<td>log $K_{Ca}$</td>
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<td>log $K_{CaL}$</td>
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<td>5.90(4)</td>
<td>6.04(8)</td>
<td>16.37</td>
<td>11.77</td>
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<td>log $K_{BaL}$</td>
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<td>8.60(4)</td>
<td>3.60</td>
<td>6.10</td>
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<td>log $K_{LaL}$</td>
<td>9.442(4), 9.57</td>
<td>9.19(5)</td>
<td>8.62(2)</td>
<td>14.38</td>
<td>9.68</td>
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<td>log $K_{BaL}$</td>
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<td>8.92(2)</td>
<td>8.34(4)</td>
<td>4.52</td>
<td>5.4</td>
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<tr>
<td>log $K_{CaL}$</td>
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<td>log $K_{Ba}$</td>
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<td>10.87(2)</td>
<td>10.44(6)</td>
<td>11.75</td>
<td>8.78</td>
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<td>log $K_{Ba}$</td>
<td>3.76(2)</td>
<td>9.76(2)</td>
<td>9.24(7)</td>
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<td>log $K_{CaL}$</td>
<td>2.49(7)</td>
<td>3.28(2)</td>
<td>7.80(2)</td>
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“Data reported previously for DOTA$^{4-}$ and DTPA$^{4-}$ are provided for comparison. Ref 21, I = 0.1 M KCl. "Protonation constants and Ca$^{2+}$ stability constants from ref 45, I = 0.1 M KCl. Other values from ref 15. Ref 30, I = 0.1 M KCl. Ref 32, I = 0.1 M KNO$_3$. DOI: 10.1021/jacs.8b08704 J. Am. Chem. Soc. 2018, 140, 17071−17078"
complex is expected to be substantially more labile than the ML species due to decreased electrostatic interactions between the ion and ligand.

The encouraging results of the thermodynamic and kinetic stability studies prompted us to evaluate the feasibility of employing macropa and macropaquin as BaSO₄ scale dissolvers. First, a suspension of BaSO₄ in pH 8 NaHCO₃ was formed by combining Ba(NO₃)₂ (4.53 mM) with excess Na₂SO₄ (13.48 mM), simulating the mixing of incompatible waters that produces BaSO₄ scale in petroleum operations. The resulting BaSO₄ suspension was treated with ligand (5 mM), and the amount of dissolved Ba²⁺ was measured by GFAAS (Figure 3). Macropa rapidly solubilized 78% of BaSO₄ in just 10 min and afforded complete dissolution after 30 min. Likewise, macropaquin dissolved 95% of BaSO₄ in 30 min. By contrast, the conventional ligands DOTA and DTPA dissolved only 40% of BaSO₄ within this same time, underscoring the inferior solubilizing properties of these ligands at pH 8.

The dissolution of BaSO₄ by macropa, DTPA, and DOTA was further evaluated in pH 11 Na₂CO₃ buffer (Figure S31) to match the caustic conditions that are applied in the industrial setting. Impressively, macropa solubilized >95% of the BaSO₄ in just 5 min. DTPA also dissolved nearly all the BaSO₄ in this same time. The improved dissolution ability of DTPA at pH 11 versus pH 8 reflects the greater proportion of the fully deprotonated ligand (DTPA⁻) present at pH 11, which favors Ba–DTPA complex formation. These results are consistent with the fact that the petroleum industry only uses this ligand Na₂SO₄ (13.48 mM), simulating the mixing of incompatible waters that produces BaSO₄ scale in petroleum operations. The resulting BaSO₄ suspension was treated with ligand (5 mM), and the amount of dissolved Ba²⁺ was measured by GFAAS (Figure 3). Macropa rapidly solubilized 78% of BaSO₄ in just 10 min and afforded complete dissolution after 30 min. Likewise, macropaquin dissolved 95% of BaSO₄ in 30 min. By contrast, the conventional ligands DOTA and DTPA dissolved only 40% of BaSO₄ within this same time, underscoring the inferior solubilizing properties of these ligands at pH 8.

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**Table 2. Conditional Stability Constants (log $K'$) and pM Values at pH 7.4 for the Alkaline Earth Complexes of the Ligands Discussed**

<table>
<thead>
<tr>
<th></th>
<th>macropa</th>
<th>macropaquin</th>
<th>macroquin–SO₃</th>
<th>DOTA</th>
<th>DTPA</th>
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<tr>
<td>log $K'_{Ca}$</td>
<td>5.42</td>
<td>3.94</td>
<td>3.19</td>
<td>10.34</td>
<td>7.63</td>
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<tr>
<td>log $K'_{Sr}$</td>
<td>9.07</td>
<td>7.54</td>
<td>5.64</td>
<td>8.35</td>
<td>5.53</td>
</tr>
<tr>
<td>log $K'_{Ba}$</td>
<td>10.74</td>
<td>10.05</td>
<td>8.76</td>
<td>5.72</td>
<td>4.63</td>
</tr>
<tr>
<td>pCa</td>
<td>6.54</td>
<td>6.04</td>
<td>6.01</td>
<td>11.29</td>
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</tr>
<tr>
<td>pSr</td>
<td>10.02</td>
<td>8.50</td>
<td>6.70</td>
<td>9.30</td>
<td>6.61</td>
</tr>
<tr>
<td>pBa</td>
<td>11.69</td>
<td>11.01</td>
<td>9.72</td>
<td>6.76</td>
<td>6.15</td>
</tr>
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*a* Conditional stability constants at pH 7.4, 25 °C, and $I = 0.1$ M KCl. 
*b* Calculated from $-\log [M^{2+}]_{free} ([M^{2+}]_{tot} = 10^{-6} \text{ M}; [L]_{tot} = 10^{-5} \text{ M}; pH 7.4; 25 °C; I = 0.1$ M KCl).

**Figure 3. Dissolution of BaSO₄ by macropa, macropaquin, DTPA, and DOTA.**

(a) Dissolution at RT and pH 8 was initiated by the addition of chelator (5 mM) to a suspension of BaSO₄ (4.53 mM Ba(NO₃)₂ and 13.48 mM Na₂SO₄). Barium content in solution was measured by GFAAS after 10, 20, and 30 min. (b) Samples from dissolution experiments after 30 min.
under conditions of high pH. The similar rates at which macropa and DTPA solubilize BaSO₄ at pH 11 suggest that macropa possesses remarkably fast Ba²⁺-binding kinetics. The macrocycle DOTA, by contrast, was unable to completely dissolve all the BaSO₄. After 30 min, only 75% dissolution was reached, signifying that the kinetics of metal incorporation for DOTA remain slow even at high pH.

We next investigated the ligand-promoted dissolution of crude barite ore, which is composed predominantly of BaSO₄, as a model for the solid deposits of natural scale that plague the petroleum industry. Barite rocks (Figure 4a) obtained from Excalibar Minerals (Katy, TX) were milled and sieved to isolate particles between 0.5 and 2 mm (Figure 4b). To simulate production tubing clogged with BaSO₄ scale, polypropylene columns were filled with barite (3 g), to which solutions of macropa or DTPA at pH 8 or 11 were added (Figure 4c). The concentration of each ligand solution was approximately 48 mM, consistent with the dilute compositions of scale dissolvers used industrially.

After a soak time of 1 h, the ligand solution was eluted from the column, and the concentration of dissolved barium was measured by GFAAS and converted to ligand efficiency (eq 4).

\[
\text{ligand efficiency} = \frac{B_{\text{aexp}}}{B_{\text{amax}}} \times 100
\]

In eq 4, \(B_{\text{aexp}}\) is the concentration of barium measured in the eluate, and \(B_{\text{amax}}\) is the maximum concentration of barium that can be chelated by each ligand, calculated from the concentration of each ligand applied to the column and assuming a 1:1 M:L binding model. As shown in Figure 4d, the ligand efficiency of macropa at pH 8 is 40%, indicating that nearly half of the ligand solution was saturated with Ba²⁺ following exposure to barite for 1 h. DTPA, by contrast, was practically incapable of dissolving barite at this pH, giving rise to a ligand efficiency of only 2%. Macropa remained equally as effective at pH 11, again displaying a ligand efficiency of 40%. By contrast, even at pH 11, the dissolution efficiency of DTPA was only 17%, less than half that observed for macropa. Collectively, these results indicate that macropa maximally dissolves barite at or below pH 8, underscoring its superior affinity for Ba²⁺ near neutral pH.

Lastly, the capacity for recovery and reuse of macropa post-BaSO₄ dissolution was assessed qualitatively (Figure 5). A sample of macropa-dissolved BaSO₄ (9.66 mM macropa, 8.74 mM Ba(NO₃)₂, 26.04 mM Na₂SO₄) was acidified to pH 1 with concentrated HCl to protonate the ligand, inducing Ba²⁺ decomplexation and precipitation as BaSO₄. The macropa solution was isolated by filtration, basified to pH 8 with 2 M NaOH, and combined with another portion of BaSO₄. Within 40 min, no visible precipitate remained in the vial, signaling that the recycled macropa dissolved all the BaSO₄. Subsequently, the ligand was recovered and reused for BaSO₄ dissolution four more times with negligible losses in efficacy or speed of dissolution (Figure S32). These results demonstrate the facile and economic reuse of macropa, an attractive feature that will facilitate its implementation in industry.

Figure 4. Barite dissolution efficiency of macropa and DTPA. (a) Large rocks of crude barite ore were crushed with a hammer. (b) The barite was sieved to isolate particles between 0.5 and 2 mm. (c) To simulate petroleum pipes clogged with BaSO₄ scale, columns were filled with barite (3 g), and then solutions of macropa or DTPA (∼48 mM) at pH 8 and pH 11 were added. (d) After a soak period of 1 h, ligand efficiency, or the percent of ligand saturated with Ba²⁺, was determined by measuring the concentration of barium in the eluate by GFAAS.

Figure 5. Ligand recovery and reuse. A solution of macropa-dissolved BaSO₄ was acidified to release the Ba²⁺ from the ligand as BaSO₄. After filtration of the precipitated BaSO₄ and basification of the solution, the recovered ligand was successfully reused for another cycle of BaSO₄ dissolution.
In summary, three ligands based on the expanded diaza-18-crown-6 macrocycle were evaluated for their abilities to chelate the large Ba2+ ion. Macropa exhibits unprecedented affinity for Ba2+ at pH 7.4, possessing a log K' value of 10.74. The Ba2+ complexes of both macropa and macropaquin display substantial kinetic stability when challenged with La3+ or HAP, whereas macropaquin−SO3 rapidly releases Ba2+ under these conditions. Additionally, macropa and macropaquin can efficiently dissolve BaSO4 under RT and near-neutral pH conditions. This feature was further reflected in dissolution studies involving authentic barite ore samples, which showed macropa to be superior to the state-of-the-art chelator DTPA. The promising Ba2+ chelation properties of this ligand will render it useful for the dissolution of BaSO4 scale deposits, fulfilling an important unmet need in the petroleum industry.

More broadly, these results reveal key features that are required for stable coordination of the heavy AE ions. Namely, the observation that picolinate donors provide superior coordination properties for Ba2+ in comparison to 8-hydroxyquinoline donors will guide future ligand design efforts for this underexplored metal ion. These results have further implications in the realm of radiochemistry, where these ligands may be applied for the chelation of Ra2+. Due to both implications in the realm of radiochemistry, where these hydroxyquinoline donors will guide future ligand design efforts, the observation that picolinate donors provide superior concerns about radiological contamination of 226Ra in NORM and the great therapeutic potential of 223Ra for the treatment of cancer, a better understanding of AE chemistry will advance efforts to chelate Ra2+ for these important applications.

**ASSOCIATED CONTENT**

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.8b08704.

- Experimental details, compound characterization, and supporting figures and tables (PDF)
- Crystallographic information (CIF)

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**Notes**

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