

Vibrational circular dichroism and *ab initio* structure elucidation of an aromatic foldamer†

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Ab initio calculations together with vibrational circular dichroism (VCD) are validated as very accurate tools for studying conformations and estimating conformational energies and helical handedness preferences of an entire, large (112 atoms), abiotic foldamer.

The rapidly increasing number of foldamer families suggests that synthesizing new interesting oligomers no longer constitutes a major obstacle.¹ However, the unambiguous elucidation of a new folded structure is often more difficult and methodological development on this front could be valuable to many. The challenge generally consists in adapting tools that have already been optimized for studying biopolymer conformations, such as NMR,² circular dichroism in the UV–vis range (CD),³ molecular dynamics^{3a,4} and, for those most rigid oligomer backbones, X-ray crystallography.^{1c,5,6} Less common techniques have proven useful as well, *e.g.* electron spin resonance.⁷ Here, we describe the first example of a successful *ab initio* calculation and vibrational circular dichroism (VCD) structure elucidation of an entire helically folded abiotic oligomer. These techniques are common to assess the conformation of small molecules, but their potency is far from being fully explored to study large objects and systems held by multiple non covalent bonds. Our purpose being to evaluate the accuracy of these techniques and to foster their use, we have applied them to a quinoline derived *R*-chiral tetramer **1** (Fig. 1), the structure of which is fully backed by crystallographic, CD and NMR data.^{2b,6}

Previous *ab initio* studies of the conformation of foldamers have been performed on truncated motifs to examine local effects.⁸ Thus, they did not involve essential interactions between sites remote in the oligomer sequences that come in proximity upon folding. *Ab initio* calculations were also performed on helicenes, which possess no conformational freedom,^{9,10} whilst semi-empirical methods failed to predict the structure of phenylene ethynylene oligomers.¹¹ Computational powers now available allow *ab initio* calculations to be performed even on relatively large objects, and a few studies of supramolecular assemblies have recently appeared.¹²

We thus ventured to optimize at a high density functional theory level (B3LYP, 6-31G* basis set) the three conformations of **1**

(C₅₂H₄₁O₁₀N₉, 112 atoms) that we had previously characterized in the solid state[‡] and which seemed the most reasonable on the grounds of sterics. Each calculation required more than 240 h cpu time for 50 cycles of optimization and more than 800 h cpu time to predict the frequency/intensity of the vibrational absorption and circular dichroism spectra. These three conformations possess either right (P) or left (M) handedness, and variable conformations at the PhC*–NH linkage (Fig. 1). In M2 and P2, the phenyl group is aligned with the helical backbone whilst in M3 it points away from the helix.

Crystal structures are not always representative of ground state conformations. However, in the case of **1**, the optimized structures were found to be remarkably similar to the helically folded conformations observed in crystals (see supporting information†). Specifically, the helical pitch (3.5 Å), the position of the first carbon of each side chain in the plane of quinoline rings and even the curvature (2.5 units per turn) are very well reproduced by the calculations. Small differences include the exact position of the phenyl ring which, unlike in crystals, does not lie flat on the helix in the optimized P2 and M2 conformers. This apparently results from of an interaction between a phenyl CH and an amide carbonyl below in the helix (Fig. 1).

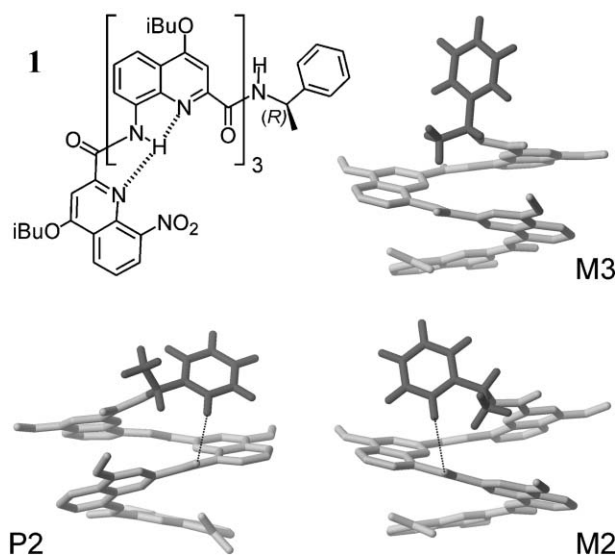


Fig. 1 Formula of tetramer **1** and stick representation of the optimized structures of three of its conformers, two left handed (M2, M3) and one right handed (P2). Isobutyl groups have been replaced by methyl groups in the calculations. Hydrogen atoms are omitted for clarity except those of the phenethyl moiety. Dotted lines indicate C_{aryl}H...O interactions.

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† Electronic supplementary information (ESI) available: experimental methods, structural details of the optimized structures and VCD spectra. See DOI: 10.1039/b604462j

Table 1 Conformation and energies of tetramer **1**

Conformers	Gibbs energy/hartree	$\Delta G/\text{kJ mol}^{-1}$	Pop. (%)
P2	-3250.501748	5.4	9.1
M2	-3250.503807	0	83.5
M3	-3250.501560	5.9	7.4

The calculated Gibbs free energies of the optimized conformations show that M2 is the most stable conformer (Table 1). The values predict that the left handed helices (M2 + M3) should account for 90.9% of the total population whilst the right handed helix (P2) should represent 9.1%. Despite the small energy differences between the three conformers (at most 5.4 kJ mol⁻¹), this prediction of the sign and strength of handedness induction in **1** by the chiral terminal phenethyl-amino group matches perfectly the values measured in solution by NMR and CD.^{6b} The surprising accuracy of a theoretical prediction made in the absence of any solvent for a phenomenon observed in solution probably resides in the fact that, for aromatic amide oligomers such as **1**, solvent does not seem to influence much the stability of the folded structures (e.g. in CHCl₃, DMSO, H₂O, MeOH)⁶ or the strength of handedness induction (e.g. in CHCl₃, DMSO).^{6a,6b}

That these results are not a mere coincidence is supported by VCD data. The three calculated VCD spectra of the M2, M3 and P2 conformers of **1** and its experimental spectrum are shown in Fig. 2. Considering the size of the system, calculated and experimental spectra are overall very similar, except for the fact that the bands predicted for conformer P2 have opposite signs: most vibrators belong to the helix backbone and are not perturbed by the conformation of the terminal chiral moiety that differentiates M2 from M3 and P2. This result validates the calculated helical structure as a whole and the prediction that the major conformer in solution has *M* helicity when the chiral phenethyl group has an *R* configuration

Careful examination of the calculated spectra also reveal a few bands that differ from spectrum to spectrum by more than a change of sign and thus that depend on the conformation of the terminal chiral group. This is the case for the amide NH stretching vibrations. Three of the four NH groups of **1** derive from an

aromatic amine and are hydrogen bonded to both neighbouring quinoline nitrogens. Their calculated stretching vibrations overlap at low frequencies (3315 cm⁻¹, Fig. 2A). The terminal amide connected to the asymmetric carbon derives from an aliphatic amine and is singly hydrogen bonded. Its vibration is expectedly calculated at higher wavenumber (\approx 3390 cm⁻¹) but, in addition, the sign and intensity of the vibration band varies with the conformation of the chiral group (Fig. 2A). Yet, among the three calculated spectra, only that of conformer M2 reproduces the intensity and the sign of the two types of amides observed experimentally, corroborating the higher stability of M2 predicted by the calculations. Similarly, the conformation of the terminal chiral group affects the VCD bandshape of the amide I (mainly C=O stretching vibrations) mode located at 1678 cm⁻¹ and of the mode observed at 1205 cm⁻¹.[§] In both cases, the simulated spectrum of M2 is the closest to the experimental spectrum (see supporting information†) and the sum of the three calculated spectra in proportions that reflect the Gibbs free energies of the three conformers fit well to the experimental spectrum.

Thus, all data consistently point to a higher stability of conformer M2. Why then do less stable P2 and M3 conformers also occur in the solid state? We note that, in both cases, obvious crystal packing effects exist. P2 co-crystallizes with M2 and is involved in a pseudo-centrosymmetry,^{6a} and the phenyl group of M3 is engaged in specific intermolecular stacking interactions.^{6b}

In summary, *ab initio* calculations and VCD together provide a detailed and accurate description of the conformation of foldamer **1** that much improves our initial qualitative analysis based on sterics.^{6b} Calculations apparently have very good prediction power in the case of oligomers such as **1**, but all relevant conformers must be examined to predict, for example, the preferred helical handedness (M2 is more stable but P2 and M3 have similar energies). Studies as this one still require powerful computer facilities, but with calculation powers constantly increasing, it is expected that such large systems may be assessed routinely in a near future.

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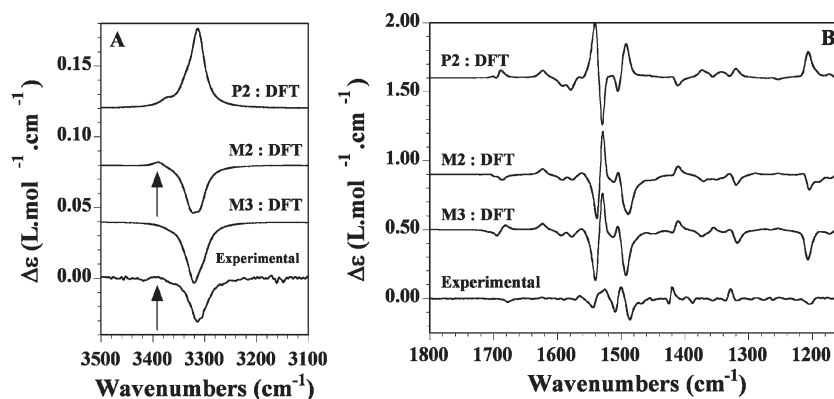


Fig. 2 Comparison of the experimental VCD spectrum of tetramer **1** in CDCl₃ with DFT calculated VCD spectra of M3, M2 and P2 conformers: (A) the NH stretching region; and (B) mid-infrared region. Calculated spectra are vertically offset for clarity. The arrow indicates the band assigned to the terminal amide NH stretching vibration. A good match between experimental and calculated spectra is formally defined by the sign and intensity of each band. The visual impression of a good match depends on the selected half-width of the bands and could be improved arbitrarily by choosing different half-widths for each band.

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Notes and references

‡ The starting geometries of P2 and M2 conformers were built from the crystal structures found for the corresponding conformers of the octamer.

§ This mode can be assigned in part to C–N stretching vibration but it is coupled with others vibrations of the helical backbone.

- 1 For reviews see: (a) D. J. Hill, M. J. Mio, R. B. Prince, T. S. Hughes and J. S. Moore, *Chem. Rev.*, 2001, **101**, 3893; (b) R. P. Cheng, S. H. Gellman and W. F. DeGrado, *Chem. Rev.*, 2001, **101**, 3219; (c) I. Huc, *Eur. J. Org. Chem.*, 2004, 17; (d) R. P. Cheng, *Curr. Opin. Struct. Biol.*, 2004, **14**, 512; (e) G. Licini, L. J. Prins and P. Scrimin, *Eur. J. Org. Chem.*, 2005, 969; (f) D. Seebach, A. K. Beck and D. J. Bierbaum, *Chem. Biodiv.*, 2004, **1**, 1111.
- 2 (a) H.-S. Lee, F. A. Syud, X. Wang and S. H. Gellman, *J. Am. Chem. Soc.*, 2001, **123**, 7721–7722; (b) C. Dolain, A. Grélard, M. Laguerre, H. Jiang, V. Maurizot and I. Huc, *Chem.–Eur. J.*, 2005, 6135–6144.
- 3 (a) A. Glattli, X. Daura, D. Seebach and W. F. van Gunsteren, *J. Am. Chem. Soc.*, 2002, **124**, 12972–12978; (b) H. Sugiura, Y. Nigorikawa, Y. Saiki, K. Nakamura and M. Yamaguchi, *J. Am. Chem. Soc.*, 2004, **126**, 14858–14864; (c) A. Tanatani, A. Yokoyama, I. Azuyama, Y. Takakura, C. Mitsui, M. Shiro, M. Uchiyama, A. Muranaka, N. Kobayashi and T. Yokozawa, *J. Am. Chem. Soc.*, 2005, **127**, 8553–8561.
- 4 R. Baron, D. Bakowies and W. F. van Gunsteren, *Angew. Chem., Int. Ed.*, 2004, **43**, 4055–4059.
- 5 D. H. Appella, L. A. Christianson, I. L. Karle, D. R. Powell and S. H. Gellman, *J. Am. Chem. Soc.*, 1999, **121**, 6206–6212.
- 6 (a) H. Jiang, C. Dolain, J.-M. Léger, H. Gornitzka and I. Huc, *J. Am. Chem. Soc.*, 2004, **126**, 1034–1035; (b) C. Dolain, H. Jiang, J.-M. Léger, P. Guionneau and I. Huc, *J. Am. Chem. Soc.*, 2005, **127**, 12943–12951; (c) E. Gillies, C. Dolain, J.-M. Léger and I. Huc, *J. Org. Chem.*, 2006, DOI: 10.1021/jo0603577.
- 7 K. Matsuda, M. T. Stone and J. S. Moore, *J. Am. Chem. Soc.*, 2002, **124**, 11836–11837.
- 8 R. D. Parra, H. Zeng, J. Zhu, C. Zheng, X. C. Zeng and B. Gong, *Chem.–Eur. J.*, 2001, **7**, 4352–4357; R. Parra, B. Gong and X. C. Zeng, *J. Chem. Phys.*, 2001, **115**, 6036–6041; R. J. Doerksen, B. Chen, D. Liu, G. N. Tew, W. F. DeGrado and M. L. Klein, *Chem.–Eur. J.*, 2004, **10**, 5008–5016.
- 9 T. Bürgi, A. Urakawa, B. Behzadi, K. H. Ernst and A. Baiker, *New J. Chem.*, 2004, **3**, 332–334; E. Botek, B. Champagne, M. Turki and J. M. André, *J. Chem. Phys.*, 2004, **120**, 2042–2048.
- 10 T. B. Freedman, X. Cao, A. Rajca, H. Wang and L. A. Nafie, *J. Phys. Chem. A*, 2003, **107**, 7692–7696.
- 11 R. A. Blatchly and G. N. Tew, *J. Org. Chem.*, 2003, **68**, 8780–8785.
- 12 (a) P. Bour, J. Kubelka and T. A. Keiderling, *Biopolymers*, 2002, **65**, 45–59; (b) V. Andrushchenko, H. Wieser and P. Bour, *J. Phys. Chem. B*, 2004, **108**, 3899–3911; (c) M. Urbanova, V. Setnicka, F. J. Delvin and J. Stephens, *J. Am. Chem. Soc.*, 2005, **127**, 6700–6711.