Pergamon

Tetrahedron: *Asymmetry* 10 (1999) 4071–4074

TETRAHEDRON: *ASYMMETRY*

Atropisomeric carbohydrate imidazolidines: a novel class of nonbiaryl atropisomers

Martín Avalos,[a] Reyes Babiano,[a,*] Pedro Cintas,[a] Francisco J. Higes,[b] José L. Jiménez,[a] Juan C. Palacios [a] and Guadalupe Silvero [a]

[a]*Departamento de Química Orgánica, Facultad de Ciencias, Universidad de Extremadura, E-06071 Badajoz, Spain*
[b]*Departamento de Química Inorgánica, Facultad de Ciencias, Universidad de Extremadura, E-06071 Badajoz, Spain*

Received 15 September 1999; accepted 27 September 1999

Abstract

Stable axially chiral atropisomers have been prepared by reaction of 2-aminosugars with *o*,*o*′-disubstituted aryl isocyanates and isothiocyanates; these rotationally restricted heterobiaryls constitute a novel class of atropisomers for use in atroposelective reactions.

Recent observations have suggested that nonbiaryl atropisomers may be useful conveyors of chirality for asymmetric induction.[1] However, unlike classical biaryl derivatives which remain among the most useful auxiliaries and catalysts,[2] atroposelective reactions involving nonbiaryl atropisomerically pure ligands are rare.[1,3] An additional interest in the dynamics and control of rotational motion about single bonds include the design of molecular brakes,[4] ratchets,[5] gears,[6,7] propellers,[6] and turnstiles,[8] which could eventually culminate in the development of a molecular machine.[9] Likewise, it is worthy to mention that the biological activity of individual rotamers has just been evaluated in the case of 1,7-naphthyridine-6-carboxamides,[10] indicating a conformational requirement for receptor binding.

We have now studied a different type of molecule as a potential atropisomerically pure auxiliary, readily available from D-glucosamine in a few steps sequence. In previous studies we have shown that unprotected aminosugars can be converted into bicyclic imidazolidinones and imidazolidinethiones by simple reaction with isocyanates and isothiocyanates under acid catalysis.[11] This synthesis can be adapted to induce atropisomerism as a result of hindered rotation about the C–N single bond, if one introduces a large aromatic substituent in the heterocyclic ring. Variable-temperature NMR studies show that some signals of bicyclic systems bearing either a naphthyl group or an *o*-monosubstituted phenyl ring are split into two at 273 K or below, but only a few imidazolidinethiones exhibit atropisomerism at room temperature. Moreover, the barriers to rotation of these bicyclic systems were also estimated from molecular mechanics calculations.[12]

* Corresponding author. E-mail: reyes@unex.es

0957-4166/99/$ - see front matter
PII: S0957-4166(99)00428-0

Fig. 1 displays the transition structures for the interconversion of *M* and *P*[13] rotamers. For *o*-monosubstituted compounds, the lower energy barrier corresponds to a transition structure in which the *o*-hydrogen atom can pass over the 2-amido (X=O) or thioamido (X=S) group without appreciable crowding, whereas an enhanced barrier occurs when the *o*-substituent passes over the 2-position of the heterocyclic ring. Anyway, the barriers to rotation are too low to make it possible to isolate rotational isomers at room temperature, because such barriers must be 23.5 kcal mol^{-1} or more.[14] However, *o*,*o*′-disubstituted derivatives will always exhibit an important steric interaction between a substituent and the C=X group for both transition structures.

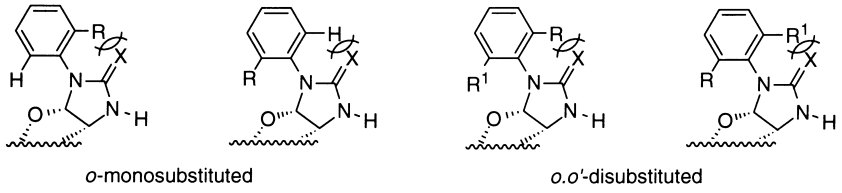
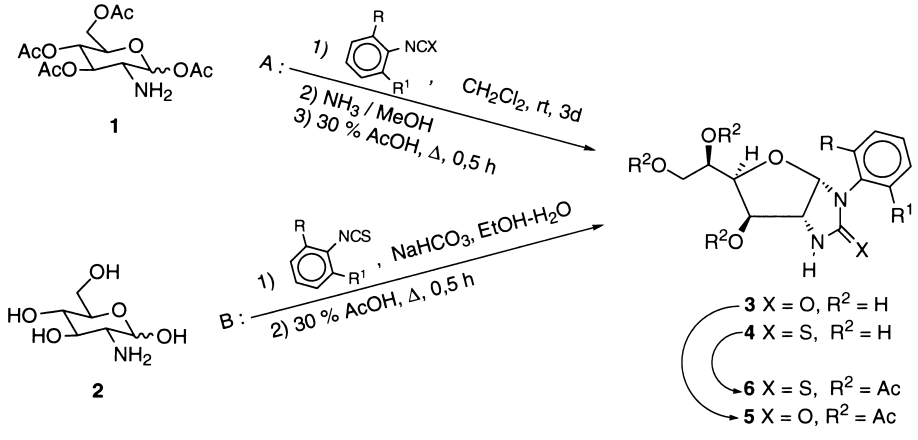


Figure 1.

Realizing that isolation is possible when the internal rotation about the pivotal bond is frozen, and deducing that di-*ortho* substituted nonbiaryls could be resolvable only if the substituents are large enough, we incorporated this structural feature into imidazolidine-2-ones and -2-thiones. Nevertheless, aryl isocyanates di-*ortho* substituted with large groups failed to react with aminosugars in an aqueous medium owing to steric hindrance. Under such circumstances, hydrolysis of the isocyanate occurs leading to the unwanted *N*,*N*′-diarylurea. Conversely, it is possible to accomplish successfully the synthesis of di-*ortho* substituted derivatives starting from *O*-protected aminosugars (e.g. **1**), thereby permitting the condensation with aryl isocyanates in an aprotic solvent (Scheme 1, method A). Subsequent deprotection followed by acid-catalyzed cyclization afforded **3**.



Scheme 1.

The formation of the atropisomeric imidazolidinethiones **4** (Scheme 1, method B) can advantageously be conducted in the presence of water arising from the condensation with the inexpensive D-glucosamine **2**, since the competing hydrolysis of aryl isothiocyanates proceeds slowly. Compounds **3** and **4** together with their *O*-acetylated counterparts **5** and **6** were a mixture of two atropisomers as revealed by NMR analyses (see Table 1), and duplicated signals did not coalesce even at 373 K. The spectra implied that the rotational isomers should be isolable at room temperature. Indeed, *M* and *P* rotamers of **5a** were isolated by preparative chromatography.

Table 1

Compound	X	R	R'	Yield[%]	Rotamer Population[a]
3a	O	Cl	Me	83[b]	65:35
3b	O	Me	Et	66[b]	50:50
4a	S	Cl	Me	62[b]	69:31
4b	S	Me	Et	24[c]	76:24
5a	O	Cl	Me	88	76:24
5b	O	Me	Et	73	53:47
6a	S	Cl	Me	85	81:19
6b	S	Me	Et	65	69:31

[a]Determined by ^{1}H NMR at 400 MHz. [b]Method A. [c]Method B.

The slower-moving spot was identified as a rotamer possessing an axial chirality determined as P by X-ray crystallography (Fig. 2).[14] *M* and *P* atropisomers of **6** (and **4**) should also show a much higher barrier to rotation by virtue of the longer C=S bond length and the larger size of the sulfur atom, and in fact rotational isomers of **6a** were also separable.

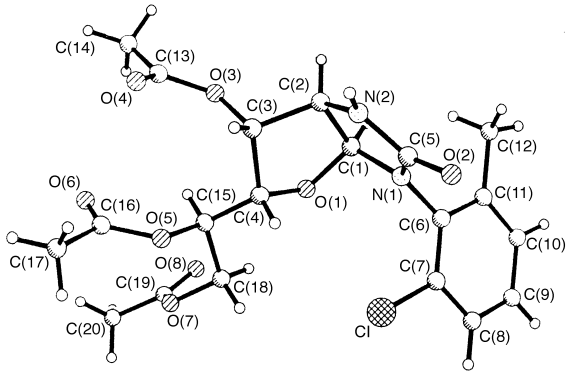


Figure 2.

These amide rotamers share a number of important features. Such substances combine axial chirality of defined configuration along with the inherent chirality provided by several stereocenters. In this context, these diastereomerically pure rotamers could be converted into enantiomeric atropisomers by oxidative degradation of the polyhydroxyalkyl sugar fragment. Likewise, these aromatic amides and thioamides contain lone pairs whose chelation potential could be harnessed for use in the development of nonracemic ligands.

In conclusion, we have found the first examples of nonbiaryl rotamers derived from carbohydrates that can be resolved at room temperature. Further application of these systems in atroposelective reactions as well as exploration of their use as molecular devices are well underway in our laboratories.

Acknowledgements

Financial support by grants from the Ministry of Education and Culture (DGICYT, PB95-0259) and the Junta de Extremadura-Fondo Social Europeo (IPR98-C040) is gratefully acknowledged. We also thank Dr. I. López for his valuable assistance with NMR experiments.

References

1. Clayden, J. *Angew. Chem., Int. Ed. Engl*. **1997**, *36*, 949–951.
2. Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; Wiley: New York, 1994.
3. (a) Curran, D. P.; Qi, H.; Geib, S. J.; DeMello, N. C. *J. Am. Chem. Soc*. **1994**, *116*, 3131–3132; (b) Bowles, P. J.; Clayden, J. M.; Tomkinson, M. *Tetrahedron Lett*. **1995**, *36*, 9219–9222; (c) Thayumanavan, S.; Beak, P.; Curran, D. P. *Tetrahedron Lett*. **1996**, *37*, 2899–2902; (d) Hughes, A. D.; Price, D. A.; Shishkin, O.; Simpkins, N. S. *Tetrahedron Lett*. **1996**, *37*, 7607–7610; (e) Kitagawa, O.; Izawa, H.; Sato, K.; Dobashi, A.; Taguchi, T. *J. Org. Chem*. **1998**, *63*, 2634–2640.
4. Kelly, T. R.; Bowyer, M. C.; Bhaskar, K. V.; Bebbington, D.; García, A.; Lang, F.; Kim, M. H.; Jette, M. P. *J. Am. Chem. Soc*. **1994**, *116*, 3657–3658.
5. Kelly, T. R.; Sestelo, J. P.; Tellitu, I. *J. Org. Chem*. **1998**, *63*, 3655–3665.
6. Eliel, E. L.; Wilen, S. H.; Mander, L. N. *Stereochemistry of Organic Compounds*; Wiley: New York, 1994; p. 1156 and references cited therein.
7. (a) Stevens, A. M.; Richards, C. J. *Tetrahedron Lett*. **1997**, *38*, 7805–7808; (b) Clayden, J.; Pink, J. H. *Angew. Chem., Int. Ed. Engl*. **1998**, *37*, 1937–1939.
8. Bedard, T. C.; Moore, J. S. *J. Am. Chem. Soc*. **1995**, *117*, 10662–10671.
9. (a) Gimzewski, J. K.; Joachim, C.; Schlittler, R. R.; Langlais, V.; Tang, H.; Johannsen, I. *Science* **1998**, *281*, 531–533; (b) Balzani, V.; Gómez-López, M.; Fraser Stoddart, J. *Acc. Chem. Res*. **1998**, *31*, 405–414.
10. Ikeura, Y.; Ishichi, Y.; Tanaka, T.; Fujishima, A.; Murabayashi, M.; Kawada, M.; Ishimaru, T.; Kamo, I.; Doi, T.; Natsugari, H. *J. Med. Chem*. **1998**, *41*, 4232–4239. These carboxamides exist in the form of two separable rotamers, *trans* and *cis* with respect to the amide bond. The potency of the *trans* rotamer is 7–20-fold higher than that of the *cis* rotamer. Moreover, the *trans* isomer can be separated into two stable axially chiral atropisomers, and the (αR)-configuration is required for high-affinity receptor binding.
11. (a) Avalos, M.; Babiano, R.; Cintas, P.; Jiménez, J. L.; Palacios, J. C.; Valencia, C. *Tetrahedron* **1993**, *49*, 2655–2675; (b) *idem*, **1993**, *49*, 2676–2690; (c) *idem*, **1994**, *50*, 3273–3296.
12. Avalos, M.; Babiano, R.; Cintas, P.; Higes, F. J.; Jiménez, J. L.; Palacios, J. C.; Silvero, G.; Valencia, C. *Tetrahedron* **1999**, *55*, 4401–4426.
13. For the configurational notation of axially chiral molecules, see: Eliel, E. L.; Wilen, S. H.; Mander, L. N. *Stereochemistry of Organic Compounds*; Wiley: New York, 1994, p. 1120.
14. Crystal data for (*P*)-**5a**: $C_{20}H_{23}ClN_2O_8$, *Mr*=454.9, crystal dimensions 0.42×0.36×0.28 mm, Siemens P4 diffractometer, MoKα radiation (λ=0.71073 Å), highly oriented graphite crystal monochromator, $\omega/2\theta$ scan mode, $2.0<2\theta<57.0°$, scan speed=variable, 1° to 60° min^{-1}, *a*=8.408(1), *b*=8.163(1), *c*=16.083(1) Å, β=100.12(1)°, *V*=1086.7(4) $Å^3$, ρcalcd=1.390 g cm^{-3}, μ=0.225 mm^{-1}, *Z*=2, monoclinic, space group $P2_1$; 3 standard reflections measured every 97 reflections, of 3917 collected reflections (*h*=−1 to 11, *k*=−1 to 10, *l*=−21 to 21), 3294 were independent (R_{int} =0.0279) and 2970 observed [$F>2\sigma(F)$]; 279 refined parameters, *R*(observed data)=0.0489, *wR*=0.0661, *R*(all data)=0.0544, *wR*=1.838, refinement on F^2. The structure was solved by direct methods and refined by full-matrix least-squares with SHELXTL-IRIS. Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre: CCDC-104131.