Pergamon

SCIENCE DIRECT®

Tetrahedron 59 (2003) 9323–9331

TETRAHEDRON

Helicity of *N*,*N*′-diaryl-*trans*-1,2-diaminocyclohexane derivatives. Implications for molecular helicity manipulations

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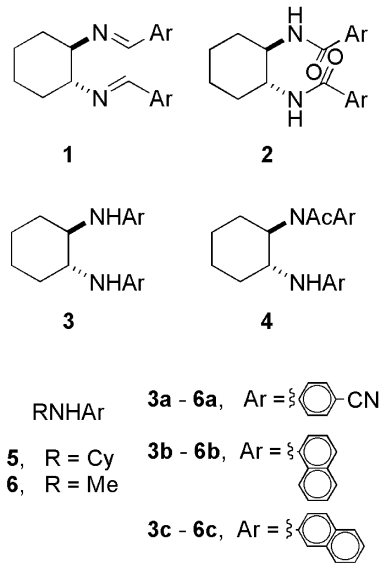
Received 6 June 2003; revised 3 September 2003; accepted 26 September 2003

Abstract—Derivatives of *trans*-1,2-diaminocyclohexane (DACH), useful as chiral ligands, scaffolds and building blocks, differ in their conformation. The conformation of *N*,*N*′-diaryl-DACH derivatives was studied by the semiempirical and DFT computational methods and by exciton-coupled circular dichroism. It was found that, contrary to *M*-helical *N*,*N*′-diimine, *N*,*N*′-diimide and *N*,*N*′-diamide derivatives, the aromatic residues in *N*,*N*′-diphenyl derivatives are oriented to form a *P-helix* for the (*R*,*R*)-DACH absolute configuration. The helicity of the bis-aryl system is modified in the case of 1-naphthyl or 2-naphthyl derivatives. Further switching of helicity has been demonstrated by either protonation or mono-*N*-acetylation of *N*,*N*′-diaryl DACH derivatives.

1. Introduction

trans-1,2-Diaminocyclohexane (DACH) has made in recent years a spectacular career in synthetic organic chemistry.[1] It is one of a few chiral vicinal diamines known[2] and is readily available in both enantiomeric forms by resolution of a crude mixture of amines obtained as side products in the process of production of 1,6-diaminohexane.[3] DACH became highly popular after the initial successful application of its bis-Schiff base derivatives **1** as chiral ligands for asymmetric epoxidation[4,5] and asymmetric epoxide ring opening.[6] Further applications of bis-Schiff base derivatives **1** followed, for example in asymmetric cyclopropanation,[7] Diels–Alder[8] and hetero-Diels–Alder reactions,[9] as well as in asymmetric enolate alkylations,[10] and nucleophilic additions to the C=N[11] and C=O[12,13] bonds. An analogue of bis-imine DACH derivative with the N=PPh_3 substituents has been synthesized as a ligand for the rhodium ions.[14] Among other numerous applications of DACH Schiff-base derivatives we mention the [3+3] cyclocondensation of DACH with aromatic dialdehydes which readily affords chiral macrocycles15 (trianglimines,[16] calixsalens[17]).

Trost introduced bis-(2-diphenylphosphinobenzamide) DACH derivatives of type **2** as chiral ligands for enantioselective allylic alkylations[18] and deracemization of Baylis–Hillman adducts.[19] *N*-Aryl derivatives of DACH have only recently been prepared as chiral ligands for transfer hydrogenation reactions.[20] *N*,*N*′-Bis(4-nitrophenyl) derivative of DACH was found to exhibit high β-hyperpolarizability in the crystal, a characteristic useful for applications in nonlinear optics.[21]



Unlike conformations of derivatives of types **1** and **2**, the structure of type **3** derivatives of DACH has received little attention. Knowledge of the conformation of *N*,*N*′-diaryl DACH derivatives is of importance to rationally design suitable derivatives of DACH as chiral ligands and scaffolds in synthesis. With this aim we have undertaken the study of structures of three *N*,*N*′-diaryl-(*R*,*R*)-DACH derivatives, with the use of molecular modeling at the DFT level of

Keywords: *trans*-1,2-diaminocyclohexane; conformation; circular dichroism; DFT; *N*-arylation; protonation.
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0040–4020/$ - see front matter © 2003 Published by Elsevier Ltd.
doi:10.1016/j.tet.2003.09.090

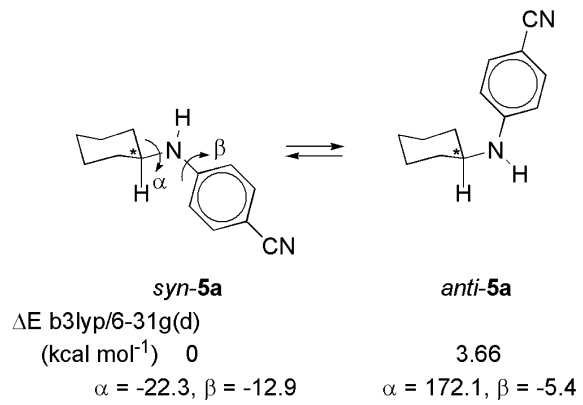
theory as well as circular dichroism (CD) spectroscopy. 4-Cyanophenyl derivative (**3a**) was chosen as a representative of the phenyl and 4-substituted phenyl derivatives since it was expected to give CD spectra more easily interpreted in terms of the exciton coupling formalism, as are the other two derivatives, 1-naphthyl (**3b**) and 2-naphthyl (**3c**). We also investigated the possibility of affecting the relative orientation of the *N*-aryl residues (helical switching) by protonation and *N*-acetylation of derivatives **3a**–**3c**.

2. Synthesis

N,*N*′-Diaryl derivatives **3a**–**3c** were obtained by the Pd-catalyzed arylation of (*R*,*R*)-DACH with the corresponding aryl bromides. We followed the method of Buchwald et al.[22] but we made some changes in the experimental conditions (ligand type, base and solvent used, reaction temperature and time) to optimize the yield of the *N*,*N*′-diaryl substituted products. Yields of **3a**–**3c** in the range 67–75% were obtained from DACH with 2 mol equiv. of aryl bromide, 0.04 mol equiv. $Pd_2(dba)_3$, 0.08 mol equiv. BINAP and 3 mol equiv. NaO*t*-Bu in toluene at 105°C. *N*,*N*′-Diaryl derivatives **3a**–**3c** could be further derivatized by the action of acetic anhydride–triethylamine–DMAP (catalyst) at ambient temperature. Under these conditions *N*-monoacetyl products **4a**–**4c** were obtained, with no detectable amount of the *N*,*N*′-diacetylated derivatives.

3. Structures of diamines 3a–3c

We approached computationally the structure of **3a** by analyzing first the conformation of a model molecule, 4-(*N*-cyclohexylamino)benzonitrile (**5a**). There are two rotations around the C–N bonds to be considered (Scheme 1). Rotation defined by angle α=H–C*–N–C_{ar} determines the position of the aryl substituent with respect to the C–H bond in the cyclohexane ring. For the equatorial C*–N bond there are two distinct conformers, *syn* (α=0–90°) and *anti* (α=90–180°). In these conformers angle β=H–N–C_{ar}–C_{ar} is close to either 0 or 180°.

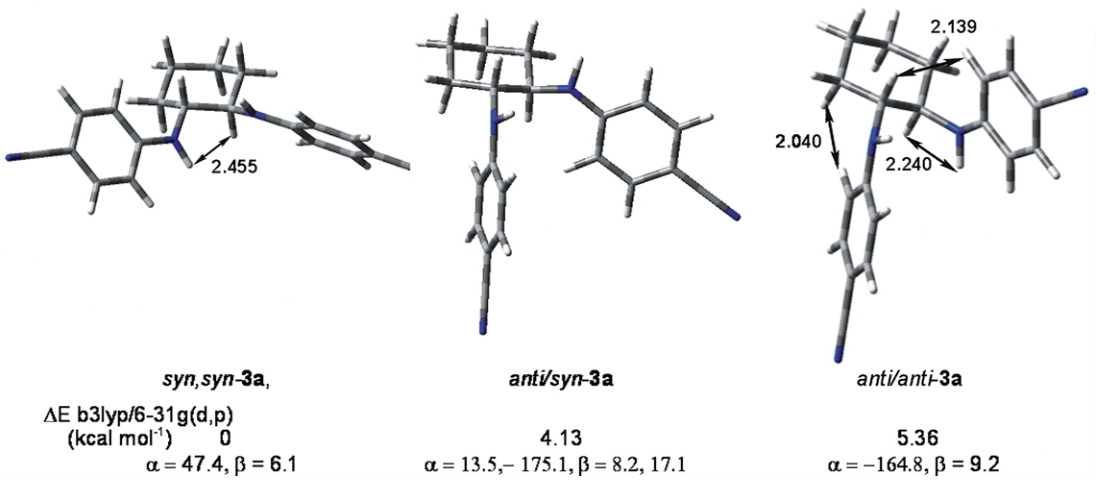


Scheme 1.

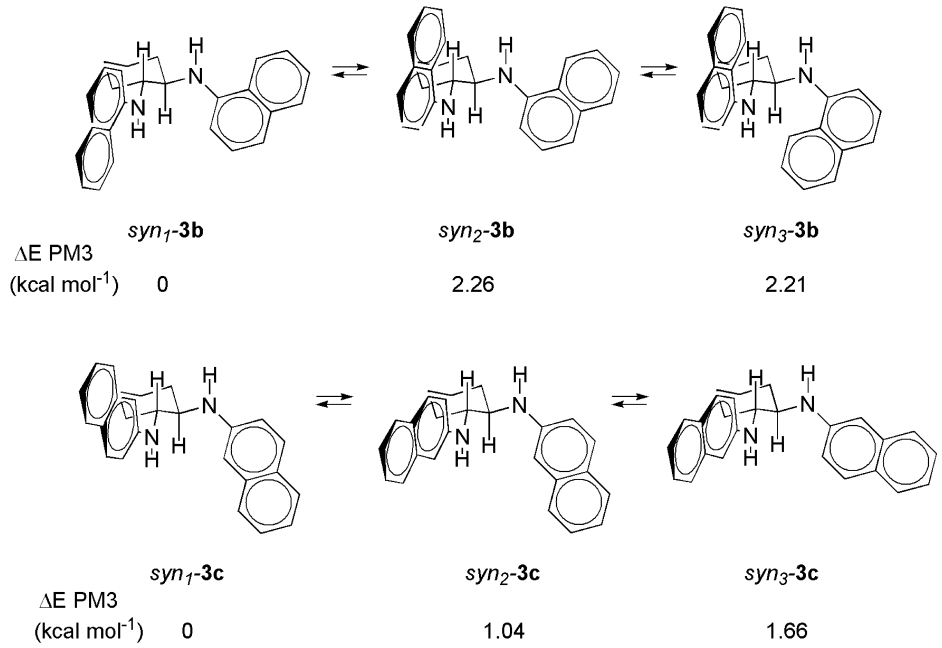
With the use of b3lyp/6-31g(d) method we optimized the structure of **5a** to obtain the *syn* conformer as the global energy minimum, whereas the *anti* conformer was found to be of 3.66 kcal mol^{-1} higher energy. The barrier to rotation around the C_{ar}–N bond (angle β) is low, calculated 3.5 kcal mol^{-1} at the b3lyp/6-31++g(d,p) level; nevertheless any deviation from β=0/180° brings about significant increase of the molecule's free energy due to the steric interactions (aryl hydrogen/cyclohexane equatorial hydrogen), as well as due to the loss of conjugation between the nitrogen lone pair and the aryl ring.

Turning now back to **3a** we optimized its structure first by the PM3 method followed by computation of the minimum-energy conformers at the b3lyp/6-31g(d,p) level. As anticipated, of the three conformers: *syn*/*syn*-**3a**, *anti*/*syn*-**3a** and *anti*/*anti*-**3a**, the first was of the lowest energy, whereas the *anti*/*syn*-**3a** conformer had the highest energy. *syn*/*syn*-**3a** and *anti*/*anti*-**3a** conformers have C_2 symmetry and because of chirality of the DACH skeleton, angles α are much different from 0. In the *anti*/*anti*-**3a** conformer which is of 3.0 kcal mol^{-1} higher energy there are at least three destabilizing interactions between the hydrogen atoms. These short-range contacts are shown (one of a pair) in Scheme 2.

In the case of *N*,*N*′-dinaphthyl derivatives **3b** and **3c** we limited the conformational analysis to the *syn*/*syn* conformers. Due



Scheme 2.



Scheme 3.

to the lack of local C_2 symmetry of the naphthyl substituents three different *syn*/*syn* conformers were considered in each case (Scheme 3).

The computed minimum energy conformer (PM3 method) in the case of **3b** was the one with additional fused benzene rings *syn* to the C(N)–H bonds. As expected, the computed free energy differences between the *syn*/*syn* conformers of **3c** were lower, compared to those of **3b**.

4. Chirality and CD spectra of 3a–3c

The CD/UV spectra of *N*,*N*′-diaryl derivatives **3a**–**3c** are shown in Figure 1.

In order to correlate the CD spectra with the helicity (conformation) of the bis(*N*-arylamine) system we calculated the electronic transitions of the model monomeric *N*-aryl-*N*-methylamines **6a**–**6c** by the mpw1pw91/cc-pvdz method and compared the results with the experimental electronic absorption spectra of the corresponding *N*-cyclohexyl analogues **5a**–**5c** (Fig. 2).

Prior to computing the electronic transitions, the geometry of the molecule **6a** was optimized by the DFT b3lyp/ccpvdz method. The structure obtained was of C_1 symmetry, due to pyramidalization of the nitrogen atom, with torsion angle β=10°.[23] This procedure was also applied to **6b** and **6c** to give similar results.

The computed transitions of **6a**–**6c** in general compare well with the experimental UV spectra of **5a**–**5c**. The most intense transitions of **6a** (at 274 nm, charge-transfer band), **6b** (at 209 nm) and **6c** (at 248 nm) are polarized approximately along the long axes of the chromophores

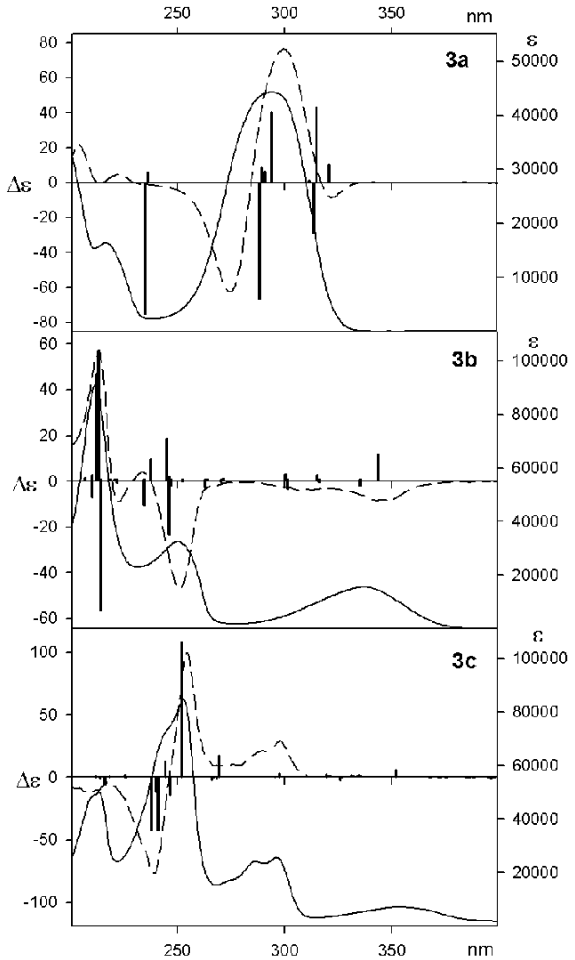


Figure 1. Experimental UV (full line) and CD (broken line) spectra of **3a**–**3c** in acetonitrile solution. Vertical bars represent computed (mpw1pw91/cc-pvdz method) rotational strengths of the electronic transitions.

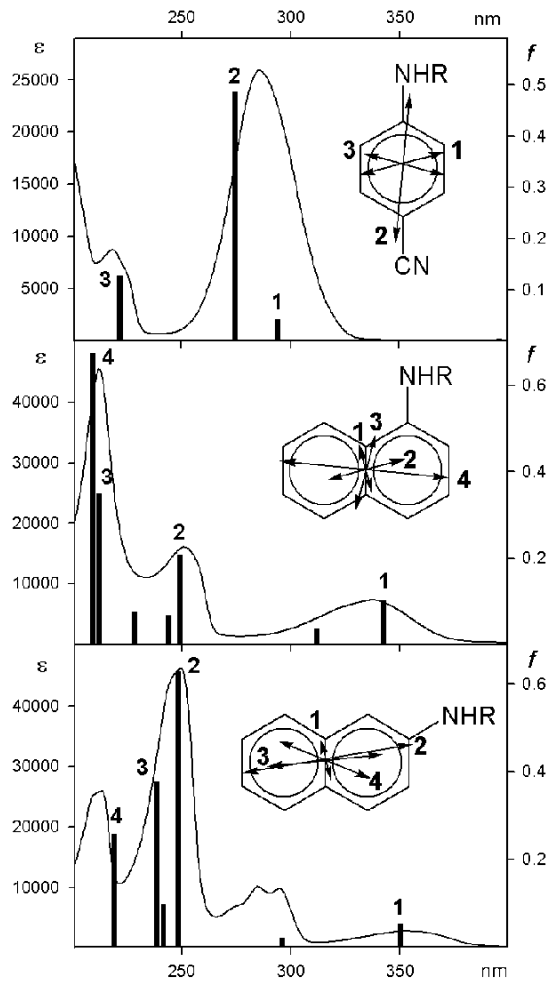


Figure 2. Experimental UV spectra (full line) of **5a**–**5c** in acetonitrile solution and computed directions of in-plane electronic transitions and oscillator strengths of **6a**–**6c** (mpw1pw91/cc-pvdz method).

and correspond to the UV maxima, accordingly of **5a** (at 286 nm, ε=25900), **5b** (at 211 nm, ε=45400) and **5c** (at 249 nm, ε=46200).

Knowledge of the directions of the electronic dipole transition moments determined by the computation made possible assignment of the preferred onformations of diamines **3a**–**3c** from their CD spectra (Fig. 1). Exciton Cotton effects associated with the most intense transitions are positive for **3a** (A=+138) and **3c** (A=+168). In the case of **3b** there are two exciton Cotton effects observed, one corresponding to a transition at 251 nm (A=−51), the other at 212 nm (A=−66). Accordingly these Cotton effects are in agreement with the helical structure of the lowest-energy conformers: *syn*/*syn* for **3a** (Scheme 2) and syn_1 for **3b** and for **3c**[24] (Scheme 3).

With the use of mpw1pw91/cc-pvdz method, we computed excitation energies and rotatory strengths for all of the lowest-energy conformers of compounds **3a**–**c**, all of them were of C_2 symmetry. Conformers syn_1-**3b** and syn_1-**3c** were fully optimized at the b3lyp/6-31g(d) level, prior to the TDDFT computations. Calculated rotatory strengths are shown in Figure 1 in comparison with the measured CD spectra.

Generally, the calculations reproduce satisfactorily the experimental CD data, the best agreement was obtained in the case of **3c**. In the case of **3a** the calculated transitions appear red-shifted relative to the measured CD bands and the calculated transition at 234 nm has no corresponding negative Cotton effect. For **3b** there is a disagreement of the calculated (positive) and measured (negative) long-wavelength Cotton effect. This Cotton effect, however, is not used for the assignment of conformation of the molecule.

5. Helical switching by protonation or acetylation of diamines 3a–3c

Protonation of arylamines **3a**–**3c** brings about not only change in conformation (helical switching) but also a change of electronic structure of the aromatic chromophore. For a model molecule, protonated *N*-methylaniline, rotation of the $-NH_2Me$ substituent about the $C_{ar}-N$ bond proceeds through a well-defined minimum, defined by the torsional angle $C_{ar}-C_{ar}-N-Me$=90°, while the planar transition state conformation ($C_{ar}-C_{ar}-N-Me$=0°) is ca. 1.5 kcal mol^{-1} higher in energy, according to computation at the mp2/6-31g(d) level of theory. This is in contrast to the preferred nearly planar structure of non-protonated *N*-methylaniline.

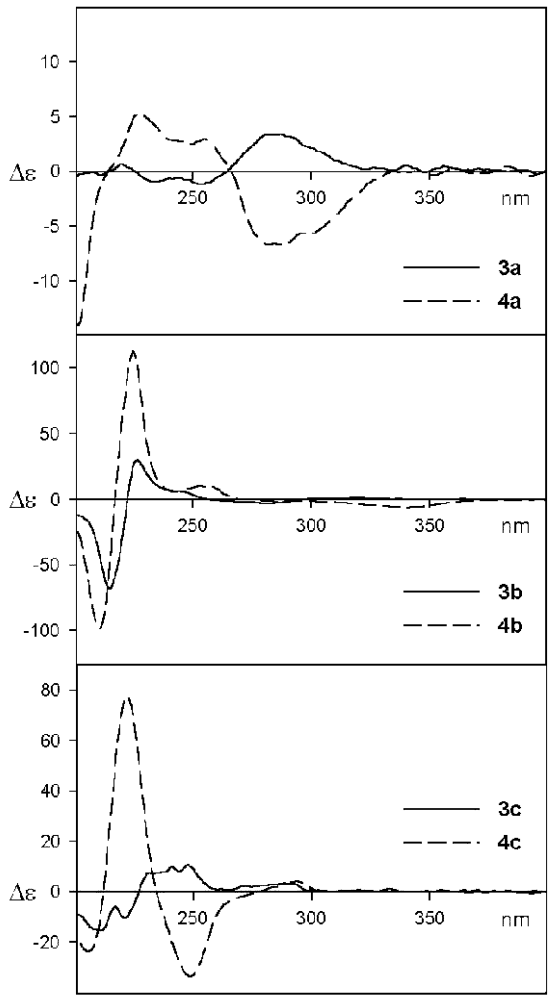


Figure 3. Experimental CD spectra of **3a**–**3c** in acidified acetonitrile solution (full line) and **4a**–**4c** in acetonitrile solution (broken line).

Not surprisingly, the CD spectra of **3a**–**3c** upon protonation with excess of methanesulfonic acid show significant changes (Fig. 3). In the case of **3a** and **3c** protonation brings about substantial reduction of magnitudes of the Cotton effects, while in the case of **3b** the Cotton effects in the range 250–200 nm change signs and magnitudes.

It can be shown that protonation alters the oscillator strength and excitation energies and, to a much smaller extent, the directions of the electronic dipole transition moments. These changes result from the well-known cancelling of the electron donor effect of the amino substituent on protonation and are well reproduced by the computed transitions at the mpw1pw91/cc-pvdz level (Fig. 4).

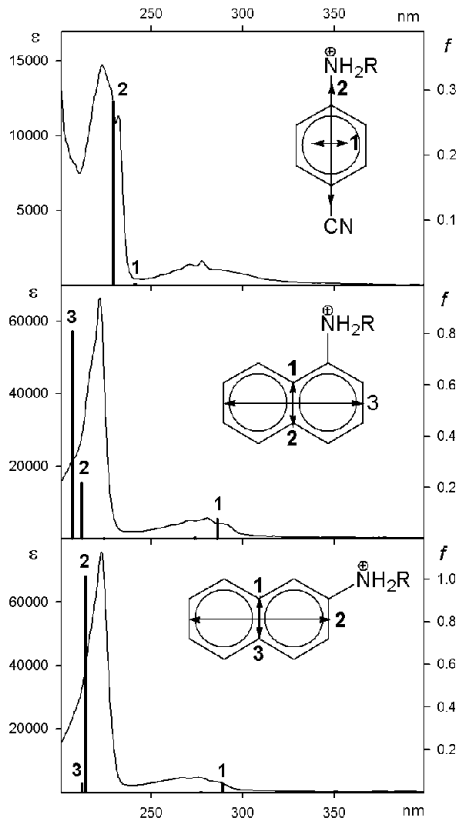
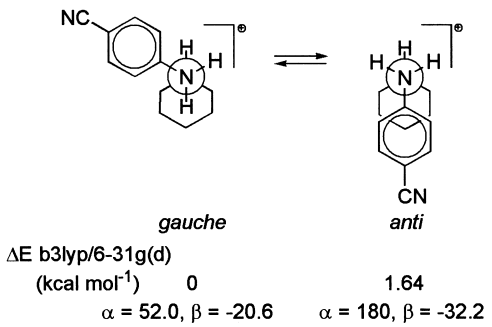


Figure 4. Experimental UV spectra (full line) of **5a**–**5c** in acidified acetonitrile solution and computed directions of in-plane electronic transitions. Vertical bars represent computed (mpw1pw91/cc-pvdz method) oscillator strengths of protonated forms of **6a**–**6c**.

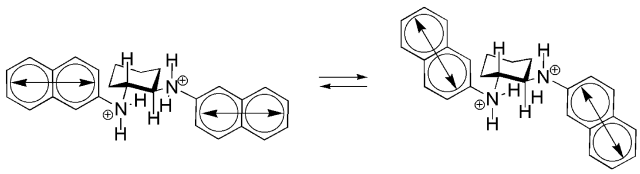
The main feature of the computational results is that the direction of the electric dipole transition moment for the most intense transition, at 229 nm for **6a**, 207 nm for **6b** and 214 nm for **6c**, is collinear with the long axis of each of the aryl rings. When compared with the experimental electronic spectra of non-protonated arylamines (Fig. 2) the computed most intense transitions are blue-shifted in the case of **5b** and **5c**, but red-shifted in the case of **5a**.

It is now evident that the observed changes in the CD spectra of **3a**–**3c** upon protonation are mainly of conformational origin. For the protonated 4-(*N*-cyclohexylamino) benzonitrile molecule (**5a**) the preferred conformation is *gauche* (Scheme 4), in sharp contrast to the non-protonated amine where the preferred conformer is *syn* (Scheme 1).



Scheme 4.

The low-energy *gauche*/*gauche* conformer of protonated **3a** is characterized by parallel directions of the electric dipole transition moments of the most intense transition at 229 nm, hence there are no exciton Cotton effects generated (the same is true about the transitions which are polarized orthogonally). Similar reasoning applied to protonated **3c** leads to two *gauche*/*gauche* rotamers, with time-averaged direction of the electric dipole transition moment in line with the direction of the N–C_{ar} bond (Scheme 5).



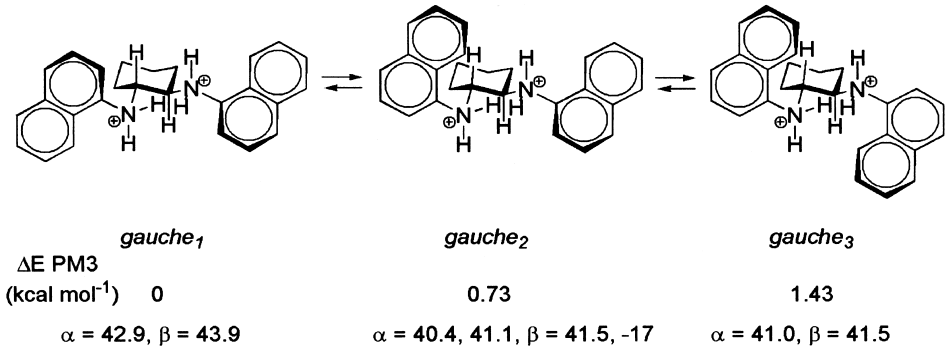
Scheme 5.

The *gauche*/*gauche* rotamers of protonated bis-arylamine **3b**, shown in Scheme 6, are of different energy and the relative directions of the transition moments (for the most intense transition located at 222 nm), which are orthogonal to the direction of the N–C_{ar} bond, are strongly dependent on the conformation. For the lowest-energy C_2-symmetry conformer $gauche_1$ the predicted exciton Cotton effect for the 222 nm transition is positive, as indeed is observed (see Figure 3).

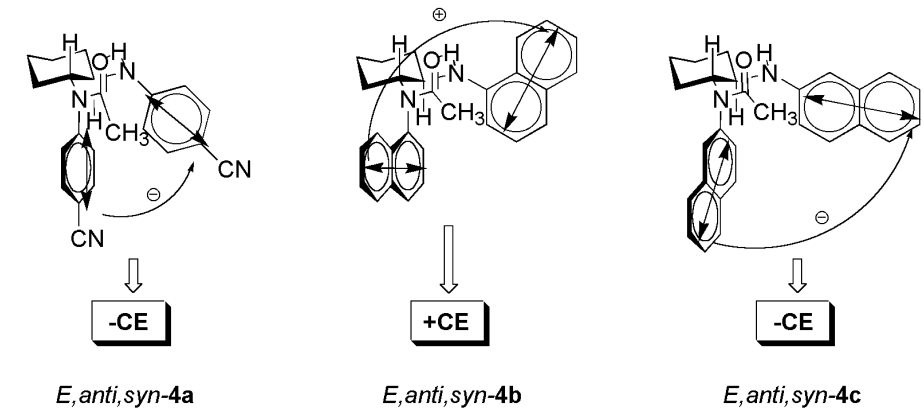
Thus, conformational switching on protonation of bis-arylamines **3a**–**3c** has been demonstrated by computational methods and by experimental CD spectra.

N-Acetylation of **3a**-**3c** leads to monoacetamides **4a**–**4c** which differ pairwise in the CD spectra (Figs. 1 and 3). In each case we observe sign reversal as well as changes of the magnitude of the Cotton effects. Since the differences in the position of the electric dipole transition moments of **3** and **4** are small, the origin of these changes can be traced to the change of the preferred conformation of diamines upon N-acetylation.[25]

N-Acetylated diamines **4a**–**4c** can exist in a number of conformers, differing in amide *Z* or *E* configuration and in orientation of the aryl substituent with regard to the vicinal C*–H bond (*anti*, *syn*). According to computational results at the PM3 semiempirical level out of the total number of eight conformers for **4a** the one having the lowest energy is stabilized by an intramolecular hydrogen bond C═O···H–N (2.25 Å) and can be described as *E*,*anti*,*syn* (Scheme 7).



Scheme 6.



Scheme 7.

In this conformer the aryl group attached to the acetamide substituent lies in the plane perpendicular to the plane of the amide group and is *anti* to the C*–H bond. This means that the electric dipole transition moments of the two 4-substituted benzonitrile chromophores form a negative helicity system. Consequently, the Cotton effect of **4a** at 282 nm is negative, i.e. of opposite sign to that of **3a**.

Likewise, the preferred conformers of **4b** and **4c**, shown in Scheme 7, readily account for the observed reverse-sign Cotton effects due to *N*-acetylation, when compared to conformers syn_1-**3b** and syn_1-**3c**, respectively.

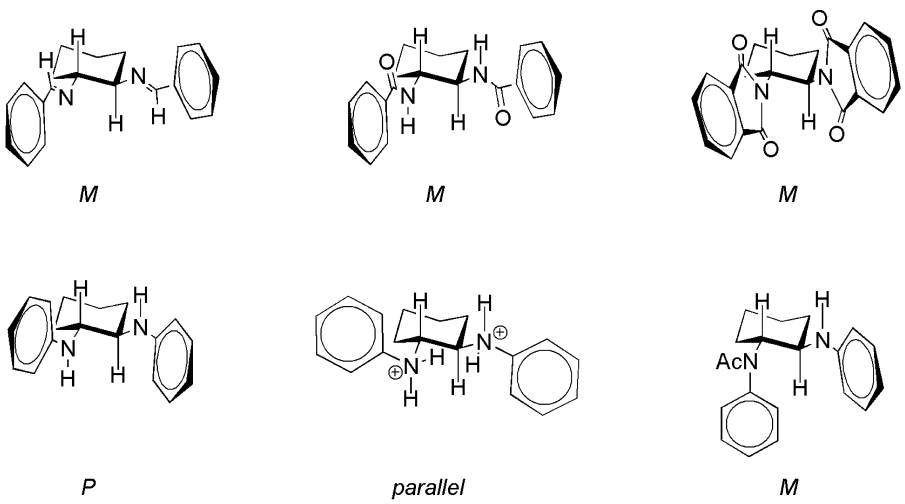
It should be noted that, according to mpw1pw91/cc-pvdz computation, acetylation of **6b** or **6c** has a similar effect on the electronic absorption spectra as does protonation of **6b** or **6c**, since in either case the participation of the amine n-orbital in the resonance of the naphthalene chromophore is eliminated. Nevertheless, protonation and *N*-acetylation result in different conformational arrangement of the aromatic chromophores in derivatives **3** and **4**.

6. Concluding remarks: molecular helicity manipulation

DACH is a rigid molecule, having two equatorial C–N bonds in a chair cyclohexane skeleton. The amine groups offer numerous possibilities for functionalization, with substitution by C, N, S, P-containing groups and with the amine nitrogen atoms of trigonal or tetragonal geometry. The C–N bonds in DACH derivatives appear to uniformly maintain the equatorial positions,[26] with the N–C–C–N dihedral angle negative for *R*,*R* configuration (*M* helicity). *M* helicity is maintained in derivatives such as diimines[15] (**1**), dibenzamides (**2**) and diimides,[27] however in *N*,*N*′-diaryl derivatives (**3**) the –NHAr substituents form a *P*-helical system for the same (*R*,*R*)-DACH configuration (Scheme 8).

Protonation of *N*,*N*′-diaryl derivatives of DACH (**3**) restores the tetragonal structure of the nitrogen atoms and is associated with parallel orientation of the aryl groups, when Ar is the phenyl group. *N*-Acetylation of *N*,*N*′-diaryl derivatives of DACH (**4**) changes the helicity of the substituents system to *M*. Further manipulations of substituent helicity are possible by substituting the phenyl substituent in Scheme 8 with other aryl/heterocyclic groups. 1-Naphthyl groups are of special interest, due to their highly unsymmetrical structure.

Numerous DACH derivatives are used as bidendate ligands for chiral catalysts where the helicity of the ligand system is further modified by the ligation process. On the other hand, DACH derivatives are expected to find use as chiral organocatalysts and reagents. For example, protonated derivatives of diamines **3** could be used for asymmetric protonation of enolates. Therefore, knowledge of their molecular helicity and ways of helical switching may be important for successful planning of the enantiodifferentiating action of these derivatives.



Scheme 8.

7. Experimental

7.1. General

All reactions were carried out with dry, freshly distilled and degassed solvents under argon atmosphere. Reagents were commercial materials (Sigma-Aldrich, Strem). Column chromatography was performed on Silica Gel (Merck 60). NMR spectra were recorded with a Varian Gemini 300 spectrometer using TMS as an internal standard. Mass spectra were recorded with an AMD 402 mass spectrometer. CD and UV spectra were measured on a JASCO J-810 spectrapolarimeter in acetonitrile solutions. FT-IR spectra (KBr pellets) were measured using a Bruker instrument.

The structures were computed by DFT methods with the b3lyp functional,[28] which includes the Becke three-parameter exchange[29] and the Lee, Yang, and Parr Correlation,[30] implemented in the Gaussian suite of programs[31] as well as by the PM3 method implemented in the CAChe WS Pro 5.0.[32] The electronic excitation energies and CD spectra were calculated with the mpw1pw91 hybrid functional, which includes Barone and Adamo's one parameter functional using modified Pardew–Wang exchange[33] and Pardew and Wang's gradient-corrected correlation.[34] For calculation of excitation energies the cc-pvdz basis set was used.[31]

7.2. Pd-catalyzed coupling of *trans*-(1*R*,2*R*)-1,2-diaminocyclohexane with aryl bromides. General procedure

An oven-dried two necked flask equipped with a stirbar and reflux condenser capped with a rubber septum, was purged with argon, charged with (±)-BINAP (49.8 mg, 0.08 mmol) and $Pd_2(dba)_3$ (36.6 mg, 0.04 mmol) and capped with a rubber septum. The flask was purged with argon, and anhydrous, degassed toluene (5 mL) was added via syringe. The mixture was heated to 80°C with stirring for 1 h. After cooling to room temperature, the septum was removed and NaO–*t*-Bu (288 mg, 3 mmol) was quickly added in one portion. The flask was capped with the septum and then purged with argon. A solution of DACH (137 mg, 1.2 mmol) and aryl bromide (2 mmol) in anhydrous, degassed toluene (5 mL) was subsequently added via a syringe. The mixture was heated with stirring for 24 h at 105–110°C (oil bath) under argon atmosphere. The mixture was allowed to cool to room temperature, taken up in ether (25 mL), filtered through the pad of Celite and concentrated in vacuo. The crude product was then purified by column chromatography on silica gel (20% CH_2Cl_2 in hexane).

7.2.1. *trans*-(1*R*,2*R*)-*N*,*N*′-Di-(4-benzonitrile)-1,2-diaminocyclohexane (3a). Solidified oil; 72% yield; ^{1}H NMR ($CDCl_3$) δ 1.26–1.30 (m, 2H), 1.40–1.46 (m, 2H), 1.80 (m, 2H), 2.28 (d, J=13.5 Hz, 2H), 3.30 (m, 2H), 4.20 (br, 2H), 6.54 (d, J=6.9 Hz, 4H), 7.39 (d, J=6.9 Hz, 4H); ^{13}C NMR ($CDCl_3$) δ 24.4, 32.2, 56.5, 98.7, 112.5, 120.3, 133.7, 150.6; IR ν (cm^{-1}) 3356, 2210, 1604, 1515, 1318, 821; HREIMS *m*/*z* 316.1691, calcd for $C_{20}H_{20}N_4$ 316.1688; UV (acetonitrile) ε (nm) 44300 (294), 16400 (216), 35800 (195); CD (acetonitrile) $\Delta\varepsilon$ (nm) −8 (322), +76 (299), −62 (274), +4 (222), +22 (204); UV (acidified acetonitrile) ε (nm) 17500 (277), 13400 (221) 38300 (193); CD (acidified acetonitrile) $\Delta\varepsilon$ (nm) +3 (287), −1 (253), +1 (220).

7.2.2. *trans*-(1*R*,2*R*)-*N*,*N*′-Di-(1-naphthyl)-1,2-diaminocyclohexane (3b). Solidified oil; 67% yield; ^{1}H NMR ($CDCl_3$) δ 1.37–1.44 (m, 2H), 1.52–1.60 (m, 2H), 1.90 (m, 2H), 2.55 (d, J=13.5 Hz, 2H), 3.64 (m, 2H), 4.67 (br, 2H), 6.81 (d, J=7.1 Hz, 2H), 7.26–7.33 (m, 4H), 7.40–7.43 (m, 4H), 7.66 (d, J=8.8 Hz, 2H), 7.77 (d, J=8.8 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 24.8, 32.1, 57.5, 105.2, 117.7, 120.1, 124.0, 124.8, 125.8, 126.4, 128.5, 134.4, 142.8; IR ν (cm^{-1}) 3395, 1592, 1515, 1473, 1408, 769; HREIMS *m*/*z* 366.2079, calcd for $C_{26}H_{26}N_2$ 366.2096; UV (acetonitrile) ε (nm) 15600 (336), 32500 (234), 91300 (212); CD (acetonitrile) $\Delta\varepsilon$ (nm) −8 (343), −47 (251), +4 (234), −9 (222), +57 (213); UV (acidified acetonitrile) ε (nm) 7900 (312), 8400 (292), 8700 (282), 18700 (244), 91700 (221), 89300 (216); CD (acidified acetonitrile) $\Delta\varepsilon$ (nm) +1 (318), −3 (280) +30 (226), −68 (215), −13 (197).

7.2.3. *trans*-(1*R*,2*R*)-*N*,*N*′-Di-(2-naphthyl)-1,2-diaminocyclohexane (3c). Oil; 75% yield; ^{1}H NMR ($CDCl_3$) δ 1.38–1.55 (m, 4H), 1.84 (m, 2H), 2.47 (d, J=13.5 Hz, 2H),

3.40 (m, 2H), 4.18 (br, 2H), 6.82–6.89 (m, 4H), 7.09–7.30 (m, 2H), 7.34–7.40 (m, 2H), 7.50–7.67 (m, 6H); IR ν (cm^{-1}) 3389, 1627, 1517, 827, 749; HREIMS *m/z* 366.2085, calcd for $C_{26}H_{26}N_2$ 366.2096; UV (acetonitrile) ε (nm) 5600 (353), 25200 (296), 23600 (286), 86100 (253), 49000 (213); CD (acetonitrile) $\Delta\varepsilon$ (nm) 28 (297), 94 (254), −74 (238), −11 (208); UV (acidified acetonitrile) ε (nm) 1200 (341), 11700 (279), 51400 (243), 86100 (222); CD (acidified acetonitrile) $\Delta\varepsilon$ (nm) +3 (280), +9 (241), −9 (221), −13 (209).

7.3. Pd-catalyzed coupling of cyclohexylamine with aryl bromides. General procedure

An oven-dried two necked flask equipped with a stirbar and reflux condenser capped with a rubber septum, was purged with argon, charged with (±)-BINAP (24.9 mg, 0.04 mmol) and $Pd_2(dba)_3$ (18.3 mg, 0.02 mmol) and capped with a rubber septum. The flask was purged with argon, and anhydrous, degassed toluene (3 mL) was added via a syringe. The mixture was heated to 80°C with stirring for 1 h. After cooling to room temperature, the septum was removed and NaO–*t*-Bu (144 mg, 1.5 mmol) was quickly added in one portion. The flask was capped with the septum and then purged with argon. A solution of cyclohexylamine (121 mg, 1.2 mmol) and aryl bromide (1 mmol) in anhydrous, degassed toluene (2 mL) was then added via a syringe. The mixture was heated with stirring for 16 h at 105–110°C (oil bath) under argon atmosphere. The mixture was allowed to cool to room temperature, taken up in ether (15 mL), filtered through the pad of Celite and concentrated in vacuo. The crude product was then purified by column chromatography on silica gel (20% CH_2Cl_2 in hexane).

7.3.1. *N*-(4-Benzonitrile)cyclohexylamine (5a). Oil, 92% yield; ^{1}H NMR ($CDCl_3$) δ 1.12–1.45 (m, 5H), 1.64–1.81 (m, 3H), 2.00–2.06 (m, 2H), 3.29 (br, 1H), 4.10 (br, 1H), 6.51 (d, *J*=8.9 Hz, 2H), 7.38 (d, *J*=8.9 Hz, 2H); IR ν (cm^{-1}) 3334, 2212, 1607, 1528, 1338, 820; HREIMS *m/z* 200.1309, calcd for $C_{13}H_{16}N_2$ 200.1313; UV (acetonitrile) ε (nm) 25900 (286), 8800 (218); UV (acidified acetonitrile) ε (nm) 1400 (271), 14700 (224).

7.3.2. *N*-(1-Naphthyl)cyclohexylamine (5b). Oil, 89% yield; ^{1}H NMR ($CDCl_3$) δ 1.22–1.51 (m, 5H), 1.68 (m, 1H), 1.85 (m, 2H), 2.17 (d, *J*=9.9 Hz, 2H), 3.47 (m, 1H), 4.26 (br, 1H), 6.62 (d, *J*=7.4 Hz, 1H), 7.17 (d, *J*=8.0 Hz, 1H), 7.24–7.7.48 (m, 4H), 7.78–7.85 (m, 2H); IR ν (cm^{-1}) 3427, 1581, 1528, 1480, 1408, 767; HREIMS *m/z* 225.1515, calcd for $C_{16}H_{19}N$ 225.1517; UV (acetonitrile) ε (nm) 7300 (337), 16100 (251), 45400 (211); UV (acidified acetonitrile) ε (nm) 5600 (280), 5000 (270), 66300 (222).

7.3.3. *N*-(2-Naphthyl)cyclohexylamine (5c). Oil, 91% yield; ^{1}H NMR ($CDCl_3$) δ 1.14–1.50 (m, 5H), 1.65–1.83 (m, 3H), 2.10–2.16 (m, 2H), 3.40 (m, 1H), 3.70 (br, 1H), 6.79–6.87 (m, 2H), 7.09–7.19 (m, 1H), 7.31–7.37 (m, 1H), 7.57–7.66 (m, 3H); IR ν (cm^{-1}) 3421, 1628, 1524, 828, 754; HREIMS *m/z* 225.1520, calcd for $C_{16}H_{19}N$ 225.1517; UV (acetonitrile) ε (nm) 2800 (353), 9900 (295), 10200 (285), 46200 (249), 26000 (213); UV (acidified acetonitrile) ε (nm) 4700 (275), 4600 (266), 75600 (222).

7.4. Monoacetylation of *N,N′*-diaryl derivatives of DACH. General procedure

To a solution of diamine (0.5 mmol), triethylamine (1 mL) and DMAP (20 mg, 0.16 mmol) in CH_2Cl_2 (3 mL) acetic anhydride (3 mL) was added dropwise at 0°C with stirring. The mixture was allowed to warm to room temperature and then stirred overnight. Water (5 mL) was added, and the mixture was stirred for additional 2 h. After separation of organic layer, the aqueous layer was extracted twice with CH_2Cl_2 (5 mL). The organic layers were collected andwashed twice with brine (10 mL), $NaHCO_3$ (15 mL), water (10 mL), and dried over $MgSO_4$. After evaporation to dryness the crude product was purified by flash chromatography on silica gel (10% AcOEt in CH_2Cl_2).

7.4.1. *trans*-(1*R*,2*R*)-*N*-Acetyl-*N,N′*-di-(4-benzonitrile)-1,2-diaminocyclohexane (4a). Solidified oil; 43% yield; ^{1}H NMR ($CDCl_3$) δ 1.05–2.20 (m, 11H), 2.99 (m, 1H), 4.87–5.01 (m, 2H), 6.50 (d, *J*=9.0 Hz, 2H), 7.10 (br, 2H), 7.47 (d, *J*=8.7 Hz, 2H), 7.60 (br, 2H); IR ν (cm^{-1}) 3336, 2211, 1625, 1606, 1524, 1173; HREIMS *m/z* 358.1775, calcd for $C_{22}H_{22}N_4O$ 358.1793; UV (acetonitrile) ε (nm) 26000 (282), 18700 (217), 52100 (195); CD (acetonitrile) $\Delta\varepsilon$ (nm) −7 (282), +3 (255), +5 (228), −14 (201).

7.4.2. *trans*-(1*R*,2*R*)-*N*-Acetyl-*N,N′*-di-(1-naphthyl)-1,2-diaminocyclohexane (4b). White solid; 62% yield after crystallization (diethyl ether–petroleum ether); mp 342–343°C, ^{1}H NMR ($CDCl_3$) δ 1.05–2.20 (m, 10H), 2.58 (d, *J*=13.5 Hz, 1H) 3.60 (m, 1H), 5.31 (m, 1H), 5.80 (br, 1H), 6.36 (d, *J*=7.4 Hz, 1H), 6.60 (d, *J*=7.4 Hz, 1H), 7.00–7.60 (m, 7H), 7.77–8.05 (m, 5H); IR ν (cm^{-1}) 3389, 3266, 1636, 1580, 1538, 1382, 810, 773; HREIMS *m/z* 408.2225, calcd for $C_{28}H_{28}N_2O$ 408.2201; UV (acetonitrile) ε (nm) 9500 (340), 8000 (283), 20200 (252), 87000 (224), 75800 (214); CD (acetonitrile) $\Delta\varepsilon$ (nm) −6 (340), +10 (252), +122 (225), −103 (210).

7.4.3. *trans*-(1*R*,2*R*)-*N*-Acetyl-*N,N′*-di-(2-naphthyl)-1,2-diaminocyclohexane (4c). Solidified oil; 82% yield; ^{1}H NMR ($CDCl_3$) δ 1.05–1.80 (m, 9H), 2.00 (m, 1H), 2.35 (m, 1H), 3.31 (m, 1H), 4.94 (m, 1H), 5.20 (br, 1H), 6.75–7.86 (m, 14H); IR ν (cm^{-1}) 3392, 3275, 1631, 1589, 812, 776; HREIMS *m/z* 408.2185, calcd for $C_{28}H_{28}N_2O$ 408.2201; UV (acetonitrile) ε (nm) 3100 (355), 14000 (284), 51000 (249), 86200 (224); CD (acetonitrile) $\Delta\varepsilon$ (nm) +4 (293), −33 (249), +77 (222), −23 (206).

Acknowledgements

This work was supported by a grant no. 4T09A 159 22 from the Committee of Scientific Research (KBN).

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