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A Versatile and Practical Solvating Agent for Enantioselective Recognition and NMR Analysis of Protected Amines

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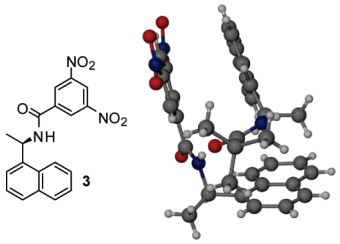
Received July 20, 2010



The 3,5-dinitrobenzoyl-derived 1-naphthylethyl amide **3** is an attractive CSA for NMR analysis of protected amines. It is readily prepared in a single step and combines practical resolution of diastereomeric complexes due to signal sharpness and effective signal separation. Crystallographic analysis shows that **3** forms a chiral cleft that can selectively bind one enantiomer of a substrate through hydrogen bonding, $\pi-\pi$ stacking, and CH/π interactions. The enantioselective complex formation causes strong upfield shifts in the ^{1}H NMR spectrum even in the presence of only 5 mol % of **3**.

The rapid advance of asymmetric synthesis and the general availability of combinatorial techniques that can produce large numbers of chiral compounds overnight have directed increasing attention to the development of fast and accurate methods for the determination of the enantiomeric composition of scalemic mixtures. The need for fast ee analysis has propelled the introduction of efficient assays based on chromatography,[1] mass spectrometry,[2] UV[3] and fluorescence spectroscopy,[4] IR thermography,[5] circular dichroism,[6] capillary electrophoresis,[7] and biochemical methods.[8] Our laboratory has developed several UV,[9] fluorescence,[10] and CD[11] probes that can be used to quantify the enantiomeric excess and amount of scalemic mixtures of a wide range of compounds.

Alternatively, NMR spectroscopy provides a useful entry to fast ee determination.[12] This generally requires the use of a chiral derivatizing agent (CDA),[13] a chiral solvating agent (CSA),[14] or a paramagnetic chiral shift reagent

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Published on Web 09/07/2010 DOI: 10.1021/jo101426a

(CSR)[15] such as lanthanide chelate complexes.[16] While CDA's have found widespread use for the elucidation of the absolute configuration of chiral compounds, the use of CSA's and CSR's is generally preferred for ee analysis because this approach is faster and less prone to errors. The accurate analysis of the enantiomeric excess of a chiral analyte requires the use of a perfectly enantiopure CDA and quantitative formation of diastereomeric products from the enantiomeric starting materials to avoid chiral discrimination effects that can originate from kinetic resolution during derivatization or purification steps. These problems can be avoided by formation of noncovalent adducts in the presence of a CSA or CSR which, even if not enantiopure, provide accurate results if signal integration is not compromised because of decreased peak resolution.

To date, few CSA's for the enantiodifferentiation of chiral amines and amides are known and proton NMR shift differences between the diastereomeric adducts formed are often less than 0.1 ppm.[17] On the basis of our experience with the Whelk-O selector and its analogues in chiral chromatography,[18] we rationalized that the 9-anthryl- and the 3,5-dinitrobenzoyl-derived amides **1**−**3** would (a) be readily available from commercially available enantiopure amines and (b) form diastereomeric complexes with a series of substrates exhibiting distinct chemical shift nonequivalences ($\Delta\Delta\delta$), which could potentially allow the use of substoichiometric amounts of the CSA.

The Whelk-O 1 chiral stationary phase was originally developed by Pirkle and co-workers for HPLC enantioseparation of compounds with a hydrogen bond acceptor and an aromatic ring in close proximity of the chiral center.[19] The Whelk-O selector consists of an amide group connecting an electron-deficient 3,5-dinitrobenzoyl group and an electron-rich naphthalene ring, Figure 1. Numerous chromatographic studies, crystallography, and NMR analysis have shown that

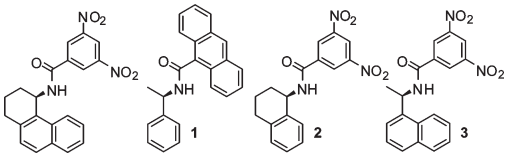

FIGURE 1. Structures of the Whelk-O selector and CSAs **1**−**3**.

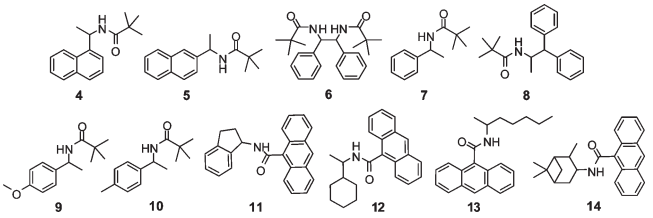

FIGURE 2. Structures of analytes tested.

the amide unit prefers to stay in the pseudoaxial position and thus affords a cleft-like structure that is essential for the chiral recognition mechanism.[20] It is generally assumed that only one enantiomer of a chiral compound can diffuse into the cleft to undergo simultaneous hydrogen bonding, $\pi-\pi$ interactions with the electron-deficient 3,5-dinitrobenzoyl group, and CH/π interactions with the naphthyl moiety of the Whelk-O selector without adopting an energetically unfavored conformation. Immobilization of this selector on silica gel has led to an impressive range of HPLC enantioseparations.[21] But the synthesis of this selector requires several steps and preparative enantioseparation of the final product, which has been a remaining drawback limiting its use in other applications, including enantioselective NMR analysis. By contrast, dinitrobenzoyl amides **2** and **3** can be prepared in a single step by the condensation of 1-amino-1,2,3,4-tetrahydronaphthalene and 1-(1-naphthyl)ethylamine with 3,5-dinitrobenzoyl chloride in 90−91% yield (see the SI).

On the basis of the above rationale, we assumed that one enantiomer of a chiral aromatic substrate should diffuse selectively into the cleft of **1**−**3** to undergo hydrogen bonding, π-stacking, and CH/π-interactions with the host while the other enantiomer might either participate in only two of these interactions inside the cleft and thus have a different orientation or it preferably resides outside the cleft. We expected that the corresponding diastereomeric adducts would give rise to distinctively different shielding effects that could easily be measured by ^{1}H NMR experiments.

To test the usefulness of **1**−**3**, we prepared a series of pivaloyl derivatives of chiral aromatic amines **4**−**10** and the anthracene analogues of aminoindan and aliphatic amines **11**−**14**, see Figure 2 and the SI. Initial NMR analysis of stoichiometric mixtures of the CSA's and racemic 1-(1-naphthyl)ethylamide **4** showed that (*R*)-**3** indeed affords diastereomeric complexes with quite different chemical shifts, Figure 3. At relatively low concentrations, the methyl signals H_a in **4** experience a significant upfield shift in the homochiral adduct and the *tert*-butyl protons H_b are downfield shifted. Interestingly,

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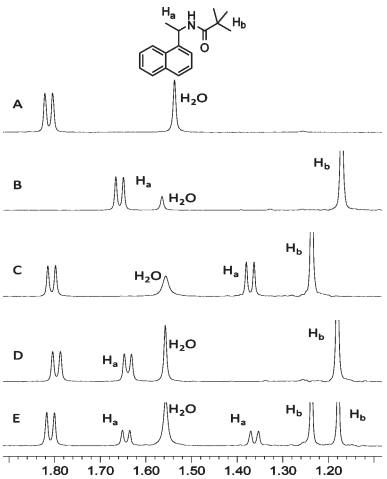


FIGURE 3. Selected excerpts of the ^{1}H NMR spectra obtained with CSA **3** and amide **4**. The methyl protons are denoted as H_a and H_b, respectively. (A) CSA **3**, (B) substrate **4**, (C) (*R*)-**3** and (*R*)-**4**, (D) (*R*)-**3** and (*S*)-**4**, (E) (*R*)-**3** and scalemic **4**. All spectra were recorded in $CDCl_3$ at room temperature, using equimolar amounts of **3** and **4** at 6.85 mM.

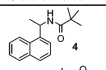
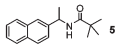
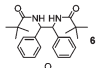
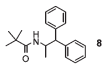
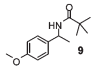
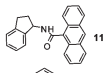
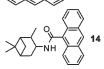
comparison of the NMR spectra of the heterochiral complex and the free analyte shows a very small change in the chemical shifts of (*S*)-**4**. The nonequivalences $\Delta\Delta\delta$ of H_a and H_b in the diastereomeric complexes formed with CSA **3** were determined as 0.282 and 0.059 ppm, Table 1.[22]

We were able to produce a cocrystal of (*R*)-**3** and (*R*)-**4**, which shows that the CSA populates a cleft-like conformation having the 3,5-dinitrobenzoyl group almost perfectly orthogonal to its naphthalene plane, Figure 4. The proton of the amide group in (*R*)-**3** points toward the front of the cleft and undergoes hydrogen bonding with the carbonyl unit of (*R*)-**4**. The N−O distance was determined as 2.79 Å. This interaction is complemented by $\pi-\pi$ stacking and CH/π forces. The distance between the cofacial 3,5-dinitrobenzoyl group and the aromatic ring of **4** is 3.66 Å. The CH/π attraction arises from the T-shaped orientation of the aromatic CH bonds of **4** and the naphthalene plane of the CSA, having a separation of 2.95 Å. Overall, this three-point interaction places (*R*)-**4** into a highly ordered arrangement inside the cleft of (*R*)-**3**. As a result, the methyl group of (*R*)-**4** intrudes into the π-cloud and diamagnetic ring current of the naphthalene unit of the CSA, which explains the strong upfield shift shown in Figure 3.

We then decided to employ CSA **3** in NMR studies with equimolar amounts of amides **5**−**14**. In all cases, we observed nonequivalences $\Delta\Delta\delta$ that are sufficient for quantitative enantiodifferentiation, see Table 1 and SI. The NMR spectra collected with substrate **9** clearly demonstrate (a) the high resolving ability of CSA **3** and (b) the conserved signal sharpness which both contribute to high overall resolution, Figure 5. Again, the NMR signals in the homochiral adduct [(*R*)-**3**−(*R*)-**9**] undergo more pronounced upfield shifts than the corresponding protons in the heterochiral complex and the *tert*-butyl groups show small downfield shifts. The nonequivalences of the aromatic signals H_a and H_b were determined as 0.103 and 0.063 ppm, respectively. The doublets of the methyl protons H_e are baseline resolved and even the peripheral methoxy groups H_c have clearly different chemical shifts. The corresponding $\Delta\Delta\delta$ values are 0.076 and 0.024 ppm, respectively. As expected, the diastereomeric adducts show the strongest NMR nonequivalences at the methine proton H_d which are separated by 0.210 ppm.

The remarkable differences in the chemical shifts of the methyl protons in the diastereomeric complexes formed between (*R*)-**3** and the enantiomers of amide **4** prompted us to further investigate the feasibility of NMR enantiodifferentiation with substoichiometric amounts of this CSA.

TABLE 1. ^{1}H NMR Nonequivalences $\Delta\Delta\delta$ of Amides 4−14 in the Presence of Equimolar Amounts of CSA 3[b]

Entry	Substrate	Protons shifted	$\Delta\Delta\delta$ (ppm)[a]
1	 4	ArC*H*N(CH_3)	0.282
		C(CH_3)$_3$	0.059*
2	 5	ArC*H*N(CH_3)	0.262
		C(CH_3)$_3$	0.035*
3	 6	(ArC*H*N)$_2$	0.050
4	 7	ArC*H*N(CH_3)	0.141
		CH_3	0.049
5	 8	ArC*H*N(CH_3)	0.010
6	 9	ArC*H*N(CH_3)	0.210
		ArCHNCH_3	0.076
		Ar*H*	0.103
		Ar*H*	0.063
		OCH_3	0.024
		C(CH_3)$_3$	0.007*
7	 10	ArC*H*N(CH_3)	0.169
		ArCHNCH_3	0.064
		Ar*H*	0.078
		Ar*H*	0.032
		ArCH_3	0.027
		C(CH_3)$_3$	0.004*
8	 11	ArC*H*N(CH_2R)	0.039
		Ar*H*	0.006
9	 12	RC*H*N(CH_3)	0.022
10	 13	RNCHCH_3	0.018
11	 14	CHCH_3	0.009

[a]All shifts are upfield compared to the NMR spectrum of the free substrate unless indicated by an asterisk. [b]The concentration of **3** and the substrates was 6.85 mM in $CDCl_3$. All NMR spectra were recorded at 25 °C.

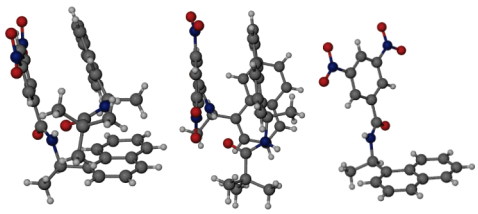


FIGURE 4. Crystal structure of the homochiral complex [(*R*)-**3**−(*R*)-**4**]. View along the cleft (left) and from the top (middle). The individual structure of the CSA is shown for comparison.

(22) During this study we found that CSA **3** can also be used for the resolution of chiral sulfoxides: Deshmukh, M.; Dunach, E.; Juge, S.; Kagan, H. B. *Tetrahedron Lett*. **1984**, *25*, 3467–3470.

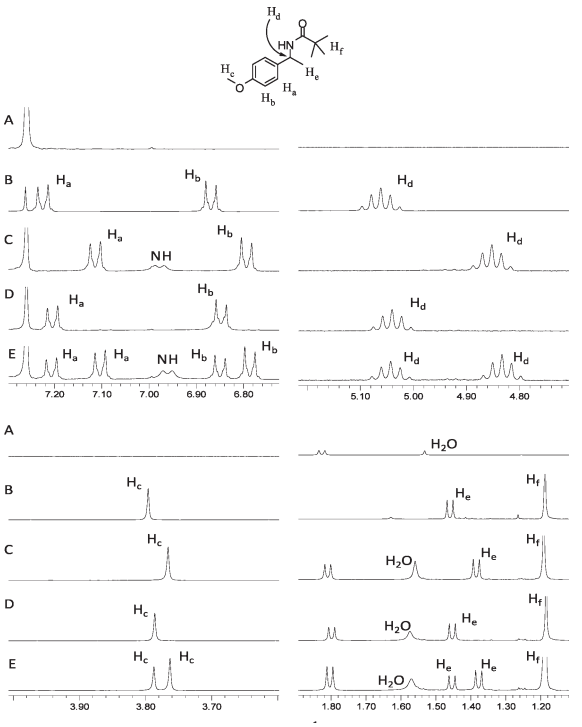


FIGURE 5. Selected regions of the ^{1}H NMR spectra obtained with CSA **3** and amide **9**. (A) CSA **3**, (B) substrate **9**, (C) (*R*)-**3** and (*R*)-**9**, (D) (*R*)-**3** and (*S*)-**9**, (E) (*R*)-**3** and scalemic **9**. All spectra were recorded in $CDCl_3$ at room temperature, using equimolar amounts of **3** and **9** at 6.85 mM.

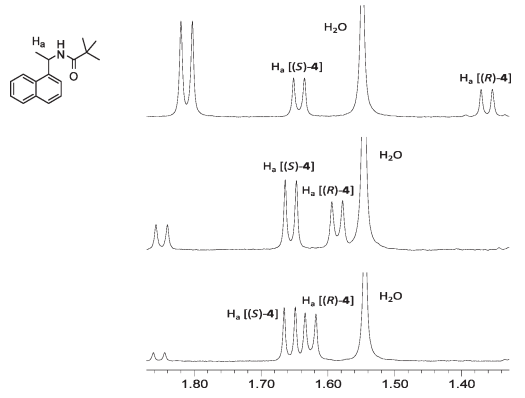


FIGURE 6. ^{1}H NMR nonequivalences of scalemic amide **4** in the presence of varying amounts of CSA **3**. (A) 100 mol % (*R*)-**3**, (B) 20 mol % (*R*)-**3**, (C) 5 mol % (*R*)-**3**. The substrate concentration was kept constant at 6.85 mM in $CDCl_3$ at room temperature.

We were pleased to find that the methyl groups adjacent to the chiral center in **4** are still baseline resolved in the presence of 20 and 5 mol % of CSA **3**, Figure 6. This experiment underscores the efficiency of CSA **3** in addition to the wide application spectrum summarized in Table 1.

Finally, we prepared 9 samples of scalemic mixtures of **4** with known enantiomeric composition to confirm a linear correlation between the actual ee values and the values determined from NMR integration results. The calculated ee values were generally within 3% of the actual enantiopurity of the samples, Figure 7.

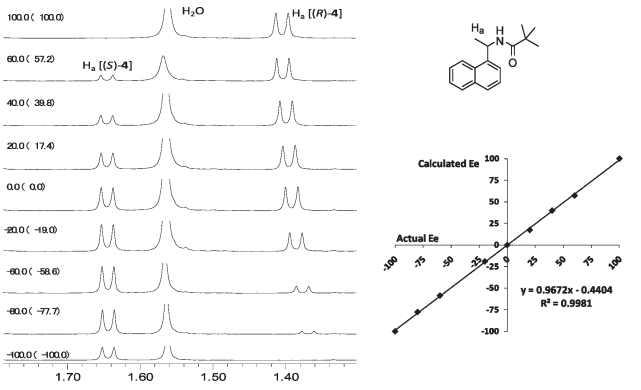


FIGURE 7. Selected region of the ^{1}H NMR spectra of scalemic mixtures of **4** in the presence of stoichiometric amounts of (*R*)-**3** (left). Linear correlation between the calculated and the theoretical ee values (right).

In conclusion, the facile synthesis of the 3,5-dinitrobenzoyl-derived 1-naphthylethyl amide **3** makes this an attractive CSA for NMR analysis of amine derivatives. It combines practical resolution of diastereomeric complexes due to signal sharpness and effective signal separation. Crystallographic analysis showed that **3** forms a chiral cleft that can accommodate the homochiral enantiomer of amide **4** through hydrogen bonding, $\pi-\pi$ stacking, and CH/π interactions. The enantioselective complex formation causes strong upfield shifts in the ^{1}H NMR spectrum even in the presence of only 5 mol % of **3**. This NMR study suggests that immobilization of **3** on silica gel could afford a powerful chiral stationary phase readily prepared from inexpensive enantiopure starting materials and therefore be economically much more attractive than the Whelk-O analogue.

Experimental Section

Synthesis of Chiral Solvating Agent 3. To a solution of (*R*)-1-naphthylethyl amine (0.08 mL, 0.50 mmol) and triethyl amine (0.08 mL, 0.57 mmol) in 2 mL of anhydrous CH_2Cl_2 was added 3,5-dinitrobenzoyl chloride (0.101 g, 0.44 mmol) dissolved in 3 mL of anhydrous CH_2Cl_2 at 0 °C. The reaction mixture was stirred at room temperature for 2 h and then extracted with 4 M HCl, $NaHCO_3$, water, and brine. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo to afford **3** (0.145 g, 0.40 mmol) in 91% yield as a yellow solid. ^{1}H NMR δ 1.18 (d, J = 7.1 Hz, 3H), 6.10 (dt, J = 6.9, 7.1 Hz, 1H), 6.59 (d, J = 7.1 Hz, 1H), 7.46−7.56 (m, 3H), 7.59 (d, J = 7.1 Hz, 1H), 7.83 (d, J = 8.2 Hz, 1H), 7.86 (d, J = 8.0 Hz, 1H), 8.04 (d, J = 8.2 Hz, 1H), 8.86 (s, 2H), 9.08 (s, 1H). ^{13}C NMR δ 20.6, 45.9, 120.9, 122.7, 128.8, 125.2, 126.1, 126.9, 127.1, 128.8, 128.9, 130.8, 133.8, 137.0, 137.4, 148.4, 161.6.

Acknowledgment. This material is based upon work supported by the NSF under CHE-0910604.

Supporting Information Available: Experimental procedures, crystallographic data, and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.