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Flexible Biphenyl Chromophore as a Circular Dichroism Probe for Assignment of the Absolute Configuration of Carboxylic Acids

Stefano Superchi, Roberto Bisaccia, Daniele Casarini, Alessandro Laurita, and Carlo Rosini*

Contribution from the Dipartimento di Chimica, Università della Basilicata, via N. Sauro 85, 85100 Potenza, Italy

Received December 30, 2005; E-mail: rosini@unibas.it

Abstract: A general and nonempirical approach to determine the absolute configuration (AC) of 2-substituted chiral carboxylic acids by circular dichroism (CD) spectroscopy has been developed. In this protocol, the chiral acids are converted to the corresponding biphenyl amides, in which a flexible biphenyl probe gives rise to a Cotton effect at 250 nm (A band) in the CD spectrum, the sign of which is related to the acid AC. Two different mechanisms of transfer of chirality from the acid stereogenic center to the biphenyl moiety are operative in amides derived from 2-alkyl- and 2-aryl-substituted acids, respectively. For both classes of compounds, a model has been defined which allows one to predict, for a given acid AC, the preferred twist of the biphenyl moiety and thus the sign of the A band in the CD spectrum, related to the biphenyl torsion. Interestingly, while in alkyl-substituted substrates the preferred biphenyl twist is determined only by steric interactions, in the aryl-substituted ones the structure of the prevalent conformer and thus the biphenyl twist are dictated by arene−arene edge-to-face stabilizing interactions. Following this protocol, the AC of a 2-substituted chiral acid can be established simply by preparing its biphenyl amides, recording the CD spectrum, and looking at the sign of the A band. From the sign of such a band, the torsion of the biphenyl can be deduced and then the acid AC. Substrates having different structures and functionalities have been investigated, always obtaining reliable AC assignments by this simple protocol.

Introduction

In the past few years, many new solutions have been proposed to the fundamental problem of the assignment of the molecular absolute configuration (AC). In addition to the established methods[1] of chemical correlation and X-ray analysis, which are very time-consuming and often not of general applicability, many other approaches based on spectroscopic techniques have now been introduced. In particular, protocols based on chiroptical spectroscopies allow a safe and reliable configurational assignment of molecules in solution. Among them a major role has been occupied by electronic circular dichroism (ECD) and, in particular, by the exciton chirality approach,[2] which constitutes a unique tool for nonempirical AC assignments. More recently, the impressive progress in ab initio calculation of chiroptical properties has allowed the prediction of vibrational circular dichroism (VCD)[3] and ECD[4] spectra, as well as of optical rotation (OR)[5] of chiral compounds, leading to straightforward assignments of AC. The exciton chirality approach requires the presence on the molecule of two or more chromophores dissymmetrically disposed and the knowledge of their spatial arrangement, thus requiring the determination of the more stable conformations. On the other hand, the computational approaches require averaging of the calculated specific chiroptical property over the exact conformer distribution. Therefore,

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in all these spectroscopic approaches, knowledge of the molecular conformation (or even the conformer distribution) is a fundamental prerequisite. As a consequence, heavy problems are encountered in treating molecules displaying high conformational mobility. In this case, the analysis is very difficult and time-consuming, and some uncertainties concerning the AC determination can arise. These approaches are therefore often not suitable to treat open-chain and monofunctional molecules, such alcohols, amines, and carboxylic acids, which display a high flexibility and, possessing low ORs and weak ECD spectra, render more uncertain the calculation of the chiroptical properties or the application of the exciton chirality model.

The problem of the application of ECD spectroscopy to AC determination of flexible molecules was recently addressed in several studies carried out by our group and solved, in the case of bifunctional compounds like acyclic diols, by transforming these substrates into cyclic, conformationally defined derivatives. Following this approach, bis-chromophoric 1,2-diarylethane-1,2-diols were converted into their conformationally fixed 2,2-dimethyl-1,3-dioxolanes,[6] while 1-arylethane-1,2-diols, having only one chromophoric group, were transformed into the corresponding 4-biphenylboronates, thus at the same time blocking their conformation and adding the required second chromophore.[7] More recently, we demonstrated that flexible bridged biphenyls can constitute unique tools for AC determination of conformationally mobile compounds.[8] In these biphenyl derivatives, a free interconversion between the *P* and *M* twists occurs at room temperature and, upon derivatization of this moiety with a chiral compound, one twist can be preferred over the other.[9,10] Therefore, the flexible biphenyl moiety can act as a chirality probe once a correlation has been established between its torsion and the AC of the chiral inducer.[11] Most importantly, the twist of the biphenyl can be easily determined from the CD spectrum, simply by looking at the sign of the Cotton effect related to the so-called A band of the biphenyl chromophore.[12] In fact, a biphenyl *P* torsion is allied to a negative Cotton effect at 250 nm due to the A band, while an *M* torsion of the biphenyl gives rise to a positive A band at 250 nm.[13,14] In our studies, a flexible biphenyl probe was successfully employed for the AC determination of nonchromophoric and conformationally mobile *threo* aliphatic diols.[8] Alkyl- and aryl-substituted diols were transformed into the corresponding biphenyl dioxolanes, thus obtaining a couple of diastereoisomers having respectively *P* and *M* twist of the biphenyl moiety. The low rotational barrier (14 kcal/mol) of the biphenyl in these compounds allowed, at room temperature, a thermodynamic equilibrium between the diastereoisomers.[8] Therefore, the most stable of them was also the major one. The mechanism of transfer of chirality from the chiral diol to the biphenyl was clarified, thus establishing a direct relationship between the diol AC and the preferred biphenyl torsion and, in turn, the sign of the A band in the CD spectrum. In this way, the problems coming from both the molecular flexibility and the absence of chromophores in the chiral bifunctional substrate were solved.

We present herein the application of such a "flexible biphenyl probe" approach to the AC assignment of 2-substituted carboxylic acids. These compounds constitute a very difficult and challenging task, being conformationally mobile and nonchromophoric and possessing a single functional group, i.e., a structural feature which does not allow the molecular flexibility to be restricted by a simple cyclization as in the diol case. Moreover, compounds belonging to this class are of high interest in organic and medicinal chemistry as natural products,[15] agrochemicals,[16] drugs,[17] synthetic precursors, resolving agents, and chiral auxiliaries for asymmetric synthesis.[18,19]

The NMR Mosher approach has been extensively used for AC assignment of chiral carboxylic acids.[20] This method requires the derivatization of the enantiopure acid with both enantiomers of a suitable chiral auxiliary that is able to induce large anisotropy effects.[21] By recording the ^{1}H NMR spectra of both the diastereomeric derivatives and measuring the chemical shift difference ($\Delta\delta$) for any proton in both compounds, it is possible to determine the relative configuration of the acid with respect to that of the chiral derivatizing agent. Although this protocol appears quite easy and direct, it is based on empirical grounds and requires the presence of well-defined and assignable NMR signals in the acid derivatives, as well as

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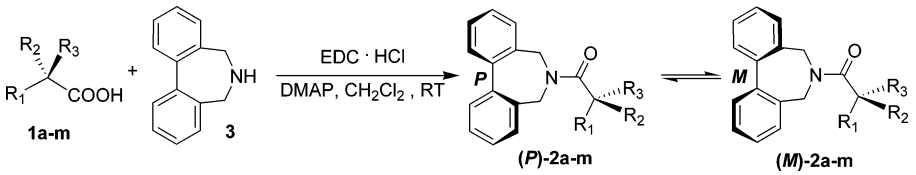
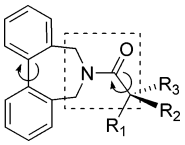
Scheme 1. Synthesis of Biphenyl Amides **2a**−**m**



their detailed conformational analysis. CD spectroscopy has been employed for AC assignment of carboxylic acids much less extensively than for other class of compounds. In fact, although the n−π* transition of the carboxyl chromophore has been used for direct AC assignment,[22] it gives rise to weak bands[23] that are not diagnostic. The in situ formation of metal complexes has been employed for the empirical assignment of AC of chelating α-hydroxy acids and α-amino acids,[24] while reliable nonempirical approaches have been instead based on the exciton coupling phenomenon.[2] In the latter case, α-hydroxy or α-amino acids were derivatized with one[25] or two[26] chromophoric moieties, and the AC was directly determined from the sign of the typical couplet feature appearing in the CD spectrum. In the case of monofunctional acid, which cannot be derivatized, Berova, Nakanishi, and co-workers[27] employed the "porphyrin tweezers" approach, where the chiral acid, linked to a suitable carrier, induces dissymmetry in a porphyrin bis-chromophore through noncovalent "host−guest" interactions. A similar approach, using a different carrier, was described by Borhan et al.[28] The relative steric size of the substituents on the chiral center induces either a clockwise or an anticlockwise disposition of the porphyrin moieties, so that a couplet feature results in the CD spectrum, corresponding to the intense Soret band (400−450 nm), from which the sign of the AC of the acid can be deduced. All these approaches display some limitations, being often suitable only for bifunctional α-hydroxy or α-amino acids or requiring a complex conformational analysis. Therefore, the discovery of a simple, reliable, and general approach for the assignment of AC to carboxylic acids is still an important target. As previously discussed, the AC assignment of carboxylic acids by CD displays some obstacles: these molecules have high conformational mobility and, often, CD signals of low intensity, which makes the spectral interpretation more difficult. As we have shown in the case of aliphatic acyclic UV-transparent diols[8] (vide supra), such problems can be, in principle, faced by the use of a flexible biphenyl system as a probe of the molecular chirality. For carboxylic acids, a completely different type of derivatization of the biphenyl moiety, with respect to the diol case, has to be developed and a new, suitable probe has to be designed. In fact, the derivative of the acid with the biphenyl probe must display a limited number of accessible conformations and must have a structure that is able to ensure an efficient transfer of chirality from the stereogenic center of the acid to the atropisomeric biphenyl moiety.

Chart 1



The amide derivatization looked to us particularly suitable to guarantee an efficient chirality transfer from the acid stereogenic center to the biphenyl probe and to ensure an easy and safe understanding of the transfer mechanism, essential condition for performing a reliable spectrum/structure correlation. Accordingly, the biphenyl amides **2**, in which the chiral acids **1** can be easily transformed by reaction with the biphenylamine **3** (Scheme 1), were chosen as suitable "biphenyl derivatives" of the chiral acids. In these derivatives, the stereogenic center of the acid could induce a preferential torsion of the biphenyl moiety, detectable by the sign of the A band in the CD spectrum, and once a reliable correlation between the acid AC and the biphenyl torsion is independently established, the former could be determined by just looking at the CD spectrum.

Several peculiar structural features make these derivatives particularly promising for our analysis. First of all, the presence of the amide bond guarantees an increased rigidity to the molecule, due to the high rotational energy around the C−N bond.[29] Therefore, in amides **2**, the two benzyl carbons of the biphenyl, the nitrogen, the carbonyl, and the α carbon (C_α) lie on the same plane (Chart 1) and the only degrees of freedom of the molecule are the flipping around the Ar−Ar biphenyl bond and the rotation around the O=C−C_α* bond linking the carbonyl to the stereogenic center. The amide chromophore is also transparent in the wavelength range of the biphenyl absorption, preventing any interference and spectral overlap between the two chromophores. Finally, an additional and important structural feature is the C_2 symmetry of amine **3**, which makes equivalent the two possible *E* and *Z* conformational isomers of amide **2**. Literature data[14e,30] and VT-NMR studies[8] indicated a low inversion *P*/*M* barrier in three-membered bridged biphenyls; therefore, we expected that, also in amides **2**, a comparable energetic barrier for the torsion of the Ar−Ar bond will occur. This implies that, at room temperature, there can be a thermodynamic equilibrium between the two atropisomeric diastereoisomers and their ratio is thus determined only by their relative thermodynamic stability.

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Chart 2

1a R_1 = Me, R_2 = Br, R_3 = H
1b R_1 = Me, R_2 = H, R_3 = Et
1d R_1 = C_6H_{10}, R_2 = OH, R_3 = H
1e R_1 = Me, R_2 = OH, R_3 = H
1f R_1 = Me, R_2 = NHBOC, R_3 = H
1g R_1 = *i*-Pr, R_2 = NHBOC, R_3 = H
1h R_1 = Me, R_2 = H, R_3 = Ph
1i R_1 = Me, R_2 = 4-*i*-Bu-C_6H_4, R_3 = H
1k R_1 = Ph, R_2 = NHBOC, R_3 = H
1j R_1 = Ph, R_2 = CF_3, R_3 = OMe
1l R_1 = Ph, R_2 = OH, R_3 = H
1m R_1 = Bn, R_2 = OH, R_3 = H

1c

Results and Discussion

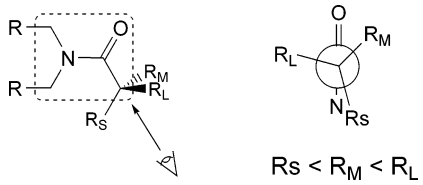
Synthesis, Absorption, and CD Spectra of Biphenyl Amides 2a−m. The series of amides **2a**−**m** was prepared (Scheme 1) from the optically active carboxylic acids **1a**−**m** (Chart 2), of known AC. To test the approach on a wide range of substrates, aliphatic acyclic acids (**1a**,**b**), cyclic acids (**1c**), aryl-substituted acids like the aryl propionic ones (**1h**,**i**) and the Mosher acid (**1j**), α-amino acids (**1f**,**g**,**k**), and α-hydroxy acids (**1d**,**e**,**l**,**m**) were chosen. The formation of amides **2** was carried out by reacting, under nitrogen atmosphere, the biphenylamine **3** (0.31 mmol) with the carboxylic acids **1a**−**m** (0.25 mmol) in the presence of the condensing agent *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide (EDC)[31] (0.41 mmol) and 4-(*N*,*N*-dimethylamino)pyridine (0.25 mmol) in anhydrous dichloromethane. After being stirred overnight at room temperature, the solution was treated with saturated $NaHCO_3$ and brine. Chemically pure amides **2a**−**m** were obtained by chromatographic purification of the crude reaction product in 50−60% yield. This procedure allowed biphenyl amides to be synthesized in good yields, not only from aliphatic and aryl carboxylic acids but also from *N*-butoxycarbonyl (BOC)-protected α-amino acids and unprotected α-hydroxy acids.

The absorption and CD spectra of amides **2a**−**m** were recorded in THF between 320 and 200 nm, and the main spectral features are collected in Table 1. As expected, all the amides studied showed in the CD spectrum a clear (positive or negative) Cotton effect, corresponding to the A band of the biphenyl chromophore at about 250 nm.[32] This means that the biphenyl moiety assumes a preferential torsion induced by the chirality

Table 1. Main UV and CD Spectral Features of Amides **2a**−**m** ($c \approx 10^{-3}$ M in THF)

amide	UV λ ($\epsilon \times 10^{-3}$)	CD λ ($\Delta\epsilon$)
2a	250(19), 208(40)	246(−2.7), 204(6.2)
2b	248(35), 215(82)	246(−6.3), 215(2.4)
2c	249(15.9), 211(40.8), 201(43)	248(4.11), 227(−2.6), 210(−5.3)
2d	249(21), 205(55.5), 210(52.7)	246(−13.9), 218 (−11.6), 205(17)
2e	250(16.3), 205(44.7)	246(−8.7), 218(−10), 206(11)
2f	251(10), 213(28.4), 205(34)	249(−5.5), 217(−4.5), 204(8)
2g	250(18.5), 211(52), 206(61.6)	248(−23), 218(−11.4), 209(15)
2h	249(14), 207(48)	248(−14.2), 217(−4.6), 204(23)
2i	250(18.4), 211(50.4), 202(61)	250(18.4), 216(3.8), 204(−30)
2j	249(20.3), 205(59)	246(30), 220(14), 203(−48)
2k	249(11.6), 203(47)	249(4.6), 216(8.7), 206(−6)
2l	250(17), 210(44), 203(47.7)	249(2.0), 222(−4), 213(6), 206(−4)
2m	250(15.4), 202(53)	248(−14.5), 218(−10), 205(12)

Chart 3



of the stereocenter located on the carboxylic acid moiety and thus that an efficient central-to-axial chirality transfer occurs. Since the sign of the A band Cotton effect tells us the preferred sense of twist, if we understand the mechanism which governs the process of chirality transfer, we can determine the AC of the stereogenic center of the carboxylic acid just by looking at the sign of that band in the CD spectrum.

Mechanism of the Central-to-Axial Chirality Transfer. To understand the mechanism by which the presence of the chiral center on the acid moiety induces a preferential torsion of the biphenyl system, and thus the correspondence between the acid AC and such torsion, it is necessary to know the most stable conformation of the biphenyl amide. As reported in the Introduction, in tertiary amides the two substituents on the nitrogen, the nitrogen itself, the carbonyl, and the carbon α to the carbonyl lie on the same plane (Chart 1); therefore, in amides **2**, the only degrees of freedom are the *P*/*M* torsion and the rotation around the single bond connecting the stereogenic center to the carbonyl carbon atom. The preferred orientation of the substituents on the stereogenic carbon can be derived from literature data. In fact, crystal analyses[33] and computational studies[34] point out that, in tertiary amides having three substituents of different size (R_S, small, R_M, medium, and R_L, large) on the carbon α to the carbonyl, the smallest group R_S (usually a hydrogen) is anti with respect to the carbonyl moiety and almost eclipsed by the nitrogen atom, describing a dihedral angle O═C−C_α−R_S in the range 150−160°. The two other substituents are on opposite sides of the amide plane, with the smallest of the two (R_M) closer to the carbonyl than the largest (R_L) (Chart 3). A very similar conformational arrangement has been also demonstrated for chiral secondary amides by NMR spectroscopy[21g] and computations.[27b]

On the basis of the conformational parameter reported above for tertiary amides, and assuming the disposition of the

(31) Sheeham, J. C.; Cruickshank, P. A.; Boshort, G. L. *J. Org. Chem.* **1961**, *26*, 2525. Sheeham, J. C.; Prestan, J.; Cruickshank, P. A. *J. Am. Chem. Soc.* **1965**, *87*, 2492.

(32) It can be noticed that the $\Delta\epsilon$ values of the A band in Table 1 can differ substantially in intensity. We believe that this behaviour originates from the different diastereomeric ratios of the amides in solution. In fact, a better induction and thus a larger ratio are expected when the size differences between the M and L substituents on the stereogenic center are larger. This effect is clearly visible comparing the cases of amides **2f** and **2g**, coming from different *N*-BOC-protected amino acids. In these examples, the A band of the methyl-substituted amide **2f** is about one-fourth as intense as that in **2g**, having a larger isopropyl substituent. A reviewer argued that, in the case of aryl-substituted carboxylic acids, the CD intensity of the A band of the biphenyl chromophore could also be due to a contribution from the exciton coupling of the A transition dipole moment with those of the allowed transitions of the aryl moiety. We agree with this analysis; however, in our cases such contributions should be almost negligible, being inversely proportional (see ref 2f, p 85) to the distance, on the wavelength scale, of the position of the interacting transitions, i.e., the A band of the biphenyl group (250 nm) and the allowed transition of the benzene chromophore (180−190 nm).

(33) Siodlak, D.; Broda, M. A.; Rzeszotarska, B.; Koziol, A. E.; Dybala, I. *Acta Biochim. Polon.* **2001**, *48*, 1179. Siodlak, D.; Broda, M. A.; Rzeszotarska, B.; Dybala, I.; Koziol, A. E.; Dybala, I. *J. Pept. Sci.* **2002**, *9*, 64.

(34) Seco, J. M.; Quiñoa, E.; Riguera, R. *J. Org. Chem.* **1999**, *64*, 4669.

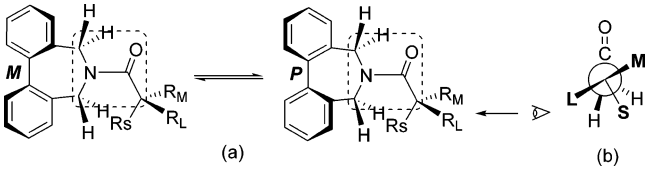


Figure 1. Conformations of biphenyl amides **2**.

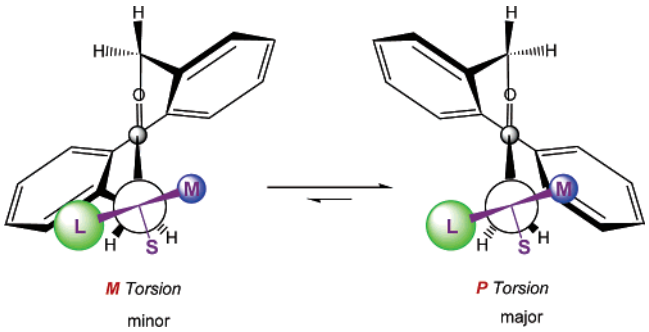


Figure 2. Schematic representation of the conformational equilibrium in biphenyl amides **2**.

substituents on the stereogenic center depicted in Chart 3 (corresponding to a given AC), the two possible diastereoisomers of the amides **2**, having either *P* or *M* torsion of the biphenyl, can be represented as in Figure 1a. In these structures, the smallest substituent (usually the hydrogen) is anti with respect to the carbonyl and directed "in between" the two benzylic protons, while the "medium" and "large" substituents are on both sides of the carbonyl, with the former closer to the C═O. Looking at these structures along the amide plane, the "pseudo-Newman" representation will result as reported in Figure 1b where, for clarity, the biphenyl system is omitted. Taking into account also the biphenyl moiety, the representations in Figure 2 can be instead depicted. From Figure 2 it can be clearly seen that, for this AC, in the diastereoisomer having *M* torsion the largest group R_L is located in a more sterically hindered area, owing to the presence one of the biphenyl rings, while the medium-size group R_M is in a less hindered region. The opposite holds for the *P* diastereoisomer, where the R_M group is closer to the biphenyl aromatic ring and the R_L group lies in a less crowded area. Therefore, for this AC, the *P* diastereoisomer, giving rise to less steric interactions, will be more stable than the *M* one.

From this analysis it follows that, for a 2-substituted chiral acid having the substituents disposed as in Chart 3, where a clockwise rotation leads from R_L to R_M, the *P* diastereoisomer of its biphenyl amide will prevail (Figure 3). Of course, the reverse will happen for carboxylic acids of opposite AC, where an anticlockwise rotation leads from R_L to R_M. As reported in the Introduction, a *P* torsion of the biphenyl chromophore gives rise to a negative A band (at 250 nm) in the CD spectrum.[13,14] Therefore, we can expect that, for an acid having the AC given in Chart 3, a negative A band will appear in the CD spectrum of the corresponding biphenyl amide.

The series of biphenyl amides **2a**−**m** constitutes a good benchmark to test the reliability and generality of this spectrum/structure correlation. Our analysis can start from amides **2a**−**e**, derived from 2-alkyl-substituted acids, where the substituents differ only in respect to their size. To apply the present model, the relative group size can be evaluated from the steric A parameters[35] reported in the literature.[36,37] Let us consider the case of (*S*)-2-bromopropionic acid (**1a**), the structurally simplest derivative. Of the two substituents on the chiral center, the bromine, having an *A* parameter of 0.48−0.67 kcal/mol, is the smallest one (R_M) while the methyl, having $A = 1.74$ kcal/mol, corresponds to R_L. Applying the model in Figure 3, it follows that in **1a** a clockwise rotation leads from R_L (Me) to R_M (Br); therefore, a *P* torsion will be induced in the biphenyl moiety of its amide **2a** and a negative A band is expected in its CD spectrum. This prediction is completely fulfilled (Table 2) by the experimental spectral features of **2a** reported in Table 1 and Figure 4. Its absorption spectrum shows the A band at 250 nm ($\epsilon \approx 19\,000$) and a more intense absorption at 208 nm ($\epsilon \approx 40\,000$), allied to the C band of the biphenyl chromophore.[12] It is known that the position of the A band is very sensitive to the torsion angle θ of the biphenyl, and Suzuki[12] calculated that, for a wavelength of 250 nm, this torsion angle is about 44−47°. In the CD spectrum, an intense signal at 204 nm ($\Delta\epsilon = 6.2$) is observed, followed by a weaker *negative* Cotton effect at 246 nm ($\Delta\epsilon = -2.7$), corresponding to the biphenyl A band, clearly confirming the expected biphenyl *P* torsion. This result shows that the sign of the A band in the CD spectrum of the biphenyl amide is really dictated by the relative disposition of the substituents on the chiral center of the starting acid, i.e., by the acid AC. In cases when the relative size of the substituents on the chiral center cannot be unambiguously established by only the steric *A* parameters because they are missing or too similar, the prevalent torsion of the biphenyl probe can be independently and reliably predicted by simple computational analyses. In fact, in the present approach, the chiral substrate is covalently bonded to the probe of chirality and a small and conformationally restricted derivative is obtained. Therefore, a computational approach to the conformational analysis is much simpler and more reliable than approaches based on very complex systems where the substrate/probe connection is due to noncovalent interactions. To independently test the reliability of the previous configurational assignment, a molecular mechanics conformational analysis was performed on **2a**. A Monte Carlo conformational search was carried out by MMFF94 molecular mechanics force field via the program Spartan 02.[38] The obtained lowest energy conformer displayed a *P* biphenyl twist, with a biphenyl dihedral angle of 44.5° and an O═C−C_α−H dihedral angle of 148.6°. A second conformation, having an *M* biphenyl twist and a similar O═C−C_α−H dihedral angle of 135.5°, was ca. 0.5 kcal/mol higher in energy, and no other conformation was found within a window of 2 kcal/mol. This result completely agreed with the torsion found experimentally, thus confirming the complementarity of the computational approach with the predictions provided by the simpler analysis based on the *A* parameters.

An NMR investigation was also undertaken on amide **2a**, to experimentally define its preferred conformation. The ^{1}H NMR spectrum of **2a** at room temperature shows a doublet at 1.92 ppm and a quartet at 4.80 ppm that have been assigned to the Me and CH (Ha) of the acid residue (Figure 5a, Me omitted), respectively, whereas the four methylenic hydrogens, due to

(35) Winstein, S.; Holness, N. J. *J. Am. Chem. Soc.* **1955**, *77*, 5562.
(36) Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Compounds*; Wiley: New York, 1994.
(37) For recent studies on steric parameters, see: Boiadjiev, S. E.; Lightner, D. A. *J. Am. Chem. Soc.* **2000**, *122*, 11328.
(38) *Spartan 02*; Wavefunction, Inc.: Irvine, CA, 2002.

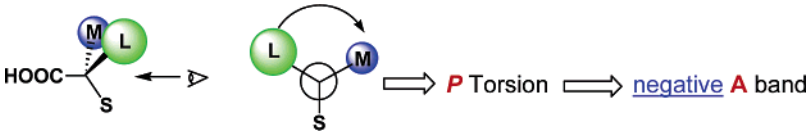
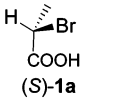
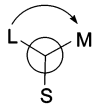
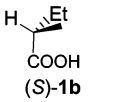
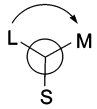
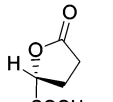
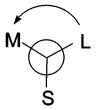
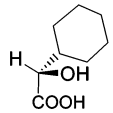
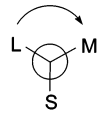
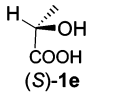
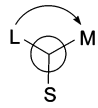
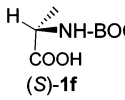
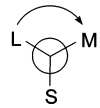
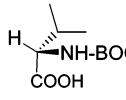
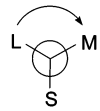


Figure 3. Mnemonic scheme relating the AC of 2-alkyl-substituted acids and the sign of the A band in the CD spectrum of their biphenyl amides.

Table 2. Structures and Schematic Representation of Carboxylic Acids **1a**−**g** and Torsion[a] of Their Amides **2**

chiral acid			predicted torsion	experimental torsion
 (*S*)-**1a**			(P)	(P)
 (*S*)-**1b**			(P)	(P)
 (*R*)-**1c**			(M)	(M)
 (*S*)-**1d**			(P)	(P)
 (*S*)-**1e**			(P)	(P)
 (*S*)-**1f**			(P)	(P)
 (*S*)-**1g**			(P)	(P)

[a] Torsion predicted from mnemonic in Figure 3 and experimentally determined by CD spectrum of the amide.

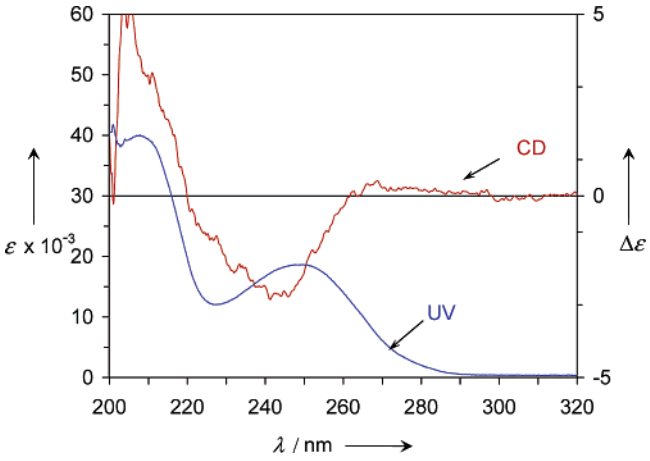


Figure 4. UV and CD spectra (THF) of amide **2a**.

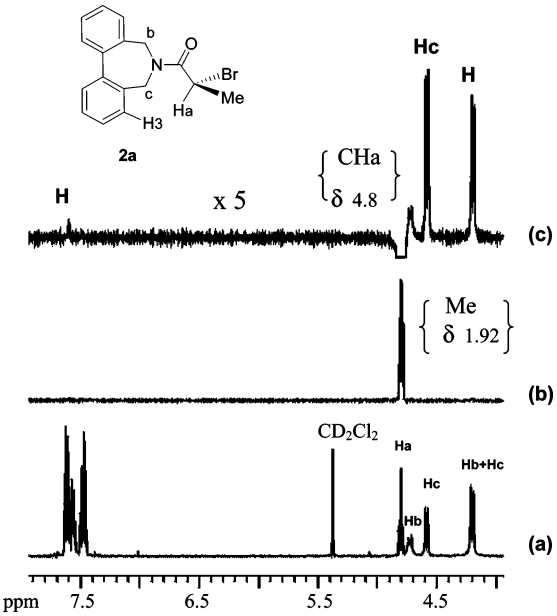


Figure 5. (a) Full ^{1}H NMR spectrum (600 MHz, CD_2Cl_2) of **2a** (Me signal at 1.92 ppm omitted). (b) NOE effects observed upon exciting the CH_3 at 1.92 ppm. (c) NOE effects observed upon irradiating the Ha at 4.80 ppm.

some overlap, show three doublets (J = 13 Hz) at 4.72, 4.58, and 4.19 ppm in the ratios 1:1:2. The two sharp signals at 4.58 and 4.19 ppm can be tentatively assigned to the protons (Hc) of the benzylic methylene on the C_α side, while the broad doublets at 4.72 and 4.19 ppm have been assigned to the less shielded hydrogens (Hb) belonging to the methylene on the CO side.[39] The eight aromatic hydrogens overlapped in two groups of signals in the ratio 3:5 at 7.44−7.50 and 7.53−7.64 ppm, preventing any individual hydrogen assignment.[40] NOE experiments at room temperature have been also carried out to get further information on the preferred conformation. Irradiation of the Me at 1.92 ppm (Figure 5b) has shown a large enhancement of the vicinal Ha, whereas no NOE enhancements have been observed on the biphenyl unit. Conversely, irradiation of the Ha at 4.80 ppm (Figure 5c) enhances the Me signal and

(39) The separations observed between the doublets have been tentatively rationalized in terms of the differently experienced anisotropic effect of the CO. Indeed, in both pairs of doublets the less shielded ones are attributable to the equatorial-like hydrogens that are nearly coplanar to the CO deshielding cone, whereas the more shielded doublets are assigned to the axial-like hydrogens that are almost perpendicular to the CO deshielding cone. The different signal broadness can be reasonably attributed to a different mobility between the two methylenic bridges that experience a rather different steric hindrance. Further support for this hypothesis comes from the observed sharpening of all the doublets when the temperature is lowered to −90 °C.

(40) The ^{1}H NMR spectrum (300 MHz, C_2Cl_4) of **2a** shows that, upon increasing the temperature, the four doublets of the benzylic hydrogens broaden and then coalesce in the range 70−80 °C to give at +118 °C two sharp doublets (J = 13.5 Hz) at 4.00 and 4.44 ppm that partially overlap the CHa signal. By simulating the line shape changes with the temperature, the exchange constant was obtained, and then a rotational barrier of 16.95 kcal mol^{-1} for the C−N bond was calculated, thus confirming the hindered rotation around this bond at room temperature.

the sharp doublets at 4.58 and 4.19 ppm, while smaller effects are detected on the broad doublet at 4.72 ppm, and only a weak enhancement is observed on the aromatic H_3 at 7.60 ppm. These results suggest that in **2a** the Ha points toward the closer methylene bridge and the phenyl group, whereas the methyl and Br point away from the biphenyl moiety, in full agreement with the amide conformation depicted in Figures 1 and 2. The torsional barrier for **2a** was also measured by ^{13}C NMR experiments at variable temperature, monitoring the line shape changes of the two NCH_2 signals at 46.6 and 48.9 ppm.[41] The two signals broaden below −30 °C and decoalesce at −65 °C to give two sharp lines at −90 °C, from which a diastereomeric *P*/*M* ratio 80:20 can be measured. The exchange constant was obtained from the line shape simulation, allowing us to calculate a biphenyl torsional barrier of 10.15 kcal mol^{-1}. This result also confirms the occurrence of a free diastereomeric equilibrium at room temperature, as assumed on the basis of literature data.

The foregoing analysis was then extended to the alkyl-substituted carboxylic acids **1b**−**e** of known AC (Table 2). The simplest acid of this group is (*S*)-2-methylbutanoic acid (**1b**), devoid of any functional group. This acid looked particularly interesting to test the sensitivity of our method with respect to small steric differences of the substituents on the chiral center. In fact, the methyl and ethyl groups on the stereogenic center of **1b** have almost the same size, with $A = 1.74$ kcal/mol for the methyl and $A = 1.79$ kcal/mol for ethyl. The CD spectrum of amide **2b**, coming from **1b**, showed a clear negative A band ($\Delta\epsilon = -6.3$), due to a *P* torsion of the biphenyl (Tables 1 and 2), as predicted by our model in Figure 3. This result points out that the biphenyl moiety of such amides is a very sensitive probe of the relative dimensions of the substituents on the acid stereogenic center and that the present method can be considered sensitive and reliable also when the substituents present minimal steric differences. The case of the cyclic acid (*R*)-**1c**, where R_M and R_L belong to a ring, provides further support to our analysis. Here the oxygen is smaller than methylene moiety, and the model depicted in Figure 3 leads us to predict a prevailing *M* torsion and thus a positive A band, in agreement with the experimental observation. The present method proved reliable also in the case of more complex and functionalized acids, like the α-hydroxy acids (*S*)-lactic acid (**1e**) and (*S*)-hexahydromandelic acid (**1d**). In these compounds the hydroxy group corresponds to a medium-size substituent, and application of the model predicts a *P* torsion of the biphenyl probe and hence a negative A band, as found experimentally (Table 2). The application of this method to the aliphatic *N*-BOC-protected α-amino acids **1f**,**g** is very interesting. In fact, according to the tabulated *A* parameters,[36] both the isopropyl and the methyl groups have a larger size than the *N*H−BOC moiety. Taking into account such steric relationship in both cases, from the analysis of the CD spectrum of the corresponding biphenyl amides, the AC of the starting amino acid was correctly assigned (Table 2).

We then extended the above analysis to 2-aryl-substituted carboxylic acids, treating first (*R*)-2-phenylpropionic acid (**1h**), the structurally simplest compound of this class. Following the model depicted in Figure 3, an *M* biphenyl torsion is expected to be preferred in its amide **2h** and thus a positive Cotton effect,

(41) (a) Casarini, D.; Coluccini, C.; Lunazzi, L.; Mazzanti, A. *J. Org. Chem.* **2005**, *70*, 5098. (b) Casarini, D.; Lunazzi, L.; Mazzanti, A. *J. Org. Chem.* **1998**, *63*, 4754.

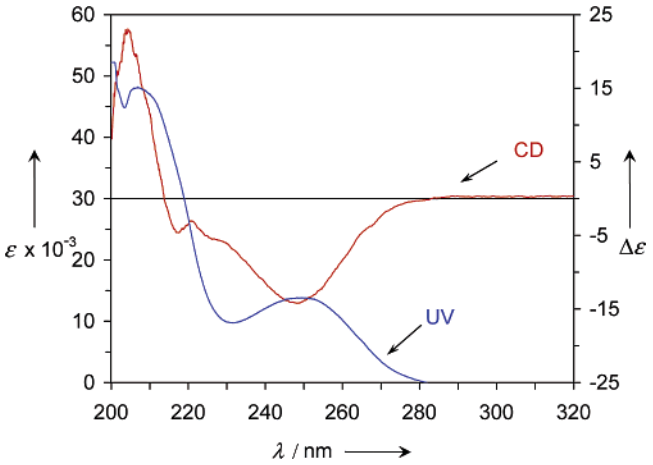


Figure 6. UV and CD spectra (THF) of amide **2h**.

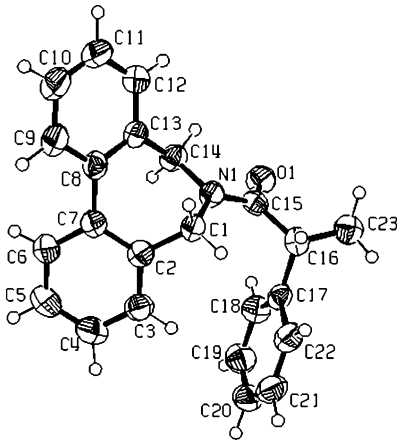


Figure 7. Crystal structure of (*R*,*P*)-**2h**; torsion angle C2−C7−C8−C13 = 42.8°.

corresponding to the A band in its CD spectrum. On the contrary, the CD spectrum of **2h** shows a clear negative Cotton effect ($\Delta\epsilon = -14.2$) at 248 nm (Figure 6), due to a prevalent *P* torsion. This result clearly shows that, in amides from 2-aryl-substituted carboxylic acids, a change occurs in the mechanism of the chirality transfer, and the presence of an aryl moiety on the stereogenic center reverses the relative stability of the *M* and *P* twisted diastereoisomers.

The crystal structure of amide **2h** (Figure 7) confirms the *P* twist of the biphenyl moiety revealed in solution by the CD spectrum, with a biphenyl dihedral angle of 42.8°, smaller than the one usually observed in three-membered bridged biphenyls.[8,30] The hydrogen on the acid stereogenic center is almost in anti position with respect to the amide carbonyl, giving with the latter a dihedral angle of ca. 140°, as reported in the literature,[33] and the same hydrogen is close to one of the benzyl methylenes, confirming the conformation assumed in Figure 1. Most importantly, the crystal structure of **2h** reveals that in this compound the phenyl ring, despite being the largest substituent, is not located in the less hindered area, as in the alkyl-substituted derivatives, but is closer to one of the biphenyl rings, orienting its "face" in correspondence to the "edge" of the latter.

Confirmation of the conformational preference of **2h** was independently obtained by a DFT ab initio computational analysis. Initially, a Monte Carlo conformational search was carried out using the MMFF94 molecular mechanics force field via the Spartan 02 software.[38] As in the case of **2a**, two lowest

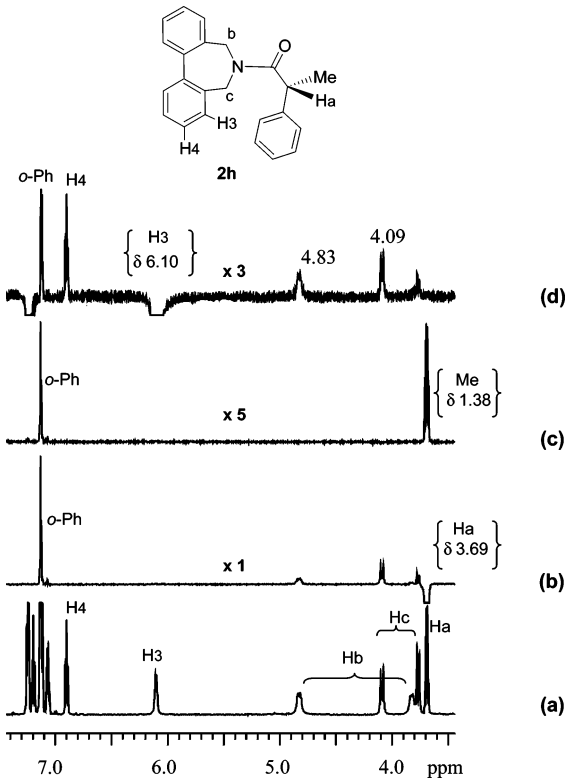


Figure 8. (a) Full ^{1}H NMR spectrum (600 MHz, C_2Cl_4/C_6D_6) of **2h** (Me signal at 1.38 ppm omitted). (b) NOE effects observed in the region 3.5−7.5 ppm upon irradiating Ha at 3.69 ppm. (c) NOE effects observed upon irradiating Me at 1.38. (d) Enhancements observed upon irradiating H_3 at 6.10 ppm.

energy conformers were obtained, displaying respectively *P* and *M* biphenyl twist. Both conformers were then reoptimized at the B3LYP/6-31G* DFT level by Gaussian 03.[42] The most stable conformer was shown to be the *P* twisted one, with the *M* diastereoisomer being 0.83 kcal/mol higher in energy. The most stable conformer afforded by this computational analysis not only displayed the same biphenyl torsion found in the crystal structure, but was almost superimposable with the latter, showing the same aryl−aryl edge-to-face arrangement and the same O=C−C_α−H torsional angle.

A careful NMR analysis of **2h** has been carried out in order to further investigate whether the prevailing conformation in solution, where CD spectra are recorded, resembles the one detected in the solid state. ^{1}H NMR spectra of all the alkyl-substituted biphenyl amides **2a**−**g** show signals of the aromatic protons in the 7.2−7.6 ppm range (see Figure 5a), while in the ^{1}H NMR spectrum of the 2-phenyl-substituted amide **2h** (Figure 8a), the H_3 and H_4 aryl protons of one of the biphenyl rings are strongly upfield-shifted. giving respectively a triplet at 6.10 ppm and a doublet at 6.90 ppm.[43] Such a shift effect can be explained just by assuming a spatial arrangement like the one in the crystal structure, where the phenyl on the stereogenic center is almost orthogonal with respect to one of the biphenyl rings, directing its anisotropic shield toward the H_3 and H_4 biphenyl protons. The same shift effect has been reported in the literature for a very similar compound[44] and analogously interpreted as due to an edge-to-face arrangement of two aromatic moieties, an effect well known in inter- and intramolecular interactions of aromatic systems[45] and ascribed to stabilizing electrostatic $\pi-\pi$ interactions of the aromatic moieties.[46] NOE experiments at room temperature supply further support for the preferred conformation of **2h** in solution. CH_3 irradiation at 1.38 ppm (Figure 8c) has large effects only on the Ha at 3.69 ppm and on the *ortho*-phenyl hydrogens at 7.13 ppm. Conversely, irradiation of the Ha (Figure 8b) generate large enhancements on the neighboring CH_3 and on the *ortho*-phenyl hydrogens, whereas moderate effects are also observed on the sharp doublets at 4.09 and 3.77 ppm belonging to a benzylic CH_2. Finally, irradiation of H_3 at 6.10 ppm (Figure 8d) shows some negative NOE (saturation transfer) at 7.26 ppm and positive effects on the *ortho*-phenyl hydrogens at 7.13 ppm, on the H_4 at 6.90 ppm, and on the doublets at 4.09 and 4.83 ppm, both attributable to the equatorial hydrogens of different methylene bridges. The NOE effects observed between the phenyl moiety on the stereogenic center and the benzyl and H_3 aryl protons of the biphenyl system further confirm that the aryl moieties of **2h** are close to each other and thus that this compound assumes a very similar conformation both in the solid state and in solution. The biphenyl torsional barrier of **2h** was obtained by ^{13}C NMR spectra at low temperature, monitoring the changes in the line shape of the CH_2 signal at 48.08 ppm. At −51 °C, the signal showed a maximum broadening of 45 Hz, from which a torsional barrier of 11.20 kcal mol^{-1} was calculated.[47] Upon decreasing the temperature to −90 °C, all the peaks sharpened again to give two groups of signals, indicating a 95:5 diastereomeric ratio.

It is very important to note that also in the ^{1}H NMR spectra of all the 2-aryl-substituted amides **2h**−**l**, the same upfield shift of the H_3 and H_4 protons is observed, suggesting for all these compounds the same prevalent conformation of **2h**, where the aryl moiety on the stereogenic center is located close to one of the biphenyl rings. In these compounds, the stabilizing $\pi-\pi$ aromatic interaction then prevails on the steric repulsion, and such a new interaction reverses the relative stability of the *M* and *P* twisted diastereoisomers. This result affords a rough quantitative estimate of the edge-to-face stabilizing interactions which agrees with the value of 2 kcal/mol reported in the literature.[46h] Between the two possible diastereomeric structures of such amides, as depicted in Figure 9, only the one having an *M* torsion allows such an aryl−aryl interaction, and therefore the *M* diastereoisomer will be now the most stable one. As a consequence, in the case of the 2-aryl-substituted carboxylic

(42) *Gaussian 03*; Gaussian, Inc.: Pittsburgh, PA, 2003.
(43) The ^{1}H NMR spectrum of **2h** has been recorded in $C_2Cl_4-C_6H_6$ in order to remove the overlap of two of the four NCH_2 hydrogens with the CHα at 3.98 ppm occurring in $CDCl_3$. In $CDCl_3$, the H_3 and H_4 signals are displayed at 6.23 and 7.10 ppm, respectively. Signals of H_3 and H_4 have been assigned by 2D NMR experiments.

(44) Hoye, T. R.; Renner, M. K. *J. Org. Chem.* **1996**, *61*, 8489.
(45) For recent examples of molecular recognition based on edge-to-face interactions, see: Superchi, S.; Donnoli, M. I.; Proni, G.; Spada, G. P.; Rosini, C. *J. Org. Chem*. **1999**, *64*, 4762. Poisson, A. P.; Hunter, C. A. *J. Chem. Soc., Chem. Commun*. **1996**, 1723. Cloninger, M. J.; Whitlock, H. W. *J. Org. Chem*. **1998**, *63*, 6253. Ercolani, G.; Mencarelli, P. *J. Org. Chem*. **2003**, *68*, 6470.
(46) (a) Hunter, C. A. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1585. (b) Hunter, C. A. *Chem. Soc. Rev.* **1994**, 101. (c) Hunter, C. A.; Saunders, J. K. M. *J. Am. Chem. Soc.* **1990**, *112*, 5525. (d) Cozzi, F.; Siegel, J. S. *Pure Appl. Chem.* **1995**, *67*, 683. (e) Shetty, A. S.; Zhang, J.; Moore, J. S. *J. Am. Chem. Soc.* **1996**, *118*, 1019. (f) García Martínez, A.; Osío Barcina, J.; de Fresno Cerezo, A.; Gutiérrez Rivas, R. *J. Am Chem. Soc.* **1998**, *120*, 673. (g) Cozzi, F.; Annunziata, R.; Benaglia, M.; Cinquini, M.; Raimondi, L.; Baldridge, K. K.; Siegel, J. S. *Org. Biomol. Chem*. **2003**, *1*, 157. (h) Tsuzuki, S.; Honda, K.; Uchimaru, T.; Mikami, M.; Tanabe, K. *J. Am. Chem. Soc.* **2001**, *124*, 104.
(47) (a) Sandström, J. *Dynamic NMR Spectroscopy*; Academic Press: New York, 1982; p 84. (b) Casarini, D.; Grilli, S.; Lunazzi, L.; Mazzanti, A. *J. Org. Chem*. **2004**, *69*, 345.

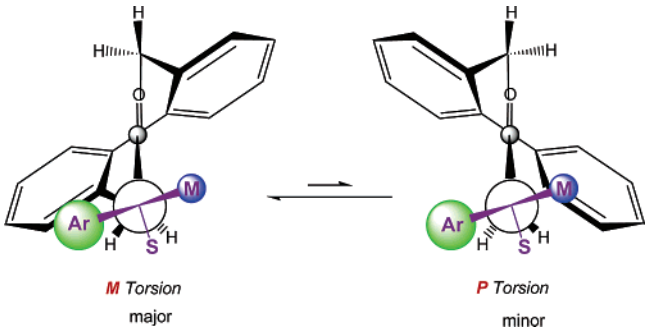


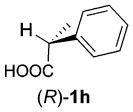
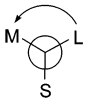
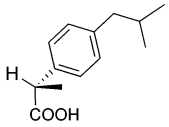
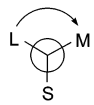
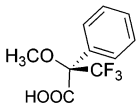
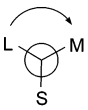
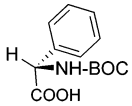
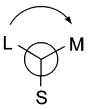
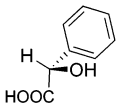
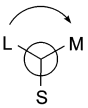
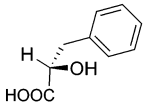
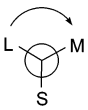
Figure 9. Schematic representation of the conformational equilibrium in 2-aryl-substituted biphenyl amides **2**.

acids, a new mechanism of central-to-axial chirality transfer occurs, and the model in Figure 10 can now allow to us predict the prevalent biphenyl torsion.

According to the model in Figure 10, if, in the 2-aryl-substituted acid, a clockwise pathway is needed to go from the aryl substituent to the medium-size one, then the *M* torsion will prevail in its biphenyl amide, and a positive A band is expected in its CD spectrum. Such a correlation can thus allow us to determine the AC of 2-aryl-substituted carboxylic acids by analysis of the CD spectrum of their biphenylamides (Table 3). The reliability of such a model has been tested on the 2-arylpropionic acid (*S*)-ibuprofen (**1i**). The CD spectrum of **2i** (Table 1), the amide from **1i**, is almost a mirror image of the one of **2h**, derived from (*R*)-**1h**, a compound that is structurally and spectroscopically similar but of opposite AC. In the CD spectrum of **2i**, an intense positive Cotton effect ($\Delta\epsilon = 18.4$), allied to an *M* torsion of the biphenyl chromophore, is observed, as expected following the model in Figure 10. To test the reliability of such an approach when applied to acids with a quaternary stereogenic center, we studied amide **2j**, derived from Mosher acid (*R*)-**1j**. According to the *A* sterical parameter, in **1j** the smallest substituent is the methoxy group, the medium-size one is the CF_3, and the largest one is the phenyl ring. Therefore, an *M* torsion and a positive A band are expected. In this case, not only does the CD spectrum clearly show the A band with the correct positive sign ($\Delta\epsilon = 30.0$, Table 1) but the band is quite intense, demonstrating an high diastereomeric ratio in favor of the *M* atropisomer and thus an efficient diastereomeric induction in the biphenyl system. As in the case of the alkyl systems, we then checked the reliability of such an approach with α-hydroxy and α-amino acids. The CD spectrum of amide **2k**, derived from (*S*)-*N*-BOC-phenylglycine (**1k**), shows a positive Cotton effect ($\Delta\epsilon = 4.6$) at ca. 250 nm (Table 1), in agreement with our model for 2-aryl-substituted acids. Even in the CD spectrum of amide **2l**, obtained from (*S*)-mandelic acid (**1l**), notwithstanding the presence of a free hydroxy group on the stereogenic carbon, the positive sign of the A band ($\Delta\epsilon = 2.0$) agrees with the model in Figure 10.

Finally, to test if 2-benzyl-substituted acids follow the rule of either the alkyl- or aryl-substituted systems, we examined

Table 3. Structures and Schematic Representation of Carboxylic Acids **1h**−**m** and Torsion[a] of Their Amides **2**

chiral acid			*predicted* torsion	*experimental* torsion
 (*R*)-**1h**			(P)	(P)
 (*S*)-**1i**			(M)	(M)
 (*R*)-**1j**			(M)	(M)
 (*S*)-**1k**			(M)	(M)
 (*S*)-**1l**			(M)	(M)
 (*S*)-**1m**			(P)	(P)

[a] Torsion predicted from mnemonic in Figure 10 and experimentally determined by CD spectrum of the amide.

the case of (*S*)-3-phenyllactic acid (**1m**), which presents a benzyl moiety on the stereogenic center. Also in this case, useful information on the conformation of amide **2m** can be deduced from its ^{1}H NMR spectrum. In this spectrum the biphenyl protons are not shifted upfield like in the aryl-substituted systems but, on the contrary, their signals are all between 7.2 and 7.6 ppm, like in the alkyl-substituted compounds. Therefore, we can say that in amide **2m** there is not an attractive interaction between the phenyl of the benzyl moiety and the biphenyl and that such an amide will assume a conformation similar to the one of the alkyl-substituted derivatives. In this case the "alkyl" model in Figure 3 can then be applied, leading to a preferred *P* torsion for this substrate and to a negative CD band at 250 nm. The CD spectrum of **2m** clearly shows the Cotton effects due to the twisted biphenyl chromophore, with no signals attributable to the benzyl chromophore. As expected from the model in Figure 3, an intense ($\Delta\epsilon = -14.5$) negative band is visible at

Figure 10. Mnemonic scheme relating AC of 2-aryl-substituted acids and sign of the A band in the CD spectrum of their biphenyl amides.

250 nm, confirming the "alkyl" conformational behavior of such compounds (Table 3).

Conclusion

In this work, we have developed a new nonempirical approach, based on CD spectroscopy, for the assignment of AC to 2-substituted chiral carboxylic acids in solution. In this approach, the chiral acids are converted to the corresponding biphenyl amides, whose flexible biphenyl moiety acts as a "probe" of the acid chirality, giving rise in the CD spectrum to Cotton effects related to the acid AC. The mechanism of transfer of chirality from the acid stereogenic center to the biphenyl moiety has been analyzed in detail, defining two different mechanisms operative in amides derived from 2-alkyl- and 2-aryl-substituted acids, respectively. Therefore, for both classes of compounds, it has been possible to define a model which allows us to predict, for a given acid AC, the preferred twist of the biphenyl moiety and thus the sign of the A band at 250 nm in the CD spectrum, related to the biphenyl torsion. Following the protocol described herein, to establish the AC of a 2-substituted chiral acid, it is simply necessary to prepare its biphenyl amide **2**, to record the amide CD spectrum, and to look at the sign of the A band (at 250 nm). From the sign of such a band, the torsion of the biphenyl can be deduced and thus the acid AC. The main advantages of the present approach are the reliability and simplicity of the AC assignment. In fact, in most cases, no conformational analysis is needed, and the correlation between the CD spectrum of the biphenylamide and the acid AC can be established taking into account only the size of the substituent on the stereogenic center, as derived from the value of the steric *A* parameter. When this value is unknown or when there is ambiguity about the relative size of the substituents, then a simple molecular mechanics conformational analysis can allow a reliable spectrum/structure correlation. A variety of substrates, with different structures and multiple functionalities, have been investigated; in particular, the present approach displayed its full validity with alkyl- and aryl-substituted acids, with α-hydroxy acids and α-amino acids.

During this investigation, it also has been shown experimentally that $\pi-\pi$ arene−arene interactions can overcome steric interactions, even stabilizing the most sterically crowded conformers. This important result is of general interest, providing further insight toward the understanding of these interactions, which affect many other areas of science, such as catalysis, materials chemistry, supramolecular chemistry, and biochemistry.

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Supporting Information Available: Full characterization and experimental procedures for compounds **2a**−**m**; VT-NMR experiments for **2a** and **2h**; absorption and CD spectra for compounds **2b**−**g** and **2i**−**m**. This material is available free of charge via the Internet at http://pubs.acs.org.

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