

Absolute Configuration Determination in Furfuryl Amines and Hydroxylamines by Circular Dichroism.

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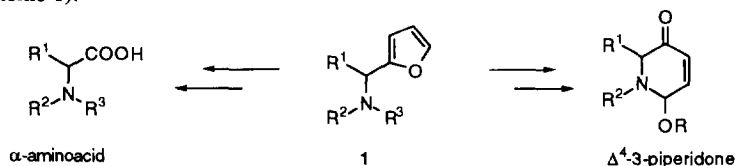
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Abstract: The absolute configuration at the α -centre in furfurylhydroxylamines and N-boc-furfurylamines can be assigned in accordance with the sign of the CE in the range 219-232 nm showed in their CD spectra. Copyright © 1996 Elsevier Science Ltd

Determination of absolute configuration is today a major challenge in several fields of the organic chemistry such as natural products or asymmetric synthesis. The most widely used strategies in this task are synthesis from the "chiral pool", X-ray diffraction analysis or chemical correlations to known compounds. In this context circular dichroism appears as a fast and as useful a technique for absolute configuration assignments when a chromophore lies close to a stereogenic centre.¹

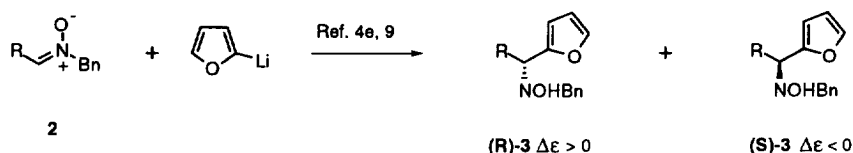
Recently, we have described a rule that correlates the absolute configuration at the α -centre in α -amino-2-alkylthiazoles with the sign of the Cotton effect observed in the range 217-230 nm in their CD spectra.² This correlation has been next applied in the configurational assignments in our enantioselective synthesis directed to this kind of compound.³ Now, we wish to report the utility of circular dichroism spectroscopy in the configurational assignment of related compounds bearing a furan ring.

It is well-known that the furan ring can be considered as an excellent synthetic equivalent of the carboxyl group.⁴ Furthermore, a variety of furyl derivatives can be converted in polyfunctionalized C₄-chains⁵ through oxidative procedures. According to these synthetic analogies, α -substituted furfurylamines **1** are considered as immediate precursors of α -aminoacid^{4d,c} or Δ^4 -3-piperidones,^{5b,c} key intermediates in the synthesis of azasugars^{5f,i} (Scheme 1).



Scheme 1

Chiral furfurylamines has been prepared either by kinetic resolutions from racemic mixtures⁶ or diastereoselective alkylations of furfurylimines.⁷ In the course of our research directed towards the synthesis of natural products, we and Dondoni's group have recently reported new methodology for the synthesis of α -substituted furfurylhydroxylamines **3** by the addition of 2-lithiofuran to chiral nitrones **2** derived from either α -alkoxyaldehydes or α -aminoaldehydes⁸ (Scheme 2). The stereochemical course in the addition step was controlled by precomplexation of nitrones with Lewis acids in the case α -alkoxynitrones^{4c} or by changing the N-protecting group in the case of α -aminonitrones.⁹ The stereochemistry at the new stereogenic centre was determined either by X-ray diffraction analysis or conversion to the corresponding α -aminoacid and comparison with previously described compounds.



Scheme 2

In order to achieve a simpler stereochemical assignment, we have undertaken a circular dichroic study of hydroxylamines **3**. To the best of our knowledge, two reports can be found in the literature concerning the chiroptical properties of furylcarbinols¹⁰ and furylcarbinamines,¹¹ however they used the exciton coupling method which needs the presence of a second chromophore close to the furan ring (i.e. a benzoate group). In our hands, all the hydroxylamines **3** studied showed a single Cotton effect (CE) in the range 219-232 nm, whose sign correlated with the absolute configuration at the α -centre of the furan ring. The chiroptical data of a representative set of the hydroxylamines **3** (Figure 1) are presented in the table 1. Compounds with an R configuration showed a positive CE, while those with S configuration exhibited a negative one. Hence, pairs of hydroxylamines epimeric at the α -centre showed CD spectra with inverted sign of their CE (compare entries 2-3, 4-5, 6-7, 9-10, 11-12, 17-18 and 19-20), and not unexpectedly, enantiomers **3g** and **3h** showed almost symmetric CD spectra. As we realised in our previous work on thiazole derivatives, changes in the nature of the groups at the α -centre of the furan ring, only slightly modified the intensity and position of the CE's, but the sign remained unaffected. We include in this study different substituents such as hydroxyalkyl, aminoalkyl, both open chain and cyclic ones, in order to show the scope and generality of the observed correlation.

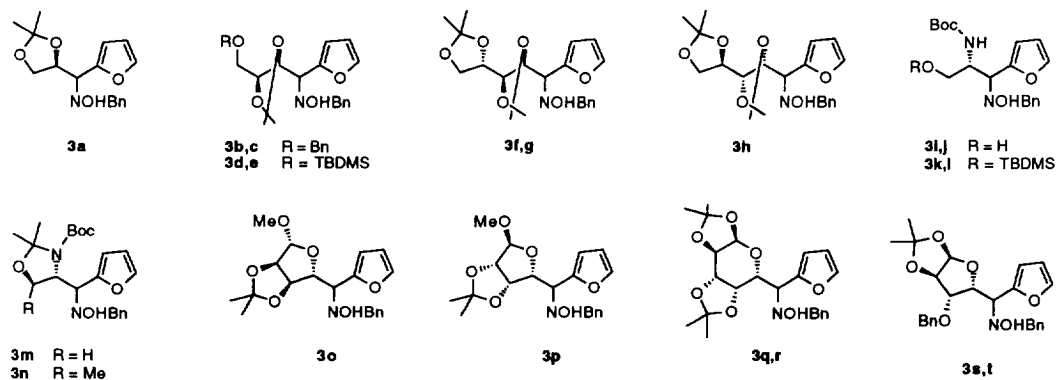
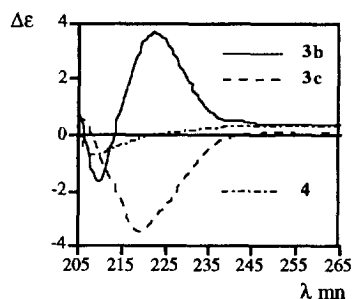
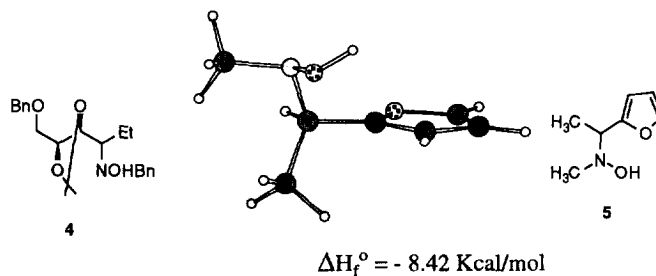
Figure 1: Furfurylhydroxylamines **3** studied by circular dichroism.

Table 1. Chiroptical data of furfurylhydroxylamines **3**.

Entry	Compound	Configuration	$\Delta\epsilon^{\max}$ (λ nm) ^a	$[\alpha]_D^{20}$ (c CHCl ₃)	λ nm (log ϵ)
1	3a	R	+ 3.49 (231)	- 13.2 (1.00)	230 (3.33)
2	3b	R	+ 3.67 (222)	- 14.8 (0.57)	231 (3.41)
3	3c	S	- 3.48 (220)	- 42.7 (1.03)	231 (3.33)
4	3d	R	+ 3.44 (227)	- 1.2 (1.97)	230 (3.40)
5	3e	S	- 3.60 (226)	- 33.5 (1.40)	224 (3.42)
6	3f	R	+ 3.66 (228)	- 28.1 (2.28)	230 (3.44)
7	3g	S	- 3.71 (224)	- 22.5 (1.02)	226 (3.41)
8	3h	R	+ 3.63 (224)	+ 22.2 (1.12)	227 (3.43)
9	3i	R	+ 3.11 (231)	+ 6.6 (0.52)	226 (3.51)
10	3j	S	- 3.37 (231)	+ 79.1 (0.84)	231 (3.47)
11	3k	R	+ 3.72 (225)	+ 9.8 (0.24)	234 (3.52)
12	3l	S	- 4.12 (223)	- 6.0 (3.26)	224 (3.58)
13	3m	R	+ 3.17 (232)	+ 32.6 (0.52)	229 (3.52)
14	3n	R	+ 3.23 (222)	+ 38.8 (0.32)	226 (3.49)
15	3o	R	+ 3.08 (226)	- 3.3 (1.25)	225 (3.51)
16	3p	S	- 3.46 (223)	+ 24.7 (1.60)	230 (3.49)
17	3q	R	+ 3.44 (223)	- 54.8 (1.36)	234 (3.55)
18	3r	S	- 3.68 (225)	- 73.2 (0.25)	225 (3.49)
19	3s	R	+ 3.24 (220)	- 35.6 (1.30)	218 (3.53)
20	3t	S	- 3.99 (219)	- 22.9 (1.52)	228 (3.53)

(a) Recorded in spectrograde methanol on a JASCO J-710 dichrograph at 20° C

The observed Cotton effects must be attributed to the long-wavelength $\pi \rightarrow \pi^*$ transition in the furan chromophore that lies close to the maximum showed in the electronic spectra for that transition. The effect of the benzyl group on the nitrogen atom is negligible as can be inferred from the fact that compound **4**, an analog of **3c** in which the furan ring has been replaced by an ethyl group, only showed a CE at 209 nm with $\Delta\epsilon = -0.71$ (Figure 2).

**Figure 2:** CD spectra of compounds **3b**, **3c** and **4**.**Figure 3:** Chem3D™ representation of the optimised low-energy conformer of **5**.

Defining the major conformers of hydroxylamines **3** present in solution, is difficult with the data in hands, however, semiempirical AM1 calculations¹² for the model compound **5** indicate that the preferred conformations are those in which the hydrogen atom at the contiguous carbon centre to the furan ring is almost eclipsed with the heterocycle-containing plane (Figure 3). For these conformers, hydroxylamino and alkyl groups are located at both sides of the furan ring, and the CE's measured could come from the different rotatory contribution for this groups, in a similar way as has been proposed for phenylcarbinamines.¹³

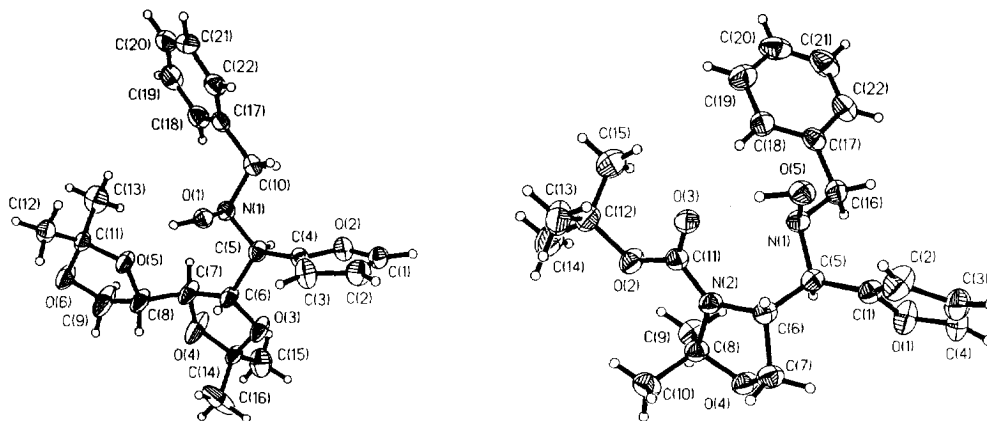
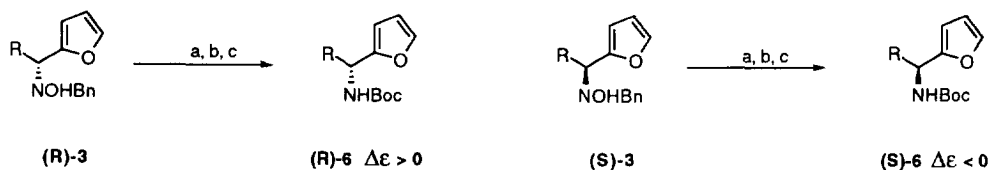


Figure 4: ORTEP representation of compounds **3f** and **3m** showing ellipsoids at 30% probability level.

Moreover, X-ray diffraction analysis of the hydroxylamines **3f** and **3m** reveal that also in solid state the α -hydrogen is almost eclipsed with the furan ring (Figure 4).¹⁴ A similar low-energy conformer has been proposed for furylcarbinol benzoates using molecular mechanics calculations.¹⁰

Furfurylhydroxylamines **3** were conveniently reduced and debenzylated, and the resulting primary amines transformed into the N-boc derivatives **6** (Scheme 3).^{4e} This furfurylamines were converted to the corresponding α -aminoacids^{4e} and used in the synthesis of several derivatives of the Polioxins family.¹⁵



Scheme 3: a) TiCl_3 , MeOH, H_2O ; b) SiO_2 , CH_2Cl_2 , H_2O ; c) Boc₂O, dioxane

The CD spectra of the N-boc-furfurylamines **6** were also examined (Figure 5, table 2), and an analogous behaviour was found. Compounds **6** with R configuration showed a $\Delta\epsilon > 0$ as compounds **3**. Similarly a $\Delta\epsilon < 0$ was found for the S configured compounds **6** as for the parent hydroxylamines. In the same way to compounds **3**, only minor changes were observed with different substituents, which did not affect the sign of the CE's (Figure 6). So, the same correlation proposed for **3** seems to work also in the case of N-boc-furfurylamines **6**. We have included in table 2 the corresponding data for (R)-N-boc-1-(2-furyl)-2-phenylethylamine **6h**;^{7b} this compound showed a $\Delta\epsilon > 0$ as was expected. It is worth noting that it has been recently reported that furfuryl amines only show weak CE's, not suitable for assignment of the absolute

configurations.¹¹ By contrast, in table 2, we show that the measured CE's, while weak, can be useful in that assignment and need not further derivatization in order to use the exciton coupling method.

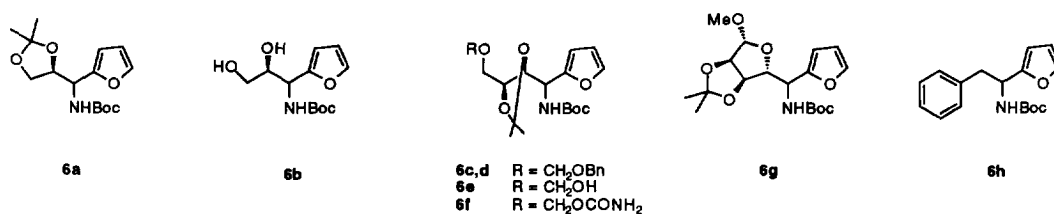


Figure 5: Furfuryl amines **6** studied by circular dichroism.

The origin of the CE's measured with compounds **6** can be justified by the same reasons claimed for compounds **3**. A similar conformational analysis was made (AM1) for the model compound **7**, resulting that, also in this case, the most preferred conformations are those that present the α -hydrogen eclipsed with the heterocyclic plane (Figure 7).

Table 2. Chiroptical data of N-boc-furfuryl amines **6**

Entry	Compound	Configuration	$\Delta\epsilon^{\max}$ (λ nm) ^a	$[\alpha]_D^{20}$ (c CHCl ₃)	λ nm (log ϵ)
1	6a	R	+ 2.17 (224)	+ 2.6 (1.10)	228 (3.34)
2	6b	S	- 1.48 (223)	- 61.0 (0.20)	222 (3.45)
3	6c	R	+3.24 (226)	- 6.3 (1.19)	218 (3.58)
4	6d	S	- 3.20 (222)	- 41.9 (0.47)	222 (3.59)
5	6e	R	+ 2.31 (223)	+ 5.0 (0.85)	229 (3.43)
6	6f	S	- 1.72 (226)	- 24.0 (1.50)	226 (3.33)
7	6g	R	+ 2.61 (224)	- 11.6 (0.26)	222 (3.53)
8	6h	R	+ 3.18 (228)	+ 33.7 (0.40)	230 (3.33)

(a) Recorded in spectrograde methanol on a JASCO J-710 dichrograph at 20° C

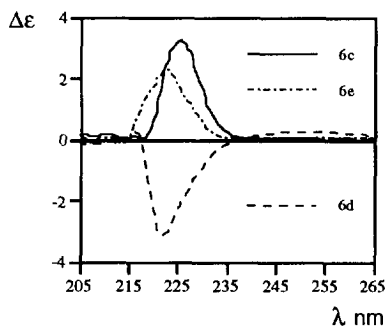


Figure 6: CD spectra of compounds **6c**, **6d** and **6e**.

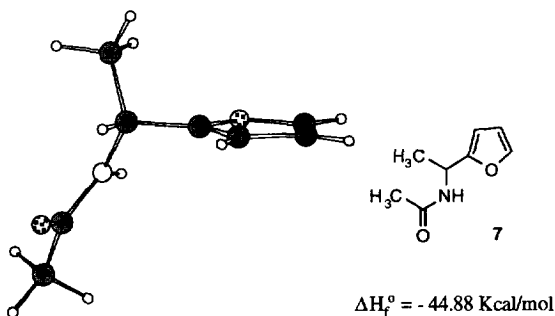


Figure 7: Chem3D™ representation of the optimized geometry for the model compound **7**.

In summary, the usefulness of the dichroism circular method to establish the absolute configuration at the α -position in α -amino-2-alkylfurans has been demonstrated. Further studies involving the generality and the scope of this method, as well as the application in the absolute configuration assignment in other α -substituted furans and the extension to other heterocyclic systems are currently in progress in our laboratory.

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