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^{1}H NMR Chiral Analysis of Charged Molecules via Ion Pairing with Aluminum Complexes

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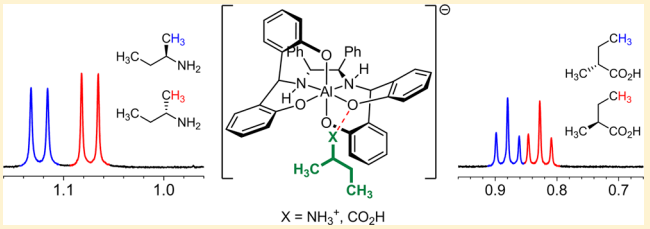
Supporting Information

ABSTRACT: Chiral analysis, such as determination of identity, concentration, and relative ratio of optically active (chiral) molecules, plays an indispensable role in contemporary synthetic, medicinal, and biological chemistry. Here, we describe the selective control of metal-centered chirality in an octahedral geometry to prepare negatively charged Al^{III} complexes, which can be used as versatile ^{1}H NMR chiral solvating agents for both positively and negatively charged chiral molecules in polar or nonpolar solvents. During the formation of ion pairs between the Al^{III} complexes and the chiral analytes such as amines and carboxylic acids, the metal-centered chirality in the Al complexes plays a crucial role in providing anisochronous chemical shifts to the ^{1}H NMR spectra. As a chiral solvating agent, Al^{III} complexes display an unprecedentedly broad substrate scope, good solvent compatibility, and operational simplicity.



INTRODUCTION

Ever since the 1911 discovery of metal-centered chirality by Alfred Werner,[1] the stereoselective generation of stereogenic metal centers has been an active research area mainly driven by potential applications such as stereoselective catalysts, supramolecular assemblies, and organometallic drugs.[2] Among possible architectures of metal complexes, chiral octahedral complexes with Δ or Λ configurations have been prepared by self-assembly of metals with chiral ligands.[3] More recently, chiral-at-metal octahedral complexes prepared from achiral ligands, exemplified by M(bpy)$_3$ (bpy = 2,2′-bipyridine), were reported by employing chiral auxiliaries,[4] chiral catalysts,[5] and chiral anions,[6] as well as long-range chirality transfer[7] and asymmetric *cis*−*trans* isomerism.[8] Although various synthetic methods are available, the development of functional chiral octahedral complexes still remains a challenge. Stereogenic metal centers, unlike carbon centers, often tend to racemize or epimerize due to the reversible metal−ligand bonds or the structural isomerism of coordination complexes. Despite such difficulties, chiral-at-metal complexes have found recent promising applications in asymmetric catalysis as Lewis acid/base catalysts,[9] hydrogen-bond donors,[10] and photocatalysts.[11]

Here, we report a general and convenient protocol for chiral analysis of charged chiral molecules by using chiral octahedral ate complexes. Stereoselective control of metal-centered Δ and Λ chirality can be demonstrated in preparation of chiral octahedral aluminum (Al) complexes with newly designed hexa-dentate N_2O_4 ligands (**1**, Figure 1a,b). In our experiments, we were able to achieve high stereoselectivity due to the relative thermodynamic stability of two rigid helical conformers of Δ and Λ configurations, supported by DFT computation and X-ray analysis (Figure 1c,d). Furthermore, our N_2O_4 ligands (**1**) bound to Al(III) as tetra-anionic ligands to provide Al−ate complexes with overall charge of −1. We therefore demonstrated that ion-pair interaction between our chiral Al−ate complex with charged chiral molecules can be applicable for universal chirality analysis by ^{1}H nuclear magnetic resonance (NMR) spectroscopy.

NMR spectroscopy is one of the most convenient and widely used analytical techniques for the determination of chemical structures. To implement in situ direct chiral analysis using NMR spectroscopy,[12] chiral analytes can be mixed with chiral solvating agents such as coordinatively unsaturated chiral lanthanide or transition-metal complexes,[13] Brønsted acids/bases,[14−16] supramolecular receptors,[17] and others[18] to generate anisochronous chemical shifts.[19] Although several chiral solvating agents are commercially available, the current methods possess several drawbacks such as line-broadening, narrow substrate scope, poor solubility, and poor resolution. Thus, compared with popular methods of chromatographic analysis, NMR spectroscopy is only infrequently used for direct chiral analysis. In light of these challenges, we here report chiral octahedral Al complexes as a highly efficient and practical chiral solvating agent that works, in principle, with any of the types of chiral charged molecules that are found in many bioactive compounds. The major advantages of chiral Al complexes as chiral solvating agents are that (a) substoichiometric amounts are only required to obtain sufficient peak resolution in polar or nonpolar solvents CD_3OD, CD_3CN, $CDCl_3$, and C_6D_6; (b)

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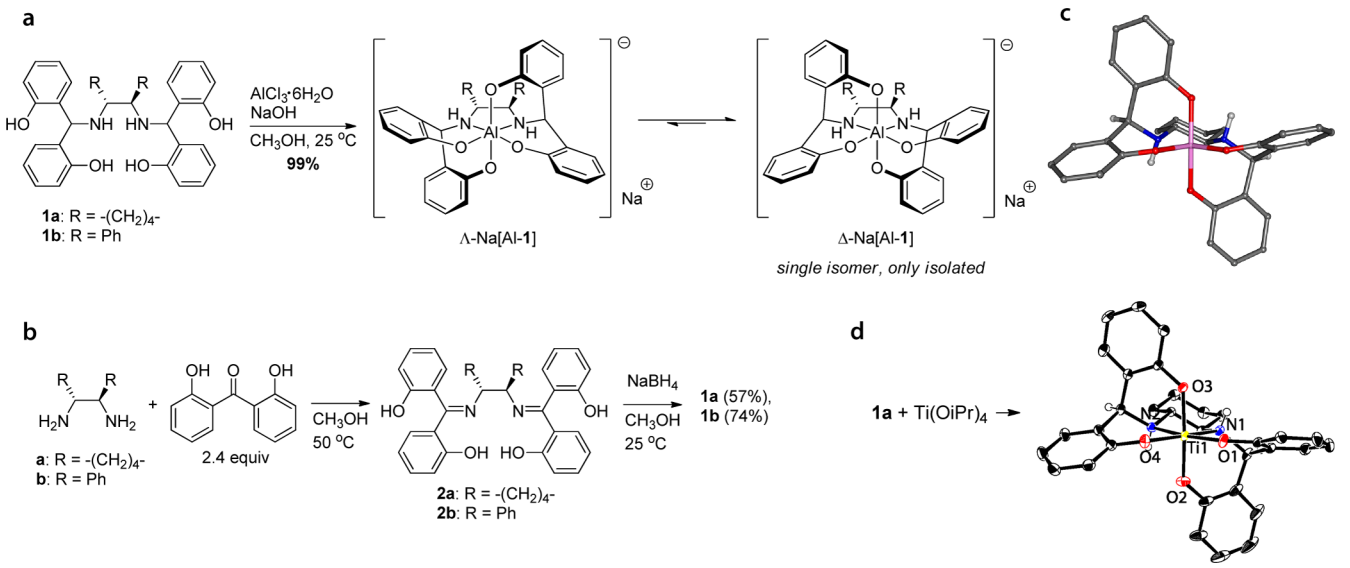

Figure 1. Stereoselective generation of chiral octahedral complexes. (a) Formation of Na[Al-**1**] and equilibrium between Δ-Na[Al-**1**] and Λ-Na[Al-**1**]. (b) Synthetic procedure for **1**. (c) Global minimum structure of Δ-[Al-**1a**]$^{-1}$ (DFT B3LYP/6-31G(d,p) basis for all atoms). (d) Crystal structure of Δ-[Ti-**1a**].

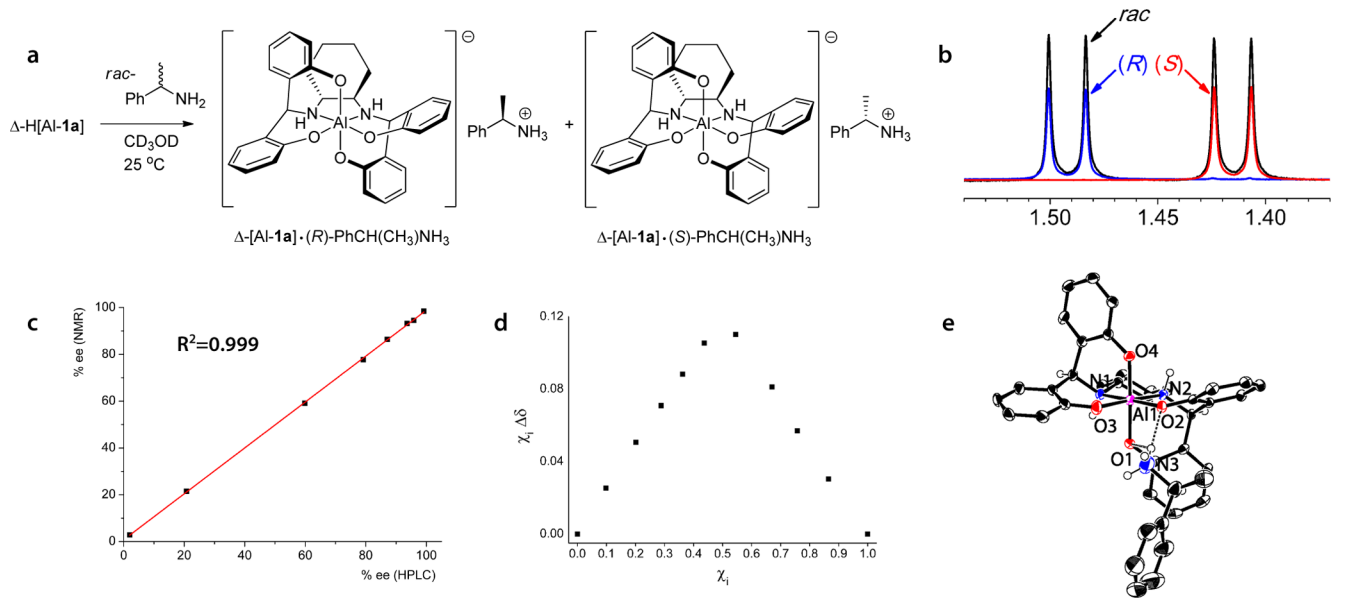

Figure 2. Chiral analysis of 1-phenylethylamine with H[Al-**1a**]. (a) Formation of diastereomeric mixtures between Δ-H[Al-**1a**] and *rac*-1-phenylethylamine. (b) Partial ^{1}H NMR spectrum showing resolved CH_3 peaks of *rac*-1-phenylethylamine upon addition of an equimolecular amount of Δ-H[Al-**1a**] in CD_3OD (20 mM). (c) Linear relationship between the % *ee* values of 1-phenylethylamine determined by HPLC and NMR. (d) Job plot for the complexation of H[Al-**1a**] and *rac*-1-phenylethylamine. (e) Crystal structure of an ionic adduct formed between Δ-H[Al-**1a**] and (*S*)-1-phenylethylamine.

chiral molecules of basic, acidic, or charged forms can be directly used for analysis; and (c) stereogenic centers at the α- to δ-position of the charged functional groups can be analyzed. In addition, the general and broad utility of chiral Al complexes has been demonstrated by chiral analysis of commercial racemic drugs, and therefore, an efficient and convenient tool for ^{1}H NMR chiral analysis of charged molecules can be developed.

RESULTS AND DISCUSSION

Stereoselective Generation of Chiral Al−Ate Complexes. By designing a new type of hexa-dentate N_2O_4 ligand (**1**) (Figure 1), we focused on the stereoselective control of metal-centered Δ or Λ chirality in the preparation of chiral octahedral Al complexes. The ligands **1a** and **1b** were readily prepared starting from a reaction between chiral 1,2-diaminoethanes and 2,2′-dihydroxybenzophenone. The resulting diimines **2a** and **2b** were reduced by $NaBH_4$ to provide the N_2O_4 ligands **1a** and **1b** in 57 and 74% overall yields, respectively (Figure 1b). Na[Al-**1**] was then quantitatively prepared by the reaction of N_2O_4 ligands (**1**) and $AlCl_3$ in the presence of NaOH (Figure 1a).

In principle, this N_2O_4 ligand prepared from achiral 1,2-diaminoethane provides an octahedral metal complex with Δ and Λ configurations in a 1:1 ratio. However, the use of chiral 1,2-diamines could shift the equilibrium by forming diastereomeric mixtures. Indeed, our experiments using chiral 1,2-

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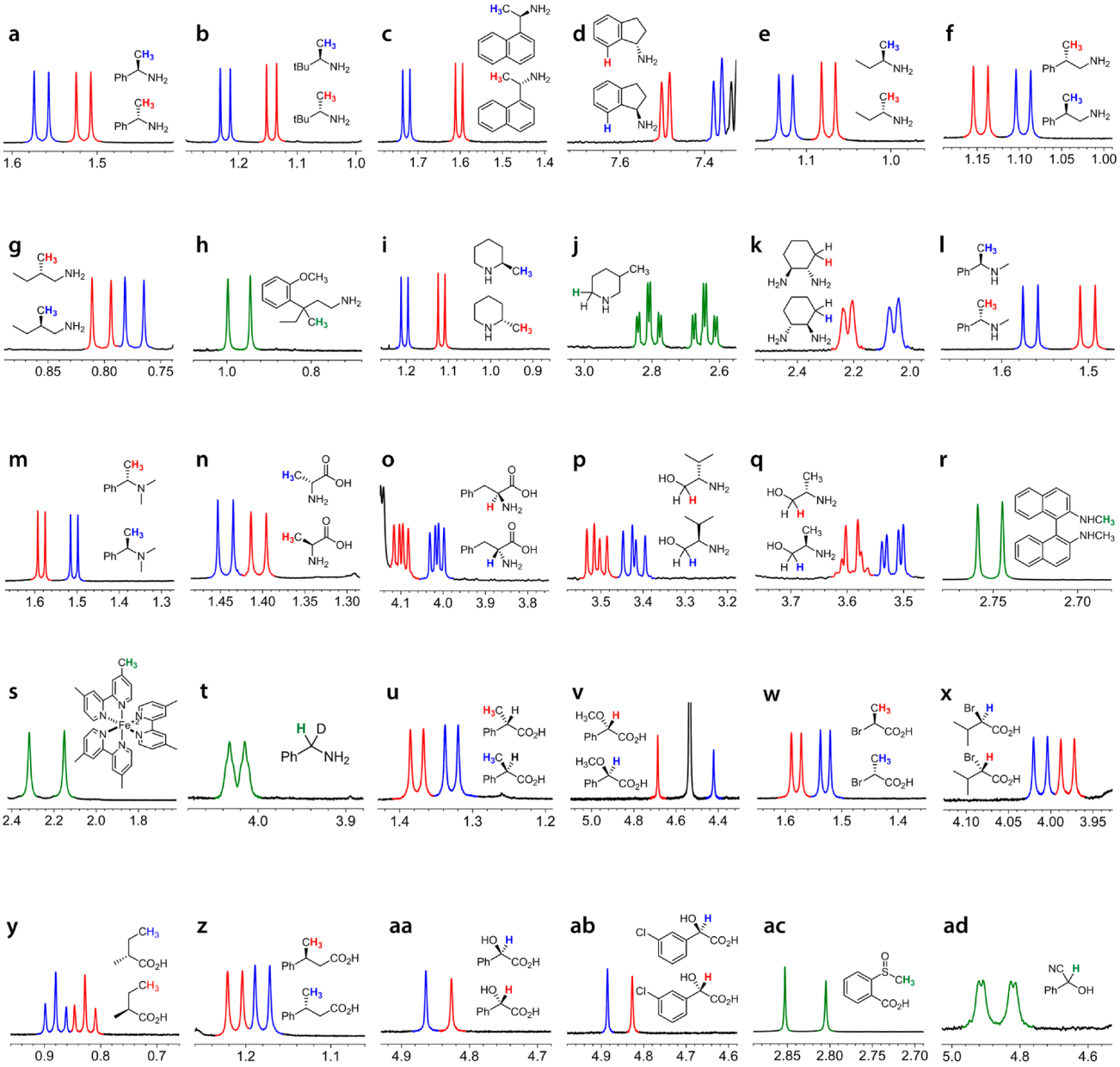

Figure 3. Chiral solvation of amines (a–r, t) and an iron complex (s) with H[Al-**1b**], and chiral solvation of acids (u–ac) and a cyanohydrin (ad) with Na[Al-**1b**]. ^{1}H NMR (400 MHz, 298 K) spectrum of a 1:1 mixture of analyte and H[Al-**1b**] was taken in CD_3OD (a–d, i–o, t), CD_3CN (e–h, p–r), or $CDCl_3$ (s) (20 mM). For analyte k, r, and s, 1:2 mixture of analyte and H[Al-**1b**] was used. ^{1}H NMR spectrum of a 1:1 mixture of analyte and Na[Al-**1b**] was taken in $CDCl_3$ (u–z), CD_3OD (ac), or CD_3CN (aa, ab, ad) (20 mM).

diaminocyclohexane indicate that only one single diastereomer of Na[Al-**1a**] was formed, as detected by ^{1}H NMR spectroscopy. DFT computation provides insight into the origin of the high stereoselectivity. The energy difference between the Δ and Λ complexes of $[\text{Al-}\mathbf{1a}]^{-1}$ is calculated to be 7.6 kcal/mol, which translates to an equilibrium constant of about 3.7×10^5. Due to the rigid octahedral geometry, the steric repulsion between phenolic groups and protons at the chiral carbon centers appears to be responsible for this high energy difference. In agreement with the computational results, no minor stereoisomer was detected when the solution was kept at elevated temperature (100 °C), indicating that the stereoisomers formed under thermodynamic equilibrium. Consistent with the computational results, the crystal structure of Ti-**1a** formed from $Ti(OiPr)_4$ and **1a** was obtained with Δ configuration (Figure 1d). Thus, both computational and experimental data support the idea that our N_2O_4 ligands (**1**) can be used for stereoselective generation of chiral octahedral complexes.

Chiral Solvation of 1-Phenylethylamine. The Al complex, initially prepared as Na[Al-**1a**], was converted to H[Al-**1a**] by addition of an equimolecular amount of trifluoroacetic acid. H[Al-**1a**] was found to be soluble in various solvents such as CH_3OH, DMSO, $CHCl_3$, CH_3CN, and C_6H_6, and showed high stability in these solvents. The pK_a of H[Al-**1a**] in DMSO was determined to be 5.2, comparable with that of 2,4-dinitrophenol (pK_a = 5.1) (Table S1). On the basis of this pK_a value, H[Al-**1a**] can form ionic adducts with aliphatic amines, in which pK_a ranges from 9 to 10 with estimated equilibrium constants over 10^3. To evaluate the chiral

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solvation ability of H[Al-**1a**] with aliphatic amines, we measured the ^{1}H NMR spectra of a 1:1 mixture of H[Al-**1a**] and *rac*-1-phenylethylamine (Figure 2a). In the polar protic solvent CD_3OD, the addition of H[Al-**1a**] to a solution of *rac*-1-phenylethylamine leads to the formation of a clear solution. Notably, the ^{1}H NMR spectra showed two methyl doublet peaks of 1-phenylethylamine that appeared between 1.39 and 1.51 ppm. These methyl peaks were well resolved, with a $\Delta\Delta\delta$ value of 0.077 ppm, large enough to integrate each doublet (Figure 2b). It is remarkable that H[Al-**1a**] is able to resolve peaks of *rac*-1-phenylethylamine in a protic solvent, CH_3OH, which is known to prevent charged interactions by establishing intermolecular hydrogen bonds.

We next demonstrated the reliability of chiral analysis by H[Al-**1a**]. As shown in Figure 2c, the ^{1}H NMR spectra were recorded with various *ee* ratios of 1-phenylethylamine in CD_3OD. To our delight, it was found that there is an excellent linear relationship between the % *ee* values of 1-phenylethylamine determined by HPLC and NMR, indicating that H[Al-**1a**] can be used for reliable quantitative analysis up to 98% *ee*.[20] In addition, we measured the ^{1}H NMR spectra by adding H[Al-**1a**] to the solution of 1-phenylethylamine. Although a 1:1 complex formed between H[Al-**1a**] and 1-phenylethylamine, according to the Job plot (Figure 2d), the peak separation value ($\Delta\Delta\delta$) constantly increased until it reached saturation at about 9 equiv of Al complex (Figure S6). Better peak resolution can be obtained with stoichiometric or excess amounts of Al complex, but a substoichiometric amount as low as about 60 mol % is enough for baseline resolution of 1-phenylethylamine. Thus, the resolving ability of H[Al-**1**] at various levels of stoichiometry allows convenient experiments using ^{1}H NMR spectroscopy.

The ^{1}H NMR spectra of enantiopure 1-phenylehtylamine and H[Al-**1a**] indicated that the methyl group of the (*S*)-enantiomer is more shielded than that of the (*R*)-enantiomer. This can be explained by the crystal structure of the ionic adduct formed between H[Al-**1a**] and (*S*)-1-phenylethylamine (Figure 2e). The crystal structure shows that the methyl group of (*S*)-1-phenylethylamine is placed toward the phenol group of [Al-**1a**]$^{-1}$, resulting in a more shielded methyl peak. Indeed, the calculated energy minimum structure is in good agreement with the crystal structure formed between H[Al-**1a**] and (*S*)-1-phenylethylamine. According to the computed energy minimum structures of the ionic adduct formed between H[Al-**1a**] and (*R*) or (*S*)-1-phenylethylamine, the methyl group of (*S*)-1-phenylethylamine is found to be more shielded than that of (*R*)-1-phenylethylamine, agreeing with the observed ^{1}H NMR spectra (Figures S22 and S23).

Chiral Solvation of Positively and Negatively Charged Compounds. We investigated the chiral solvating ability of the Al complexes for amines or positively charged compounds. For aliphatic amines, H[Al-**1**] was directly mixed with chiral analytes to form diastereomeric mixtures. When an equal mixture of H[Al-**1a**] and chiral primary, secondary, or tertiary alkyl amines was prepared in CD_3OD or CD_3CN, a baseline separation of analyte peaks was observed in most cases (Figure S10). In the case of analyte peak overlapping with the cyclohexyl region of [Al-**1a**]$^{-1}$, H[Al-**1b**] prepared from 1,2-diphenylethylenediamine was used to achieve a clean resolution of the analyte peaks (Figure 3 and Figure S11). Remarkably, in addition to chiral amines with chiral carbon at the α-position, H[Al-**1b**] was successfully applied for those chiral amines with chiral carbon centers in the β- and γ-positions. It was possible to achieve long-range peak separation due to the rigid and sizable metal-centered chirality of the Al complexes. Additional functional groups such as amino, carboxylic acid, methoxy, and hydroxyl groups are all compatible with the chiral analysis with H[Al-**1b**]. Moreover, chiral solvation of positively charged compounds by H[Al-**1b**] can be extended to molecules with axial chirality, metal-centered chirality, and an enantiomeric methylene group, as shown in Figure 3 panels r, s, and t, respectively. Thus, chiral Al complexes can be a universal chiral solvating agent for positively charged chiral compounds.

Other interesting types of analyte for chiral analysis are the chiral carboxylic acids. Due to their high polarity and acidity, these acids are commonly derivatized prior to the chromatographic analysis. For direct chiral analysis of carboxylic acids by ^{1}H NMR spectroscopy, chiral amines or supramolecular receptors have been used as chiral solvating agents.[15,17b,c] However, to the best of our knowledge, anionic compounds have not been used for chiral solvation of acids. Since ion pair interactions can be extended to form oligomeric or caged complexes, we hoped that the metal-centered chirality could effectively induce anisochronous chemical shifts in such types of ion pairs. Indeed, when 2-phenylpropionic acid was mixed with Na[Al-**1b**] in $CDCl_3$ in a 1:1 ratio, a clean peak separation of the ionic complexes was observed in ^{1}H NMR spectra (Figure 3u). A titration experiment showed that Na[Al-**1b**] forms 1:1 adducts with 2-phenylproionic acid, which led us to propose an ion-paring model of 1:1 adducts (Figures S5 and S24). In the proposed models, the methyl of (*R*)-2-phenylpropionic acid is expected to be more shielded in ^{1}H NMR spectra because the methyl group is pointing toward the phenyl group of [Al-**1b**]$^{-1}$. Remarkably, chiral solvation with Na[Al-**1b**] was successfully applied to various carboxylic acids with chiral carbon centers at the α- and β-positions with bromo, hydroxy, and methoxy groups (Figures 3u–ab). Moreover, a chiral carboxylic acid with sulfur-based chirality (Figure 3ac) and a chiral cyanohydrin (Figure 3ad) were successfully resolved in ^{1}H NMR spectra.

In contrast to common chiral solvating agents working in nonpolar solvents, H[Al-**1b**] or Na[Al-**1b**] can be an efficient chiral solvating agent in polar or nonpolar solvents. Indeed, for ^{1}H NMR chiral analysis of amines in CD_3OD, no baseline peak separation was observed with several chiral solvating agents except with (18-crown-6)-2,3,11,12-tetracarboxylic acid,[14] albeit its scope was limited to cyclic secondary amines (Figures S14–S17). In addition, for ^{1}H NMR chiral analysis of carboxylic acids, Na[Al-**1b**] showed a wider analyte scope than other chiral solvating agents such as 1-(1-naphthyl)ethylamine[15e] (Figure S18).

Chiral Solvation of Commercial Racemic Drugs. To demonstrate the practical utility of our system, we conducted direct chirality analysis of commercial drugs, which can comprise complementary analytical techniques together with chromatographic methods. Since the ^{1}H NMR chiral analysis using our Al complexes is applicable to both positively and negatively charged chiral molecules, racemic drugs with chargeable functional groups such as amines or carboxylic acids can be appropriate analytes. We selected 9 commercial racemic drugs for chiral solvation with H[Al-**1b**] or Na[Al-**1b**] complexes (Figure 4). These drugs include basic or acidic functional groups with chiral carbon centers at the α-, β-, γ-, and δ-positions. Indeed, all racemic drugs were sufficiently well resolved in the ^{1}H NMR spectra for *ee* determination (Figure 4). Because our protocol is simple, fast, and convenient, chiral

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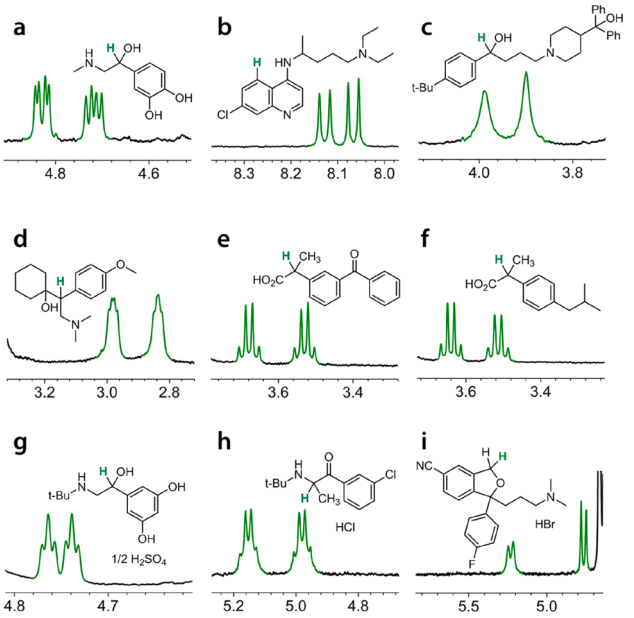

Figure 4. Chiral solvation of commercial racemic drugs by X[Al-**1b**] (X = H^+ or Na^+). ^{1}H NMR (400 MHz, 298 K) spectrum of a 1:1 mixture of analyte and X[Al-**1b**] (X = H for a–d, X = Na for e–i) was taken in CD_3CN (a–c and h), $CDCl_3$ (e and f), C_6D_6 (d and i), and CD_3OD (g) (20 mM).

solvation with our Al complexes will have great potential in the field of chirality analysis for many bioactive chiral molecules.

CONCLUSIONS

We have demonstrated a stereoselective generation of metal-centered chirality in Al complexes formed by newly designed hexa-dentate N_2O_4 ligands (**1**). The origin of stereoselectivity was explained by DFT computation together with ^{1}H NMR and X-ray crystallographic data. These anionic Al complexes with metal-centered chirality can be successfully applied as chiral solvating agents for both positively and negatively charged chiral compounds. Efficient peak separation of racemic analytes was achieved in either polar or nonpolar solvents, as well with stereogenic centers at the α- to δ-position of the charged functional groups, by simple addition of X[Al-**1b**] (X = H or Na). Moreover, racemic drugs with various functional groups and with chiral carbon centers at different positions were all successfully analyzed according to their ^{1}H NMR spectra. This simple protocol will find wide application in the analysis of the chirality of charged chiral compounds.

EXPERIMENTAL SECTION

General Procedure for Chiral Solvation of Charged Compounds. In a 5 mm NMR tube, 0.64 μL of *rac*-1-phenylethylamine was dissolved in 0.5 mL of CD_3OD. ^{1}H NMR spectra (400 MHz) was taken of the solution (**data-1**). To the solution, 3.2 mg of H[Al-**1b**] was added and the mixture was shaken until the solution became clear. ^{1}H NMR spectra (400 MHz) was taken of the solution (**data-2**). With the comparison of two spectra of **data-1** and **data-2**, resolved peaks at 1.48–1.60 ppm were analyzed. For the determination of *R*/*S* configuration, enantiopure or enantioriched samples can be analyzed.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b09555.

Experimental procedures, spectroscopic and calculation data, and crystallographic details (PDF)
Crystallographic details for Δ-[Ti-**1a**] (CIF)
Crystallographic details for an ionic adduct formed between Δ-H[Al-**1a**] and (*S*)-1-phenylethylamine (CIF)

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) (a) Werner, H. *Angew. Chem., Int. Ed.* **2013**, *52*, 6146. (b) Werner, A. *Ber. Dtsch. Chem. Ges.* **1911**, *44*, 1887.

(2) For recent reviews, see: (a) Gong, L.; Chen, L.-A.; Meggers, E. *Angew. Chem., Int. Ed.* **2014**, *53*, 10868. (b) Crassous, J. *Chem. Commun.* **2012**, *48*, 9684. (c) Miyake, H.; Tsukube, H. *Chem. Soc. Rev.* **2012**, *41*, 6977. (d) Bauer, E. B. *Chem. Soc. Rev.* **2012**, *41*, 3153. (e) Meggers, E. *Eur. J. Inorg. Chem.* **2011**, 2911. (f) Meggers, E. *Chem. Commun.* **2009**, 1001. (g) Crassous, J. *Chem. Soc. Rev.* **2009**, *38*, 830.

(3) Amouri, H.; Gruselle, M. *Chirality in Transition Metal Chemistry: Molecules, Supramolecular Assemblies and Materials*; Wiley: Chichester, U.K., 2008.

(4) (a) Gong, L.; Wenzel, M.; Meggers, E. *Acc. Chem. Res.* **2013**, *46*, 2635. (b) Huang, B.; Wang, L.; Gong, L.; Meggers, E. *Chem. - Asian J.* **2013**, *8*, 2274. (c) Chen, L.-A.; Ding, X.; Gong, L.; Meggers, E. *Dalton Trans.* **2013**, *42*, 5623. (d) Fu, C.; Wenzel, M.; Treutlein, E.; Harms, K.; Meggers, E. *Inorg. Chem.* **2012**, *51*, 10004. (e) Wenzel, M.; Meggers, E. *Eur. J. Inorg. Chem.* **2012**, 3168. (f) Lin, Z.; Celik, M. A.; Fu, C.; Harms, K.; Frenking, G.; Meggers, E. *Chem. - Eur. J.* **2011**, *17*, 12602. (g) Meggers, E. *Chem. - Eur. J.* **2010**, *16*, 752. (h) Gong, L.; Mulcahy, S. P.; Harms, K.; Meggers, E. *J. Am. Chem. Soc.* **2009**, *131*, 9602.

(5) (a) Gong, L.; Lin, Z.; Harms, K.; Meggers, E. *Angew. Chem., Int. Ed.* **2010**, *49*, 7955. (b) Fontecave, M. *ChemCatChem* **2010**, *2*, 1533.

(6) (a) Moussa, J.; Chamoreau, L. M.; Amouri, H. *Chirality* **2013**, *25*, 449. (b) Damas, A.; Moussa, J.; Rager, M. N.; Amouri, H. *Chirality* **2010**, *22*, 889. (c) Lacour, J.; Moraleda, D. *Chem. Commun.* **2009**, 7073. (d) Pérollier, C.; Bernardinelli, G.; Lacour, J. *Chirality* **2008**, *20*, 313. (e) Pérollier, C.; Constant, S.; Jodry, J. J.; Bernardinelli, G.; Lacour, J. *Chem. Commun.* **2003**, 2014. (f) Monchaud, D.; Jodry, J. J.; Pomeranc, D.; Heitz, V.; Chambron, J.-C.; Sauvage, J.-P.; Lacour, J. *Angew. Chem., Int. Ed.* **2002**, *41*, 2317. (g) Lacour, J.; Jodry, J. J.; Ginglinger, C.; Torche-Haldimann, S. *Angew. Chem., Int. Ed.* **1998**, *37*, 2379.

(7) (a) Ousaka, N.; Takeyama, Y.; Yashima, E. *Chem. - Eur. J.* **2013**, *19*, 4680. (b) Tashiro, S.; Shionoya, M. *Chem. Lett.* **2013**, *42*, 456. (c) Ousaka, N.; Takeyama, Y.; Yashima, E. *Chem. Sci.* **2012**, *3*, 466. (d) Ousaka, N.; Takeyama, Y.; Iida, H.; Yashima, E. *Nat. Chem.* **2011**, *3*, 856.

(8) Seo, M.-S.; Kim, K.; Kim, H. *Chem. Commun.* **2013**, *49*, 11623.

DOI: 10.1021/jacs.5b09555
J. Am. Chem. Soc. 2015, 137, 14190–14195

(9) (a) Wang, C.; Chen, L.-A.; Huo, H.; Shen, X.; Harms, K.; Gong, L.; Meggers, E. *Chem. Sci.* **2015**, *6*, 1094. (b) Shen, X.; Huo, H.; Wang, C.; Zhang, B.; Harms, K.; Meggers, E. *Chem. - Eur. J.* **2015**, *21*, 9720. (c) Hu, Y.; Zhou, Z.; Gong, L.; Meggers, E. *Org. Chem. Front.* **2015**, *2*, 968. (d) Ma, J.; Ding, X.; Hu, Y.; Huang, Y.; Gong, L.; Meggers, E. *Nat. Commun.* **2014**, *5*, 4531. (e) Huo, H.; Fu, C.; Harms, K.; Meggers, E. *J. Am. Chem. Soc.* **2014**, *136*, 2990.

(10) (a) Huo, H.; Fu, C.; Wang, C.; Harms, K.; Meggers, E. *Chem. Commun.* **2014**, *50*, 10409. (b) Chen, L.-A.; Xu, W.; Huang, B.; Ma, J.; Wang, L.; Xi, J.; Harms, K.; Gong, L.; Meggers, E. *J. Am. Chem. Soc.* **2013**, *135*, 10598. (c) Chen, L.-A.; Tang, X.; Xi, J.; Xu, W.; Gong, L.; Meggers, E. *Angew. Chem., Int. Ed.* **2013**, *52*, 14021.

(11) Huo, H.; Shen, X.; Wang, C.; Zhang, L.; Röse, P.; Chen, L.-A.; Harms, K.; Marsch, M.; Hilt, G.; Meggers, E. *Nature* **2014**, *515*, 100.

(12) For reviews, see: (a) Wenzel, T. J.; Chisholm, C. D. *Chirality* **2011**, *23*, 190. (b) Wenzel, T. J. *Discrimination of Chiral Compounds Using NMR Spectroscopy*; Wiley-VCH: Weinheim, 2007. (c) Schneider, H.-J.; Hacket, F.; Rüdiger, V.; Ikeda, H. *Chem. Rev.* **1998**, *98*, 1755. (d) Parker, D. *Chem. Rev.* **1991**, *91*, 1441.

(13) (a) Zhao, Y.; Swager, T. M. *J. Am. Chem. Soc.* **2015**, *137*, 3221. (b) Aspinall, H. C. *Chem. Rev.* **2002**, *102*, 1807.

(14) (a) Chisholm, C. D.; Fülöp, F.; Forró, E.; Wenzel, T. J. *Tetrahedron: Asymmetry* **2010**, *21*, 2289. (b) Wenzel, T. J.; Bourne, C. E.; Clark, R. L. *Tetrahedron: Asymmetry* **2009**, *20*, 2052. (c) Lovely, A. E.; Wenzel, T. J. *Chirality* **2008**, *20*, 370. (d) Lovely, A. E.; Wenzel, T. J. *Tetrahedron: Asymmetry* **2006**, *17*, 2642. (e) Lovely, A. E.; Wenzel, T. J. *Org. Lett.* **2006**, *8*, 2823. (f) Lovely, A. E.; Wenzel, T. J. *J. Org. Chem.* **2006**, *71*, 9178.

(15) (a) Nemes, A.; Csóka, T.; Béni, S.; Farkas, V.; Rábai, J.; Szabó, D. *J. Org. Chem.* **2015**, *80*, 6267. (b) Quinn, T. P.; Atwood, P. D.; Tanski, J. M.; Moore, T. F.; Folmer-Andersen, J. F. *J. Org. Chem.* **2011**, *76*, 10020. (c) Yang, X.; Wang, G.; Zhong, C.; Wu, X.; Fu, E. *Tetrahedron: Asymmetry* **2006**, *17*, 916. (d) Fulwood, R.; Parker, D. *J. Chem. Soc., Perkin Trans. 2* **1994**, 57. (e) Kűhn, M.; Buddrus, J. *Tetrahedron: Asymmetry* **1993**, *4*, 207. (f) Fulwood, R.; Parker, D. *Tetrahedron: Asymmetry* **1992**, *3*, 25.

(16) (a) Couffin, A.; Boullay, O. T. d.; Vedrenne, M.; Navarro, C.; Martin-Vaca, B.; Bourissou, D. *Chem. Commun.* **2014**, *50*, 5997. (b) Moon, L. S.; Pal, M.; Kasetti, Y.; Bharatam, P. V.; Jolly, R. S. *J. Org. Chem.* **2010**, *75*, 5487. (c) Cavalluzzi, M. M.; Bruno, C.; Lentini, G.; Lovece, A.; Catalano, A.; Carocci, A.; Franchini, C. *Tetrahedron: Asymmetry* **2009**, *20*, 1984. (d) Chinchilla, R.; Falvello, L. R.; Nájera, C. *J. Org. Chem.* **1996**, *61*, 7285. (e) Chinchilla, R.; Foubelo, F.; Nájera, C.; Yus, M. *Tetrahedron: Asymmetry* **1995**, *6*, 1877.

(17) (a) Pham, N. H.; Wenzel, T. J. *J. Org. Chem.* **2011**, *76*, 986. (b) Ema, T.; Tanida, D.; Hamada, K.; Sakai, T. *J. Org. Chem.* **2008**, *73*, 9129. (c) Ema, T.; Tanida, D.; Sakai, T. *J. Am. Chem. Soc.* **2007**, *129*, 10591. (d) Shirakawa, S.; Moriyama, A.; Shimizu, S. *Org. Lett.* **2007**, *9*, 3117. (e) Dignam, C. F.; Richards, C. J.; Zopf, J. J.; Warker, L. S.; Wenzel, T. J. *Org. Lett.* **2005**, *7*, 1773.

(18) (a) Bian, G.; Fan, H.; Huang, H.; Yang, S.; Zong, H.; Song, L.; Yang, G. *Org. Lett.* **2015**, *17*, 1369. (b) Jain, N.; Patel, R. B.; Bedekar, A. V. *RSC Adv.* **2015**, *5*, 45943. (c) Liu, L.-z.; He, C.-h.; Yang, L.; Huang, Y.; Wu, Q.; Duan, W.-g.; Wang, H.-s.; Pan, Y.-m. *Tetrahedron* **2014**, *70*, 9545. (d) Bian, G.; Fan, H.; Yang, S.; Yue, H.; Huang, H.; Zong, H.; Song, L. *J. Org. Chem.* **2013**, *78*, 9137. (e) Iwaniuk, D. P.; Wolf, C. *J. Org. Chem.* **2010**, *75*, 6724. (f) Kelly, A. M.; Pérez-Fuertes, Y.; Fossey, J. S.; Yeste, S. L.; Bull, S. D.; James, T. D. *Nat. Protoc.* **2008**, *3*, 215. (g) Pérez-Fuertes, Y.; Kelly, A. M.; Fossey, J. S.; Powell, M. E.; Bull, S. D.; James, T. D. *Nat. Protoc.* **2008**, *3*, 210.

(19) (a) Seco, J. M.; Quiñoá, E.; Riguera, R. *Chem. Rev.* **2012**, *112*, 4603. (b) Lesot, P.; Courtieu, J. *Prog. Nucl. Magn. Reson. Spectrosc.* **2009**, *55*, 128. (c) Freire, F.; Quiñoá, E.; Riguera, R. *Chem. Commun.* **2008**, 4147. (d) Seco, J. M.; Quiñoá, E.; Riguera, R. *Chem. Rev.* **2004**, *104*, 17. (e) Meddour, A.; Courtieu, J. *Tetrahedron: Asymmetry* **2000**, *11*, 3635. (f) Jakubcova, M.; Meddour, A.; Péchiné, J.-M.; Baklouti, A.; Courtieu, J. *J. Fluorine Chem.* **1997**, *86*, 149.

(20) *Ee* values determined by ^{1}H NMR and HPLC are within ±1% *ee*.

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