Organic & Biomolecular Chemistry

Cite this: *Org. Biomol. Chem.*, 2012, **10**, 8579

www.rsc.org/obc

COMMUNICATION

Synthesis of chiral bis-oxazines: a preliminary assessment of helical conformational framework†

Harish R. Talele and Ashutosh V. Bedekar*

Received 26th June 2012, Accepted 20th September 2012
DOI: 10.1039/c2ob26669e

A series of novel naphthalene attached bis-oxazines were synthesized and characterized. The bis-oxazines were studied by VT-NMR analysis to assess the possibility of conformational twist. The bis-oxazine prepared from (*l*)-methylvalinate show a helical conformational twist in the single crystal X-ray analysis. Three isomers of bis-oxazines were prepared from chiral α-methylbenzyl amines, the *meso* isomer showed small optical rotation probably indicating the helical conformational twist in the molecule.

The "helical" shape has a distinct place in nature and has inspired man to adopt it for the construction of objects of functional utility and aesthetic value. This shape is the basis for the design of architectural and artistic objects. Chemists have synthesized molecules which acquire a helical shape, either as supramolecular assemblies or as a single molecular unit. The inherent, internal helical shape is a result of distortion caused by crowding in the structure, benzo[*c*]phenanthrene or [4]helicene **1** is an example of such phenomena (Fig. 1). The construction of such distorted aromatic molecules is a topic of continuous developments.[1] The synthesis and separation of π-helical isomers of [6]helicene by Newman[2] has triggered significant growth in this area.[3] The other type is σ-helicenes and [4]triangulane **2**, one of the smallest molecules to show such helical shape.[4] Another small molecule capable of showing helical form is 1,10-phenanthroline-*N*,*N*-dioxide **3**, which was synthesized by oxidation of 1,10-phenanthroline with HOF.[5] 4,5-Dialkyl phenanthrene **4** was envisaged to show similar helical shape due to the twisting of two terminal rings arising from internal strain.[6] Naphthalene derivatives with substitutions at C_1 and C_8 positions show peculiar *peri* interactions.[7a] Such 1,8-disubstituted naphthalene moieties having chiral distorted forms, such as 1,8-di(*tert*-butyl)-naphthalene derivative **5** is known to racemize at ambient conditions due to low enantiomerization barrier.[7b–d] Recently an adamantyl derivative of similar compound **6** was reported where this barrier was quite large and the isomers were stable at room temperature. The single enantiomer of **6** was separated and its absolute configuration was established.[8] Several other examples of distorted structures of 1,8-naphthalene derivatives were also known.[9] Another group of such compounds is 1,8-diamino naphthalene **7**, also known as proton sponge.[10]

The derivatives of naphthalene with substitutions at 1,8 positions show twisted, distorted structure giving rise to helical isomers due to *peri* interaction. Such compounds, referred to as [2]helicenes, with sufficiently high barrier of interconversion at ambient conditions can be resolved.[8] In this communication we present our efforts towards synthesis of naphthalene unit attached with heterocyclic rings on C_1–C_2 and C_7–C_8 bonds. The molecules were studied to ascertain the presence of isomers caused by the conformational twist.

The reaction of 2-naphthol with primary amines and an excess of formaldehyde gives an angularly fused naphthalene derivative of 1,3-oxazine *via* an aromatic Mannich reaction.[11] Recently we have prepared heterohelicenes possessing a 1,3-oxazine ring,[12a] however not many similar examples[12b] are available in the literature, though some biologically and medicinally active derivatives are known.[13] Basically 1,3-oxazines were derived forms of Betti

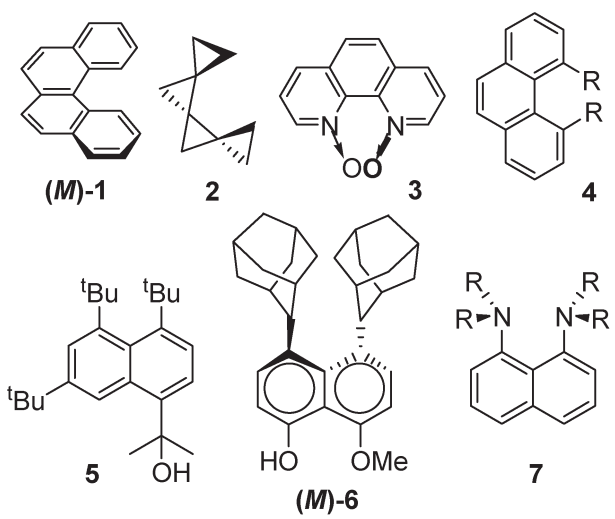
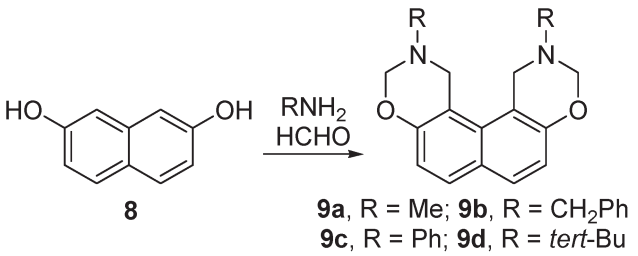


Fig. 1 Examples of small helical molecules, besides [4]helicene.

Department of Chemistry, Faculty of Science, M.S. University of Baroda, Vadodara 390 002, India. E-mail: avbedekar@yahoo.co.in; Tel: +91 0265 2795552

†Electronic supplementary information (ESI) available: Experimental procedures, spectroscopic and X-ray data of the reported compounds is available. CCDC 882285. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2ob26669e



Scheme 1 Synthesis of bis-oxazines.

bases where the amine and phenol were linked with a methylene bridge.[14]

In the initial study 2,7-dihydroxy naphthalene **8** was treated with primary amines and an excess of aqueous formaldehyde. A series of primary amines were chosen for this experiment and a number of bis-oxazine derivatives **9a–9d** were synthesized (Scheme 1).

The derivatives of **9** were purified and characterized by usual spectral and analytical techniques. The H-NMR showed a symmetrical pattern and the two methylene protons appeared as two sharp singlets. The inside hydrogens of Ar–CH_2–N appeared at the high field region while the ones flanked by two electronegative atoms, O–CH_2–N, appeared at down field region. This clearly establishes the absence of a helical form in the solution state at ambient conditions, as that would have made the two hydrogens unequal. This can also be due to rapid flipping of the two conformations of the flexible oxazine rings. This hypothesis was examined by performing H-NMR analysis at low temperature (Fig. 2). The outside protons remained unchanged as sharp singlet when the H-NMR was run at −58 °C, while the inside hydrogens appeared as a broad signal. Even though we were unable to see two separate signals at this condition, there appears to have a tendency of this conformation to gain slight rigidity. The low temperature H-NMR study does not indicate the presence of helical form but definitely hints towards the possibility of acquiring a rigid conformational deviation or slow rate of isomerization. This VT-NMR study was almost similar for all four samples of **9a–9d**, indicating no role of substituent on N.

The next set of naphthalenes attached with bis-oxazine units were synthesized by choosing chiral primary amines. The purpose of introducing a chiral centre in the likely cavity of the helical fold was to introduce a bulk and give it a diastereomeric character. In the preliminary study two derivatives were synthesized in single step from **8** and (*S*)-α-methylbenzyl amine for **10a** and with (*l*)-methylvalinate for **11** (Scheme 2).

The H-NMR spectra of both these compounds were different compared to **9**. The inside hydrogens of Ar–CH_2–N in **10a** appeared as two signals, one d (δ 4.18; J = 16.4 Hz, 1H) and other d (δ 4.05; J = 16.4 Hz, 1H). However, it was interesting to observe a different pattern for the outside hydrogens, O–CH_2–N. These hydrogens showed one d (δ 4.83, J = 10.0 Hz, 1H) and another dd (δ 5.08, J = 10.0, 1.2 Hz, 1H). This could be attributed to the diastereotopic nature of the hydrogens or the twisting of the conformational framework of the oxazine. A similar H-NMR pattern was observed for compound **11**, but one of the outside hydrogens which showed dd (δ 4.94, J = 9.6, 1.6 Hz, 1H) at room temperature slowly merged to a d at +40 °C. The

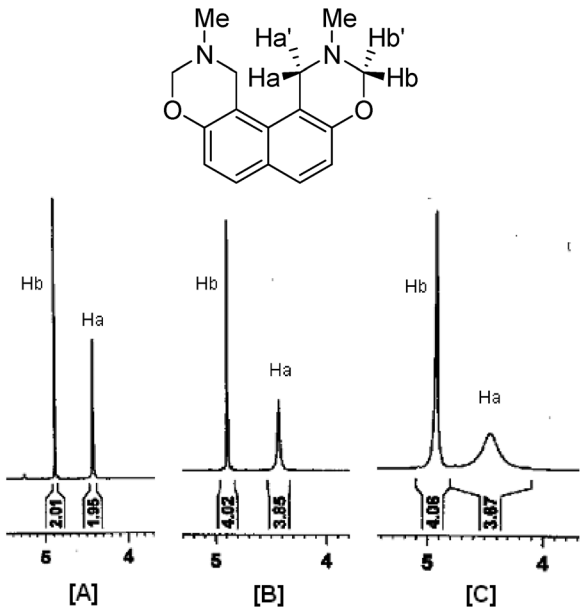
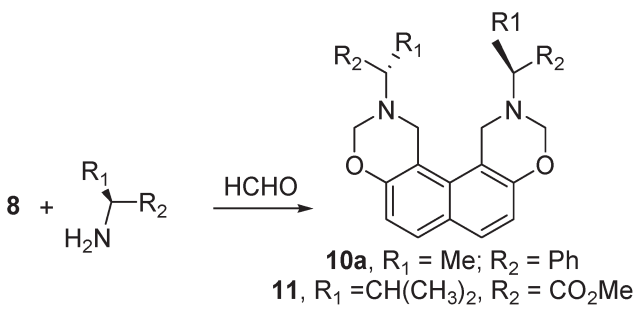


Fig. 2 Variable temperature ^{1}H-NMR of compound **9a**. **[A]** = −20 °C; **[B]** = −35 °C; **[C]** = −58 °C. The down field signal is for Hb and Hb′, remains unchanged at low temperature, while the inside Ha and Ha′ appear at the up field and show broadening of the signal.



Scheme 2 Synthesis of bis-oxazine from (*S*)-α-methylbenzyl amine and (*l*)-methylvalinate.

HPLC analysis of both these compounds on chiral stationary phase column showed single peak, probably indicating the absence of two isomers in solution at ambient conditions.

The single crystal X-ray diffraction analysis of compound **11** was carried out in order to ascertain the deviation in the structure, if any.[15] The ORTEP diagram is presented in Fig. 3 where a slight twist is noticeable between the conformations of two oxazine rings, although the similar deviation between the two bonds of naphthalene C_8–C_{14} and C_{14}–C_{15} is not found, unlike in the case of recently reported compound **6**.[8]

The other isomers of compound **10** were synthesized with appropriate amino compounds (Scheme 3). The enantiomer pair, **10a** and **10b**, was prepared in a single step from **8** and (*S*)-α-methylbenzyl amine and (*R*)-α-methylbenzyl amine, respectively. As per our expectation the optical rotation of **10a** and **10b** was found to be almost similar with opposite sign. The third *meso* isomer **10c** was prepared in stepwise manner from **8**, *via* mono oxazine **12** by selecting the chiral amine in both optical

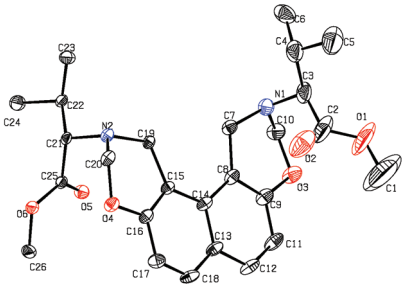
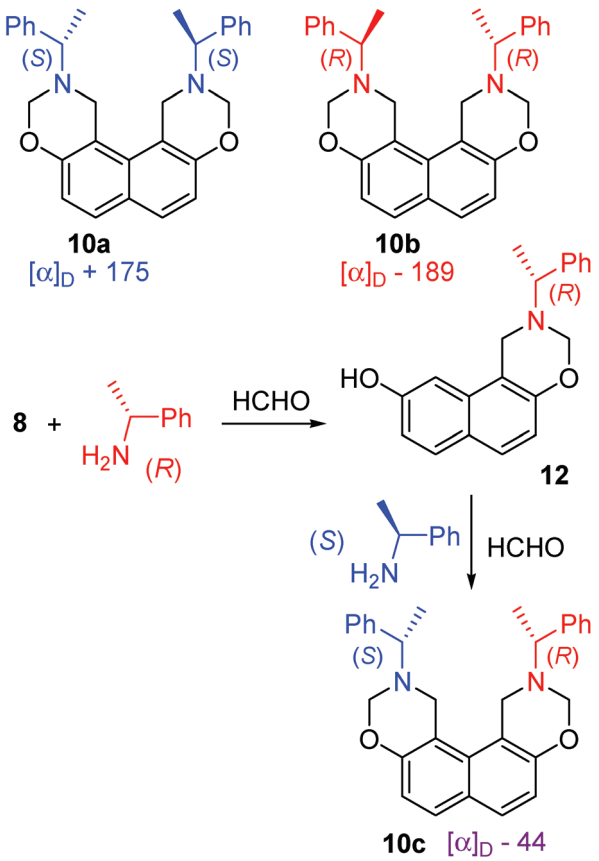


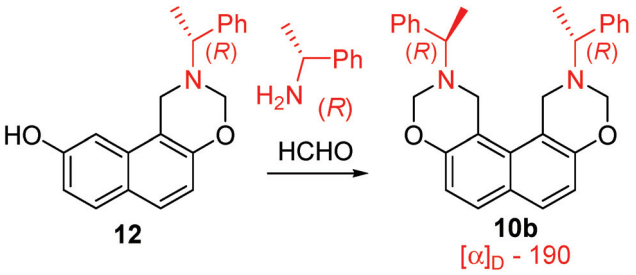
Fig. 3 ORTEP diagram of compound (*l*)-**11**.



Scheme 3 Synthesis of isomers of **10**.

forms. The H-NMR spectra of both isomers of **10a** and **10b** are identical, while that of **10c** is slightly different. The splitting pattern in **10a** and **10c** is almost similar, but very small deviation in the chemical shift was detected.

The optical rotation of a *meso* isomer is expected to be zero, if no other chiral unit is present. The observed optical rotation of **10c** was found to be −44, hence it may indicate the presence of a third chiral element. During the review process a referee expressed the possibility of isomerisation of the chiral centre of one of the oxazines. In order to check this hypothesis the isolated and purified sample of **12** was subjected to the second oxazine formation with the same set of reagents. The optical rotation of the sample, **10b**, prepared in the stepwise manner and the one prepared in single step is almost the same (Scheme 4).



Scheme 4 Stepwise synthesis of **10b**.

That additional chiral element in **10c** could be the helical twist created by the two half chair conformations of 1,3-oxazines pointing towards the opposite directions. If this hypothesis is considered then we may have created an asymmetric synthesis of the helical chiral unit in this molecule. The X-ray crystal analysis of **11** indicates the configuration of the helical system to be *P* if the direction of the two half chair conformations was considered, in reference with the known configuration of the L-valine ester.

In this communication we have presented the syntheses and characterization of a few new naphthalene fused bis-oxazines with the hope of producing twist and deviation in its conformational framework.

Acknowledgements

This work was supported by a generous grant of a SERC project of the Department of Science and Technology, New Delhi (SR/SI/OC-42/2006). We thank DST and CSIR (SRF) for the fellowship to HRT, Mr S. Sahoo of Sun Pharma Advance Research Centre, Vadodara for the NMR analysis and Prof. B.V. Kamath for the facilities and constant encouragement.

Notes and references

1 R. A. Pascal, Jr., *Chem. Rev.*, 2006, **106**, 4809.
2 (*a*) M. S. Newman, H. V. Anderson and K. H. Takemura, *J. Am. Chem. Soc.*, 1953, **75**, 347; (*b*) M. S. Newman and D. Lednicer, *J. Am. Chem. Soc.*, 1956, **78**, 4765.
3 (*a*) S. Grimme, J. Harren, A. Sobanski and F. Vögtle, *Eur. J. Org. Chem.*, 1998, 1491; (*b*) T. J. Katz, *Angew. Chem., Int. Ed.*, 2000, **39**, 1921; (*c*) A. Urbano, *Angew. Chem., Int. Ed.*, 2003, **42**, 3986; (*d*) M. C. Carreno, A. Enriquez, S. Garcia-Cerrada, M. J. Sanz-Cuesta, A. Urbano, F. Maseras and A. Nonell-Canals, *Chem.–Eur. J.*, 2008, **14**, 603; (*e*) Y. Shen and C.-F. Chen, *Chem. Rev.*, 2012, **112**, 1463.
4 A. De Meijere, A. E. Khlebnikov, R. R. Kostikov, S. I. Kozhushkov, P. R. Schreiner, A. Wittkopp and D. S. Yufit, *Angew. Chem., Int. Ed.*, 1999, **38**, 3474.
5 S. Rozen and S. Dayan, *Angew. Chem., Int. Ed.*, 1999, **38**, 3471.
6 R. N. Armstrong, H. L. Ammon and J. N. Darnov, *J. Am. Chem. Soc.*, 1987, **109**, 2077.
7 (*a*) V. Balasubramaniyan, *Chem. Rev.*, 1966, **66**, 567; (*b*) R. W. Franck and E. G. Leser, *J. Org. Chem.*, 1970, **35**, 3932; (*c*) J. E. Anderson, R. W. Franck and W. L. Mandella, *J. Am. Chem. Soc.*, 1972, **94**, 4608; (*d*) J. E. Anderson and R. W. Franck, *J. Chem. Soc., Perkin Trans. 2*, 1984, 1581.
8 H. Aikawa, Y. Takahira and M. Yamagauchi, *Chem. Commun.*, 2011, **47**, 1479.
9 For representative examples of distorted 1,8-disubstituted naphthalenes, see: (*a*) D. Sayferth and S. C. Vick, *J. Organomet. Chem.*, 1977, **141**, 173; (*b*) M. G. Hutchings and I. Watt, *J. Organomet. Chem.*, 1979, **177**, 329; (*c*) J. F. Blount, F. Cozzi, J. R. Damewood, L. D. Iroff, U. Sjöstrand and K. Mislow, *J. Am. Chem. Soc.*, 1980, **102**, 99;

(*d*) R. Soorlyakumaran and P. Boudjouk, *Organometallics*, 1982, **1**, 218; (*e*) S. Cohen, M. Thirumalaikumar, S. Pogodin and I. Agranat, *Struct. Chem.*, 2004, **15**, 339; (*f*) P. Kilian, A. M. Z. Slawin and J. D. Woollins, *Inorg. Chim. Acta*, 2005, **358**, 1719; (*g*) S. M. Aucot, D. Duerden, Y. Li, A. M. Z. Slawin and J. D. Woollins, *Chem.–Eur. J.*, 2006, **12**, 5495; (*h*) V. A. Ozeryanskii, A. F. Pozharskii, A. K. Artaryan, N. V. Vistorobskii and Z. A. Starikova, *Eur. J. Org. Chem.*, 2009, 1241.

10 (*a*) R. W. Alder, P. S. Bowman, W. R. S. Steele and D. R. Winteman, *Chem. Commun.*, 1968, 723; (*b*) F. Gerson, E. Haselbach and G. Plattner, *Chem. Phys. Lett.*, 1971, **12**, 316.

11 (*a*) W. J. Burke, W. A. Nasutavicus and C. Weatherbee, *J. Org. Chem.*, 1964, **29**, 407; (*b*) I. Szatmári and F. Fülöp, *Curr. Org. Synth.*, 2004, **1**, 155; (*c*) B. P. Mathew and M. Nath, *J. Heterocycl. Chem.*, 2009, **46**, 1003.

12 (*a*) H. R. Talele, S. Sahoo and A. V. Bedekar, *Org. Lett.*, 2012, **14**, 3166; (*b*) M. Heydenreich, A. Koch, I. Szatmári, F. Fülöp and E. Kleinpeter, *Tetrahedron*, 2008, **64**, 7378.

13 (*a*) T. Urbański, *Nature*, 1951, **168**, 562; (*b*) J. B. Chylińska, T. Urbański and M. Mordarski, *J. Med. Chem.*, 1963, **6**, 484; (*c*) J. B. Chylińska, M. Janowiec and T. Urbański, *Br. J. Pharmacol.*, 1971, **43**, 649; (*d*) M. Mordarski and J. B. Chylińska, *Arch. Immunol. Ther. Exp.*, 1971, **19**, 533; (*e*) B. P. Mathew, A. Kumar, S. Sharma, P. K. Shukla and M. Nath, *Eur. J. Med. Chem.*, 2010, **45**, 1502; (*f*) N. Gyémánt, H. Engi, Z. Schelz, I. Szatmári, D. Tóth, F. Fülöp, J. Molnár and P. de Witte, *Br. J. Cancer*, 2010, **103**, 178.

14 M. Betti, *Gazz. Chim. Ital.*, 1900, **30 II**, 310.

15 The details of the X-ray structure are deposited at the Cambridge Crystallographic Data Centre (CCDC-882285)†

