Molecular Mechanics Calculations and Comparison of Proton, Fluorine, and Carbon NMR Diastereomer Discrimination via Nonbonding Interactions between Fluorine-Labeled Enantiomeric Amides and Enantiomerically Pure Chiral Solvating Agents

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Diastereomer discrimination of fluorine-labeled enantiomers in chloroform solutions was studied with and without two chiral solvating agents (1S and 2S) using ^{1}H, ^{13}C, and ^{19}F NMR spectroscopy. Although by ^{13}C NMR spectroscopy the diastereomer discrimination is not observable, changes of chemical shifts for some carbon atoms unambiguously show formation of nonbonding interactions between the enantiomers and the chiral solvating agents. The position and the ratio of signal sets in both hydrogen and fluorine NMR spectra correspond to the enantiomeric composition in the solution. On the basis of changes in the chemical shifts of enantiomers in chloroform solutions of chiral solvating agent, binding constants and binding energy differences were calculated. Using the MM2 force field, calculations were performed on binding complexes between the chiral solvating agent 2S and enantiomers 6. It was shown that demand for energy differences between diastereomeric nonbonding complexes of racemic amides and the chiral solvating amides necessary to obtain their NMR diastereomer discrimination is low for ^{1}H, intermediary for ^{19}F, and high for ^{13}C NMR.

Introduction

The occurrence of nonbonding interactions between donor and acceptor molecules via charge-transfer complexes,[1,2] hydrogen bonding,[3] and lyophilic–lyophilic[4] packing is a well-established phenomenon. If one of the binding components is an optically pure compound and the other is a racemate in a highly concentrated solution, diastereomer discrimination can occur.[5]

Recently, we discovered that nonbonding interactions between enantiomers and chiral solvating molecules and enantiomers produce different ^{1}H NMR chemical shifts and the integrated areas correspond to the ratio of enantiomers in the mixture.[6] The influence of two kinds of nonbonding interactions on diastereomer discrimination, namely, hydrogen bonding[7] and charge-transfer complex formation, were established.[8] The enantiomeric recognition that occurred through hydrogen bonding between two enantiomers, studied by ^{1}H NMR, strongly depends on their ratio, overall concentration in solution, polarity of solvent, and temperature. Maximal discrimination was observed in highly concentrated chloroform solutions, in nonequal ratios of enantiomers, and at low temperatures (–40 °C). In polar solvents like dimethyl sulfoxide the effect totally disappears due to preferable hydrogen bonding with the solvent rather than with the

enantiomers. We were also able to observe diastereomer discrimination in optically active surfactant aggregates via hydrogen bonding and a similar effect was observed in micellar media of surfactant enantiomers which can form charge-transfer complexes.[9] Although ^{19}F NMR spectroscopy was employed in diastereomer discrimination through solute–solute interactions of 2,2,2-trifluoro-1-phenylethanol in neat optically active α-phenylethylamine as early as 1966,[10] to the best of our knowledge there is not a single report which deals with ^{19}F NMR spectroscopic and molecular mechanics calculation of amide enantiomeric bindings with chiral solvating amide molecules. In all of our[6–9] previous studies of diastereomer discrimination through nonbonding interactions (mainly hydrogen bonding and charge-transfer interactions), only ^{1}H NMR spectroscopy was successfully used.[11] In our previous studies with the enantiomeric amides as model compounds and enantiomerically pure chiral solvating amide we were unable to find any evidence that nonbonding interactions between enantiomers can produce enantiomeric nonequivalence in other than proton NMR spectra.

Results and Discussion

Here, we present the influence of the binding energy between racemic amide and two electronically different chiral solvating molecules on their ^{1}H, ^{19}F, and ^{13}C NMR diastereomer discrimination. The compounds studied are shown in Figure 1. Since the racemic amides 3–7 have fluorine atoms, they can be used in hydrogen, fluorine, and carbon NMR spectroscopic studies of nonbonding complexes with two electronically different optically pure and very chloroform soluble chiral solvating agents 1S and 2S.

In the proton NMR spectra of a chloroform solution of racemic amides 3 and 5–7 with both chiral solvating

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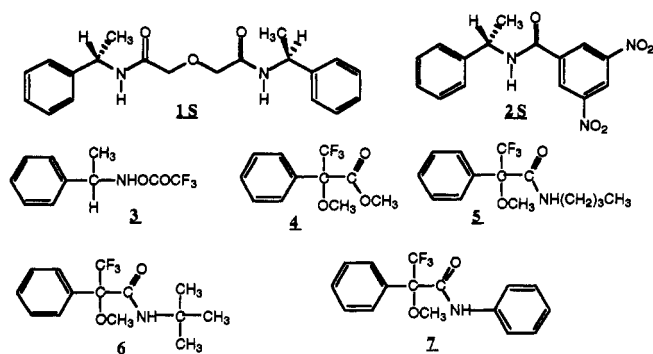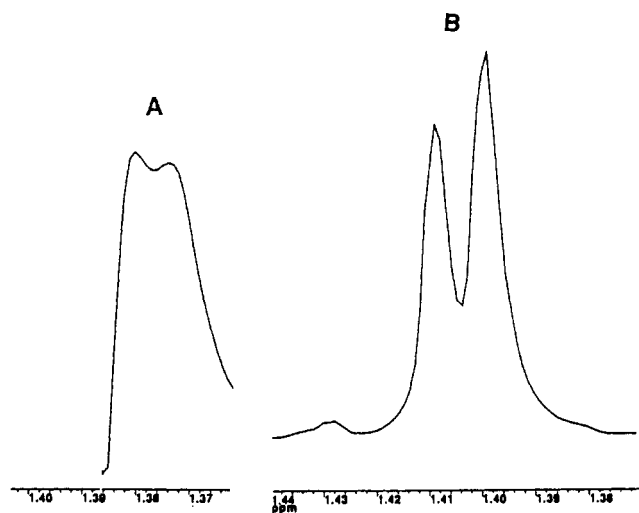
Figure 1.

Figure 2. ¹H NMR singlet of the *tert*-butyl group of 6 (0.02 M
6R + 0.03 M **6S**) in (A) 1 M **1S** and (B) 1 M **2S** chloroform
solution at room temperature.

molecules **1S** and **2S** two sets of signals were observed.
The proton NMR of racemic amide **6** in chloroform solution
of chiral solvating agents **1S** and **2S** is presented in Figure
2. The best diastereomer discrimination was achieved with
a high molar ratio of chiral solvating agent to racemic
amide, in nonpolar solvent and at low temperature.[12] In
all cases at least five times higher concentration of chiral
solvating agent over the racemic amide was used. The
low temperature (−55 °C) helps the separation of the
enantiomeric signals, but because of higher viscosity of
the chloroform solution, the shimming signal was too low
and consequently the ¹H NMR signals were broader.

There are not many broad windows in the proton NMR
spectra of chiral solvating molecules **1S** and **2S** for
observation of their diastereomeric complexes with racemic

(11) In the present publication our goal is neither the NMR deter-
mination of enantiomeric purity nor enantiomeric separation through
solute–solute interactions between the enantiomers and chiral solvating
agents which is generally present in large excess. The reader is advised
to find recent progress in those fields in four excellent reviews. For an
NMR determination of enantiomeric purity, see: Parker, D. *Chem. Rev.*
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W. H. Commercial Available Brush-Type Chiral Separation for the Direct
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tography*; Ahuja, E., Ed.; ACS Symposium Series 471; American Chemical
Society: Washington, DC, 1991; p 41. Dobashi, A.; Dobashi, Y.; Hara,
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Washington, DC, 1991; p 164. Pirkle, W. H.; Pochapsky, T. C. *Chem.
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(12) For more information on nonbonding interactions and optimal
conditions in proton NMR diastereomer discrimination of similar racemic
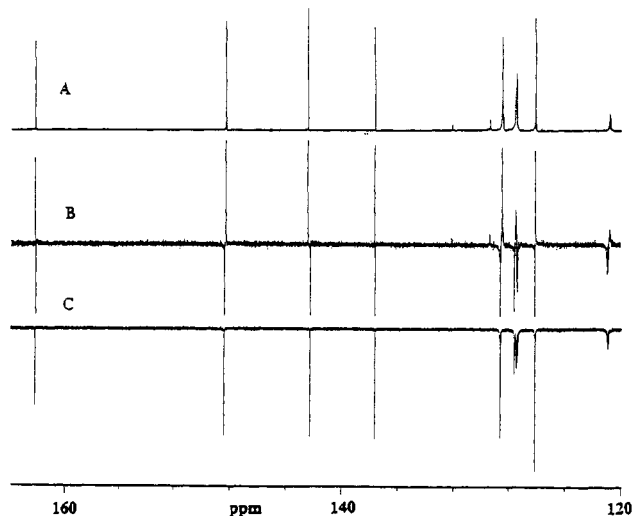amides, see refs 6 and 7.

Figure 3. ¹³C NMR spectra of the aromatic region of chloroform
solutions of (A) 0.5 M **2S** with racemic **5**, (C) 0.5 M **2S**, and (B)
their computer assisted subtraction.

amides **3** and **5–7**. The ¹³C NMR spectra have very sharp
signals and a more than 10 times larger window in ppm
values than the proton spectra. Thus, it is reasonable to
expect that better diastereomer discrimination should be
obtainable in the carbon spectra. Our attempts to observe
any differences in carbon NMR spectra between the two
enantiomers with or without the chiral solvating molecules
in highly concentrated (2 M) chloroform solutions were
unsuccessful. Although each pair of enantiomers shows
only one set of signals, the position of the ¹³C NMR signals
for both the chiral solvating molecules and the racemic
amides in the mixture differ from the chemical shift of the
pure components. For example, the chloroform solution
of the chiral solvating agent **2S** (0.5 M) and racemic **5** (0.2
M) shows one set of signals for both the chiral solvating
agent and the racemic molecules, but their chemical shifts
differ considerably from the ones obtained from the pure
components (Figure 3).[13] This observation proves that
the interactions between the chiral solvating molecule **5**
and the racemic molecules **2S** affects their ¹³C NMR
spectra, but the differences in the binding energies for the
two diastereomeric complexes are too small to produce
diastereomer discrimination in their carbon NMR spectra.

Fluorine NMR offers unique opportunities studying
diastereomer discriminations through nonbonding inter-
actions. The fluorine NMR window is even broader than
that of carbon NMR, and fluorine atoms can be placed
either on the studied amides or on the chiral solvating
molecule. In our case the chiral solvating molecules do
not have fluorine atoms, and all signals in fluorine NMR
will come from racemic **4–7** regardless of the high
concentration of the chiral solvating molecules **1S** or **2S**
in the solution. It will be also very interesting to compare
the diastereomer discrimination of the same compounds
in proton and fluorine NMR spectra.

Although the racemic amide **3** shows two sets of signals
in the ¹H NMR spectra, in the presence of both **1S** and
2S the ¹⁹F NMR spectrum shows one signal. It is well
established from our previous work on diastereomer
discrimination that the difference in enantiomeric signals

(13) NMR spectra were saved on a floppy disk and transferred to the
Macintosh IIfx MacFID program. All further manipulations with that
data were performed on the Macintosh IIfx computer.

strongly depends on their position with respect to the chiral center: the closer the hydrogen to the chiral center, the higher the differences in ^{1}H NMR shifts.[6] Consequently, the combination of the remote position of fluorines in **3** from the chiral carbon and the low binding energy between the chiral solvating molecules and the enantiomers produces insufficient or no difference in the fluorine spectra. In molecules **4-7**, the trifluoromethyl group is directly bound to the chiral carbon. The fluorine spectra of racemic **4** with both **1S** and **2S** shows only a singlet at room temperature and at -55 °C. This is understandable in the case of chiral solvating molecule **1**, since there is no considerable intermolecular nonbonding interaction between **1** and **4**. Substantially weak associations (interactions) can occur through the hydrogen bonding between the amide hydrogen of **1S** and the ester carbonyl oxygen of **4** and even weaker interactions between the trifluoromethyl group of **4** and the aromatic group of **1**.[14] In fact, those nonbonding interactions were used in the molecular modeling of the complex between **1** and **4**. Molecular modeling calculations of these 1:1 diastereomeric complexes show no or a very small difference in energies. The maximal energy difference of those diastereomeric complexes obtained by conformational analyses and full MM2 optimization was 0.02 kcal/mol, which is far within the margin of computational error. These results are in full agreement with our previous findings that diastereomer discrimination of racemic esters which do not possess any other group or fragment to form nonbonding interactions with an enantiomerically pure amide cannot be achieved by ^{1}H NMR spectroscopy. In the case of **2S** weak nonbonding interactions such as $\pi-\pi$ stacking (charge-transfer interactions) can increase the association constant between ester **4** and **2S**. Molecular modeling calculations take into account the electrostatic interactions ($\pi-\pi$ stacking) between two aromatic groups. With this added nonbonding interaction the energy difference is still below 0.2 kcal/mol. The NMR spectra of the studied compound are an average of all possible associates in solution. Although the calculated energy difference for the diastereomeric associates between optically pure **2S** and racemic **4** is relatively small ($\sim$0.2 kcal/mol) we believe that, because of the high NMR shielding effect of the 3,5-dinitrobenzoate group, ^{19}F NMR enantiomeric nonequivalence should be observed. Unfortunately, the results of the molecular modeling predicts a slightly higher binding energy than occurs in solution as evidenced by lack of nonequivalence observed in ^{19}F NMR spectra.

Compounds **5-7** have an amide bond and can form hydrogen bonding with both chiral solvating molecules. Although their ^{1}H NMR spectra in chloroform solutions with either optically pure **1S** or **2S** contain two sets of signals that correspond to the ratio of enantiomers, two singlets in their ^{19}F NMR spectra were observed only with **2S** as a chiral solvating molecule. We assume that there is a need for stronger binding in diastereomer discrimination in fluorine NMR spectra than in hydrogen. Chiral solvating agent **2S** differs in many ways from **1S**. In the best possible scenario chiral solvating agent **1S** can make

Figure 4. HOMO-LUMO interactions of acceptor chiral solvating molecule **2S** with donor amide molecule **6S**.

two hydrogen-bonding interactions if both amide bonds are in a-cis conformations. It is well established that amide bonds in the crystal and solid state are in the preferred trans conformation.[15] Our molecular mechanics calculations show that the energy difference for amide **5** in a-cis and s-trans is only 2.1 kcal/mol whereas in the case of sterically more demanding amide **6**, the difference is 11.6 kcal/mol. To perform two-point nonbonding interactions (two hydrogen bonds) between **5** and **1S** at least two amide bonds have to be in the a-cis conformation which costs more than 4 kcal/mol. This energy cannot be obtained from their binding energies, which are lower than 2 kcal/mol. These energy differences are even higher in the case of the calculated nonbonding complex between **1S** and amide **6**. Even with that energetically unfavorable conformation two point interactions in the diastereoisomeric associates for all our amides studied with chiral solvating agent **1S**, the computer-generated differences are negligible (lower than 0.1 kcal/mol).

Chiral solvating agent **2S** differs from **1S** in at least two very important features. **2S** has a highly electron deficient 3,5-dinitrobenzoate moiety which can form charge-transfer interactions with the phenyl group of the amides **5-7**. The **2S** amide proton is much more acidic in comparison with amide proton of **1S** and can form a much stronger hydrogen bond with racemic amides **5-7**. The calculated AM1 HOMO-LUMO interactions between amide **6S** and **2S** show that donor-acceptor association of these two molecules is energetically favorable (Figure 4) which definitely supports the idea of $\pi-\pi$ aromatic stacking. Considering all supporting data obtained by molecular modeling it is quite possible that multipoint interactions between **2S** and racemic amides **4-7** exist. Keeping the conformations of amide bonds in the energetically favored s-trans conformation three-point nonbonding interactions were selected by computer simulations: one hydrogen bond between the amide groups, hydrogen bonding between the amide group of the racemic amide and the nitro group of **2S**, and $\pi-\pi$ stacking between the two aromatic groups. In chloroform solutions there are many possible associations between the studied molecules including formation of a long array of donor-acceptor-donor-acceptor interactions ($\pi-\pi$ stacking). The chemical shift of their mixture should be an average of all possible associates in the mixture. Computer-simulated one-point associations between **1S** and racemic amide **6** are presented in Figure 5. The energy differences between the diastereomeric complexes (associates) in their minimum obtained after conformational analysis of both molecules is below 0.05 kcal/mol. This energy difference is too small to produce any considerable change in chemical shift of their ^{19}F NMR spectra, especially if this is one of many molecular

(14) There is evidence that very weak nonbonding interactions between the fluorine atom of fluorinated alkane and aromatic compounds can exist. These interactions are extremely weak. For studies of interactions between fluorinated ethers and aromatic compounds, see: Ladika, M.; Jursic, B.; Sunko, D. E. *Spectrochim. Acta* 1986, *42A*, 1397 and references cited therein.
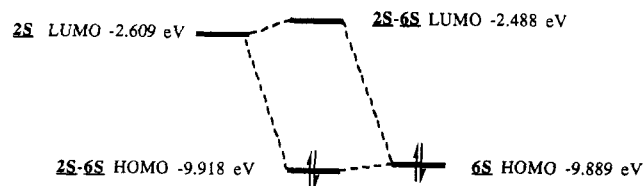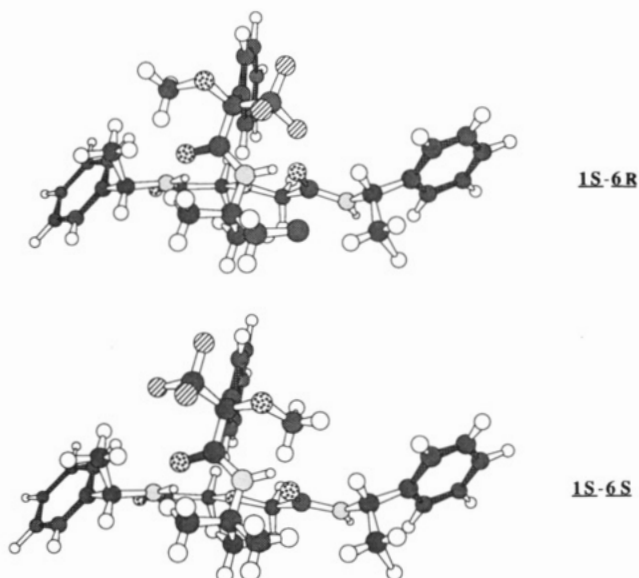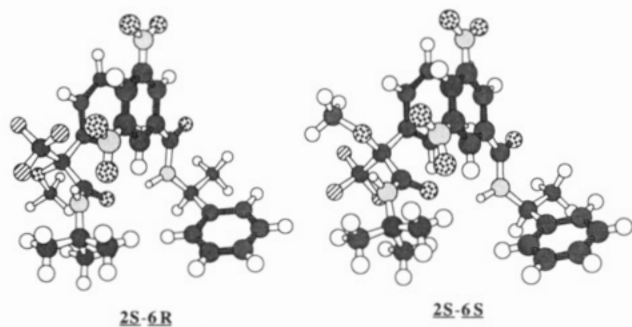
(15) Lister, D. G.; MacDonald, J. N.; Owen, N. L. *Internal Rotation and Inversion*; Academic Press: New York, 1978; p 228. Bassindale, A. *The third Dimension in Organic Chemistry*; Wiley: New York, 1984; p 74.

1S-6R

1S-6S

Figure 5. Computer-simulated molecular complexes between chiral solvating agent 1S and racemic amide 6.


2S-6R   2S-6S

Figure 6. Computer-generated molecular complexes between chiral solvating agent 2S and racemic amide 6.

associates present in the solution. The nonbonding complexes between 2S and racemic amide 6 simulated by molecular mechanics calculations is presented in Figure 6. These complexes were selected after full systematic conformational search with Chem-X. In this case we have three point interactions between the chiral solvating agent molecule and the racemic amide. The energy differences between the two diastereomeric associates is around 0.5 kcal/mol. Although the energy difference is relatively small it is sufficient to produce spectroscopic discrimination of the enantiomers.

Computational results are in qualitative agreement with the obtained chemical shifts in the ^{19}F NMR spectra presented for 1S and 2S and racemic amide 6 in Figure 7. These spectra show that considerable interactions between 1S and amide 6 exist, but there is no preference in stronger binding any of the enantiomers. With 2S higher nonbonding interactions with amide 6 occur (judged by the chemical shift) with a difference in energies of enantiomer binding. Experimentally, we determined the binding constant for two of these enantiomers with enantiomerically pure 2S by following the change of chemical shift of the enantiomeric signal with changing its concentration in chloroform solution of 2S. The obtained binding constant for 2S–6R is 0.985 L mol^{-1} and for 2S–6S is 0.831 L mol^{-1}. The calculated energy from these two constants is ~0.23 kcal·mol^{-1}, which is consid-
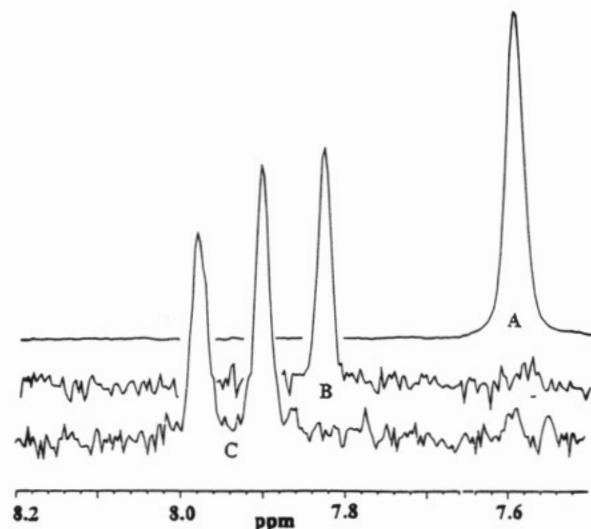
Figure 7. ^{19}F NMR spectra of a chloroform solution of amides 6S (1.6 M) and 6R (0.4) (case A), 1S (1 M), 6S (0.025 M), and 6R (0.025 M) (case B), and 2S (0.5 M), 6S (0.025 M), and 6R (0.025 M) (case C).
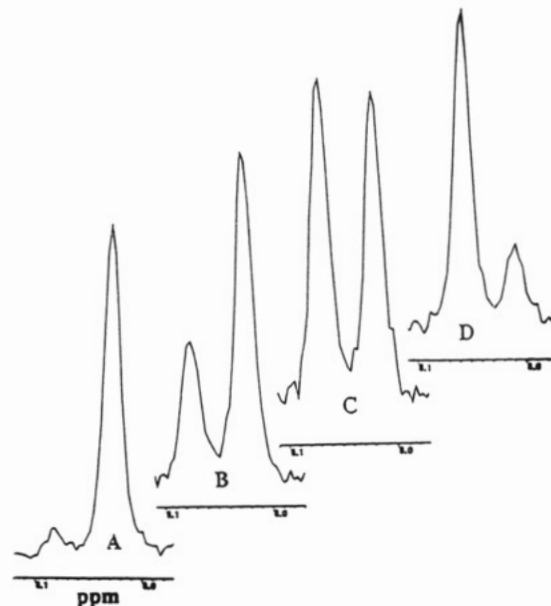
Figure 8. ^{19}F NMR spectra of a chloroform solution of 2S (0.5 M) and amide 7 (0.05 M) in an enantiomeric ratio 7R to 7S of (A) 5:95, (B) 20:80, (C) 50:50, and (D) 80:20.

erably lower than obtained from Chem-X calculations (~0.5 kcal). The higher calculated energy difference can be explained by the fact that calculations were performed in gas phase where the nonbonding interactions are much stronger than in chloroform solution.

Finally, this approach can be used for determination of the enantiomer composition of fluorinated amide enantiomers in their mixtures. The ratio of signals corresponds to the enantiomeric composition in the chloroform solution. For example, in Figure 8 the determination of enantiomeric composition of amide 7 by ^{19}F NMR in chloroform solution with 2S as chiral solvating agent is presented. It is clear from the spectra that the intensity of the signals follows the ratio of enantiomers in the mixture. Unfortunately, a small amount of one enantiomer (~1%) in the enantiomeric mixture cannot be detected with this method.

Conclusion

As demonstrated, the noncovalent binding interactions between an enantiomer and chiral solvating molecule is presented. In order to be able to determine the enantiomeric composition in a mixture certain binding energy barriers between the enantiomers and chiral solvating molecules must be overcome. This is the reason that in some cases the diastereomer discrimination with the chiral solvating molecule cannot be detected. The necessary binding energies of the diastereomeric complexes for their discrimination strongly depends on the spectroscopic method. It was shown with the same nonbonding complexes that relatively small energy is required for ^{1}H NMR (the discrimination was observed with all studied amides), higher for ^{19}F NMR (the discrimination was observed only with chiral solvating agents that can make multipoint interactions with enantiomers), and very high for ^{13}C NMR spectroscopy (only a small shift without the discrimination was observed). Finally, the calculated difference in energy of **6R** and **6S** enantiomers binding to the chiral solvating agent **2S** is relatively close to the experimental value considering the fact that molecular modeling was performed in the gas phase.

Experimental Section

General. Melting points (uncorrected) were determined on an Electrotermal IA 9000 digital melting point apparatus. ^{1}H, ^{13}C, and ^{19}F NMR spectra of deuteriochloroform solutions were recorded on a Gemini 300-MHz spectrometer with TMS as internal reference for ^{1}H NMR, chloroform as internal reference for ^{13}C NMR, and trifluoroacetic acid as external reference for ^{19}F NMR. All values are given in ppm. Mass spectra were recorded on a Hewlett-Packard 5890 gas chromatograph with a Hewlett-Packard 5971 mass selective detector. All starting materials and reagents were purchased from Aldrich and were used without further purification. The preparation and characterization of **1S** are published elsewhere,[7] and **2S** was obtained from Aldrich.

Binding Constants. The binding constant and binding energy differences for racemic **6** and **2S** were determined from changes of fluorine chemical shifts in their ^{19}F NMR spectra. The concentration of the chiral solvating agent in chloroform was constant (0.1 M), while the concentration of the enantiomer was varied from 3×10^{-3} to 1×10^{-1} mol/L. The binding constants are represented with the equilibrium $A + D = AD$, $K^{AD} = [AD]/([A][D])$ where A is an enantiomer, D is the chiral solvating molecule, and AD is the complex between the enantiomer and chiral solvating molecule. The concentration of the chiral solvating molecule was held constant, and the concentration of the enantiomer was changed. The change of chemical shift in ^{19}F NMR spectra was followed with changes of concentration of the enantiomer. The constants were calculated by the Benesi-Hildebrand method,[16] which was modified for the NMR spectroscopic studies.[17] The differences in binding energies were calculated from

$$\Delta G = -RT \ln (K^{AD}_R/K^{AD}_S)$$

where K^{AD}_R is binding constant of **6R** to **2S** and K^{AD}_S is binding constant of **6S** to **2S**.

Molecular Mechanics Calculations. Molecular mechanics calculations were performed on a 66-MHz IBM compatible 486PC with the Chem-X[18] computational package for MM2[19] calculations and HyperChem[20] for semiempirical single point AM1[21] calculations. The molecules were built with Chem-X, optimized, and copied into the HyperChem program where single-point AM1 calculations were performed. For every structure reported herein a systematic conformational search with Chem-X was performed. The lowest energy structure was selected and fully optimized. The electrostatic interactions as default parameters of Chem-X were used to calculate the nonbonding interactions (hydrogen bonding and π-π donor-acceptor aromatic interactions).

(S)-N-(1-Phenylethyl)trifluoroacetamide (3S).[22] Into a pyridine (300 mL) solution of (S)-1-phenyl-1-ethylamine (2.42 g; 0.02 mol) was added trifluoroacetic anhydride (4.24 mL; 6.3 g; 0.03 mol). The reaction mixture was stirred at room temperature overnight, and the solvent was evaporated. The semisolid residue was dissolved in chloroform (300 mL), and the chloroform solution was washed with 10% HCl (3 × 100 mL), water (3 × 100 mL), 10% KOH (3 × 100 mL), and again with water (3 × 100 mL). The chloroform layer was dried (MgSO4) and evaporated. The solid residue was recrystallized from petroleum ether. The yield was 91% (4.05 g), mp 94.2–94.9 °C: IR (KBr) 3337, 3084, 2997, 1698, 1547, 1197, 881, 761, 700 cm^{-1}; ^{1}H NMR δ 7.31 (m, 5H, Ph), 7.15 (broad, s, NH), 5.08 (quintet, J = 7.0 Hz, 1H, CH), 1.53 (d, J = 6.9 Hz, 3H, CH3); ^{13}C NMR δ 156.3 (q, J = 0.49 Hz, CO), 140.9, 128.7, 127.8, 126.0 (aromatic carbons), 49.8 (CCH3), 20.9 (CH3); MS m/z 51, 63, 72, 77, 79, 96, 105, 127, 132, 148, 202, 203, 216 (100), 217 (M$^+$, 98), 218 ((M + 1)$^+$, 11).

(R)-N-(1-Phenylethyl)trifluoroacetamide (3R) was synthesized in 95% (4.2 g) yield by following the procedure for the S enantiomer. All spectroscopic characteristics were the same as for its enantiomer **3S**.

Methyl (S)-2-Methoxy-2-phenyl-3,3,3-trifluoropropionate (4S). (S)-2-Methoxy-2-phenyl-3,3,3-trifluoropropionic acid (250 mg; 1.07 mmol) was dissolved in benzene (50 mL), and oxalyl chloride (0.5 mL; 727 mg; 5.7 mmol) was added. The reaction mixture was stirred at room temperature overnight, and the solvent was evaporated. The oily residue was dissolved in methanol (200 mL) and stirred at room temperature (~0.5 h). The methanol was evaporated and the oily residue dissolved in chloroform (100 mL). The chloroform solution was washed with 10% KOH (3 × 100 mL) and water (3 × 100 mL), dried over anhydrous magnesium sulfate, and evaporated to an oily residue to give 257 mg (97%): IR (neat) 3050, 2939, 2840, 1736, 1592, 1592, 1510, 1462, 1422, 1239, 1160, 1130, 1074, 1026, 1009 cm^{-1}; ^{1}H NMR δ 7.51 (m, 2H), 7.39 (d + t, 3H), 3.95 (s, COOCH3), 3.54 (q, J = 1.2 Hz, OCH3); ^{13}C NMR δ 167 (CO), 132.2, 129.6, 128.4, 127.2 (4s, aromatic), 123.2 (q, J = 3.72 ppm, CF3), 55.31 (s, COOCH3), 52.80 (s, OCH3); MS m/z 51, 59, 77, 91, 105, 119, 139, 141, 159, 179, 189 (100), 218, 248 (M$^+$, 1.6), 249 ((M + 1)$^+$, 0.2).

Methyl (R)-2-methoxy-2-phenyl-3,3,3-trifluoropropionate (4R) was synthesized in 93% (246 mg) yield by following the procedure for the S enantiomer. All spectroscopic characteristics were the same as for its enantiomer **4S**.

(16) Benesi, H. A.; Hildebrand, J. H. *J. Am. Chem. Soc.* **1949**, *71*, 2703.

(17) Forster, R.; Fyfe, C. A. In *Progress in N. M. R. Spectroscopy;* Emsley, J. W., Feeney, J., Sutcliffe, L., Eds.; Pergamon Press: New York, 1991; Vol. 4, p 1.

(18) MM2 is the most general method for molecular mechanics calculations for organic molecules. This is an all atom force field. Chem-X assigns atoms types and parameters not normally available to MM2, extending the range of chemical compounds that this force field can accommodate. The program is distributed by Chemical Design International Ltd., Roundway House, Cromwell Park, Chipping Norton, Oxfordshire, OX7 5SR, U.K.

(19) For the original MM2 force field, see: Allinger, N. L. *J. Am. Chem. Soc.* **1977**, *99*, 8127.

(20) HyperChem computational package is available from Autodesk, Inc., 2320 Marinship Way, Sausolito, CA 94965.

(21) AM1 is one of options in the HyperChem computational package. AM1 is a modified MNDO method proposed and developed by Dewar and co-workers at the University of Texas at Austin. The HyperChem computational package can accommodate a large number of atoms. For more information about the AM1 semiempirical force field, see: Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3902. Dewar, M. J. S.; Dieter, K. M. *J. Am. Chem. Soc.* **1986**, *108*, 3902. Stewart, J. J. P. *J. Comput. Aided Mol. Design* **1990**, *4*, 1.

(22) Compound 3 has been synthesized previously. One of the literature procedures starts with the corresponding amine and trifluoroacetic anhydride in ether (Huebsch, W. J. *Monatsh. Chem.* **1966**, *97*, 1541). Nevertheless, we present our procedure and full spectroscopic characterization of the compound.

(*S*)-*N*-Butyl-2-methoxy-2-phenyl-3,3,3-trifluoropropiona-mide (5S). (*S*)-2-Methoxy-2-phenyl-3,3,3-trifluoropropionic acid (250 mg, 107 mmol) was dissolved in benzene (50 mL), and oxalyl chloride (0.5 mL; 727 mg; 5.7 mmol) was added. The reaction mixture was stirred at room temperature overnight, and the solvent was evaporated. The oily residue was dissolved in chloroform (100 mL), and butylamine (0.3 mL; 223 mg; 3 mmol) was added. The reaction mixture was stirred at room temperature (~2 h) and extracted with 10% HCl (3 × 50 mL), water (3 × 50 mL), 10% KOH (3 × 50 mL), and water (3 × 50 mL). The chloroform layer was dried (MgSO$_4$) and evaporated. The oily residue was dissolved in ~2 mL petroleum ether (bp 30–50 °C), and the solution was left to crystallize at –15 °C. The yield was 280 mg (96%), mp 39–40 °C: IR (KBr) 3296, 3063, 2962, 2876, 1673, 1541, 1450, 1180, 1156, 1124, 1015, 719 cm^{-1}; ^{1}H NMR δ 7.54 (m, 2H), 7.38 (m, 3H), 6.87 (broad s, 1H, NH), 3.39 (q, J = 1.2 Hz, OCH$_3$), 3.31 (nonet, J = 7.2 Hz, NCH$_2$), 1.57 (quintet, J = 7.6 Hz, 2H, NCH$_2$CH$_2$); ^{13}C NMR δ 166 (CO), 132.6, 129.2, 128.3, 127.5 (aromatic carbons), 123.7 (q, J = 3.82 Hz, CF$_3$), 83.9 (q, J = 0.35 Hz, CCF$_3$), 54.7 (OCH$_3$), 39.0, 31.3, 19.8, 13.5 (*n*-butyl carbons); MS *m/z* 51, 57, 77, 91, 105, 119, 139, 158, 170, 189, 190, 214, 259 ((M – 30)$^+$).

(*R*)-*N*-Butyl-2-methoxy-2-phenyl-3,3,3-trifluoropropiona-mide (5R) was synthesized following the procedure for prepa-ration of the *S* enantiomer. The yield was 97% (290 mg). The physical and spectroscopic characteristics are the same as for its enantiomer 5S.

(*R*)-*N*-(1′,1′-Dimethylethyl)-2-methoxy-2-phenyl-3,3,3-tri-fluoropropionamide (6S). The compound was synthesized by following the procedure for preparation of amide 5S. The yield was 92% (274 mg), mp 59–59.5 °C: IR (KBr) 3296, 3062, 2960, 2875, 1673, 1534, 1450, 1274, 1180, 1166, 1123, 1014, 719 cm^{-1}; ^{1}H NMR δ 7.53 (m, 2H), 7.36 (m, 3H), 6.58 (broad s, 1H, NH), 3.38 (q, J = 1.5 Hz, OCH$_3$), 1.36 (s, 9H, C(CH$_3$)$_3$); ^{13}C NMR δ 165 (CO), 132.8, 129.0, 128.2, 127.4 (aromatic signals), 123.7 (q, J = 3.84 Hz CF$_3$), 83.7 (q, J = 0.34 Hz, CCH$_3$), 54.5 (OCH$_3$), 51.3

(CMe$_3$), 28.1 (C(CH$_3$)$_3$); MS *m/z* 57, 77, 91, 105, 119, 127, 170, 189 (100%), 190, 202, 246 ((M – 43)$^+$).

(*R*)-*N*-(1′,1′-Dimethylethyl)-2-methoxy-2-phenyl-3,3,3-tri-fluoropropionamide (6R) was synthesized following the pro-cedure for the preparation of enantiomer 5S. The yield was 89% (260 mg). The physical and spectroscopic characteristics are the same as for its enantiomer 6S.

(*S*)-*N*-Phenyl-2-methoxy-2-phenyl-3,3,3-trifluoropropi-onamide (7S). The compound was synthesized by following the procedure for the preparation of amide 5S. The yield was 92% (284 mg), mp 75.1–75.6 °C: IR (KBr) 3290. 3061, 2948, 2848, 1687, 1598, 1527, 1445, 1279, 1162, 1107, 990, 759 cm^{-1}; ^{1}H NMR δ 8.55 (broad s, 1H, NH), 7.60 (m + d, J_d = 7.5 Hz, 2H + 2H), 7.43 (m, 2H), 7.35 (t, J = 8.4 Hz, 2H, *m*-anilides), 7.15 (t, J = 7.5 Hz, *p*-anilides), 3.51 (q, J = 1.8 Hz, OCH$_3$); MS *m/z* 51, 65, 77 (100), 90, 105, 120, 139, 158, 179, 189, 190, 208, 238, 250, 279, 309 (M$^+$, 9.1), 310 ((M+1)$^+$, 1.8).

(*R*)-*N*-Phenyl-2-methoxy-2-phenyl-3,3,3-trifluoropropi-onamide (7R) was synthesized following the procedure for preparation of enantiomer 5S. The yield was 96% (295 mg). The physical and spectroscopic characteristics are the same as for its enantiomer 7S.

Supplementary Material Available: PDB text files of MM minimized-structures of 1S, 2S, 6R, 6S and complexes 1S–6 and 2S–6 (20 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.