5-Dethia-5-oxacephams: Toward Correlation of Absolute Configuration and Chiroptical Properties†

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The relationship between chiroptical properties of differently substituted 5-dethia-5-oxacephams and their respective molecular structures was investigated. The amide chromophore of the β-lactam unit in these compounds was found to be nonplanar with a shallow pyramidal configuration at the nitrogen atom. Due to the nonplanarity, the β-lactam system becomes inherently dissymmetric, which is supported by a high magnitude of the n $\rightarrow \pi^*$ CD band. It was also found that the helicity of the lactam moiety in investigated oxacephams is controlled by the absolute configuration at the C(6) carbon atom. On this basis, a helicity rule correlating a positive (negative) sign of the n $\rightarrow \pi^*$ Cotton effect with a negative (positive) O=C−N−C(6) torsional angle for policyclic β-lactam derivatives possessing a nonplanar amide chromophore was formulated.

Introduction

The isolation in 1976 by Beecham[1] of clavulanic acid (**1**), a potent β-lactamase inhibitor, and the synthesis by the Merck group[2] of 5-oxacephalosporins **2**, which are more active than natural congeners, demonstrated that the high biological activity of β-lactam antibiotics is not dependent on the presence of the sulfur atom (Figure 1). Subsequent isolation of other clavams **3**[3] having the (5*S*)-configuration and activity against a number of species of fungi, synthesis of oxapenems **4**[4] that exhibit high activity in both enantiomeric forms, and introduction of 5-oxacephamycins **5** (representing the third and fourth generations of β-lactam antibiotics) to the clinical use by Shionogi[5] have consolidated the trend of a search for the new oxa analogues of penicillins and cephalosporins (Figure 1). Recently, a novel series of 5-oxacephem derivatives exhibiting potent and selective inhibition against human chymase has been reported.[6]

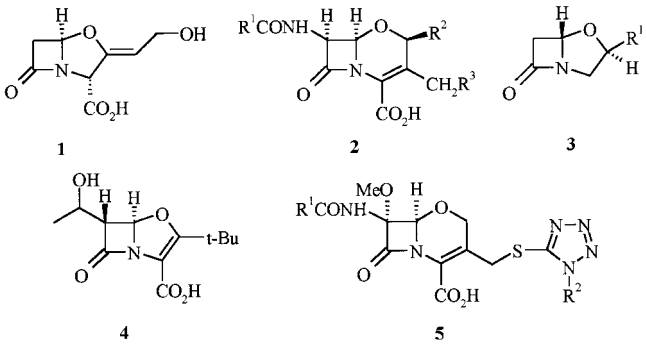

Figure 1. Oxa analogues of β-lactam antibiotics.

The most common strategy for the synthesis of oxabicyclic β-lactams, having the sulfur atom replaced by the oxygen atom, involves nucleophilic substitution at C(4) of the azetidin-2-one ring, which can constitute the ring closure step,[7] or which can be followed by the formation of five- or six-membered rings.[8] The weak point of such a strategy is the low asymmetric induction if the C(3) atom of the azetidin-2-one ring is unsubstituted, or preferential formation of the 3,4-*trans*-functionalized β-lactam ring if C(3) atom bears a substituent.[7,8] Very recently, we have discussed three possible synthetic strategies for the formation of 5-dethia-5-oxacephams.[9]

The biological properties of clavams[1,3] and oxacephems[2,5,6] are closely related to their structures and physicochemical and chemical properties. For example, cla-

† Dedicated to Professor Janusz Jurczak on the occasion of his 60th birthday.

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vam **1** with a (5*R*)-configuration at the ring junction exhibit strong β-lactamase inhibition and weak antibacterial activity while clavams **3** with an (*S*)-configuration at C(5) exhibit antifungal activity. Therefore, development of efficient synthetic methods for new azetidinone derivatives, e.g., oxacephams, and structure−activity relationship studies of the target compounds call for reliable determination of the absolute stereochemistry of these bioactive substances. The configuration of chiral azetidinones has been assigned mostly by chemical correlation[10] and NMR and X-ray analysis[9,11,12] as well as by the combination of all these methods.[13] Circular dichroism (CD) spectroscopy has also been used successfully for this purpose, and it appears to be a convenient, sensitive, and fast technique for the stereochemical assignments of β-lactams and their polycyclic derivatives.[12−15] Although numerous papers on oxacephem[2,5,6,16] and oxacepham[9,13,17−20] derivatives have been published to date, to the best of our knowledge, study of the chiroptical properties of this important class of compounds has not been reported previously. In the present work we attempt to fill this gap, at least to some extent.

The above arguments encouraged us to apply CD spectroscopy systematically to find a stereochemical assignment of oxacephams. The aim of this paper is to establish a general correlation between the signs of CD bands and the stereochemistry of oxacephams, based on the analysis of the CD spectra of a variety of 2-, 3-, 4-, and 7-substituted 5-dethia-5-oxacephams. Moreover, the applicability of both the lactam sector and the helicity rules to the stereochemical analysis of oxacephams will be examined. As model compounds for the present study bi-, tri-, and tetracyclic oxacephams **6**−**34** (Figure 2) have been selected.

Results and Discussion

The electronic absorptions and chiroptical data for compounds **6**−**34** are presented in Table 1. The investigated compounds exhibit, in general, two CD bands around 220 and 190 nm. The 220 nm CD band can be assigned to the n → π^* electronic transition of the β-lactam moiety, whereas the band around 190 nm corresponds to the $\pi \rightarrow \pi^*$ excitation of the same unit. In the case of compounds **13**, **15**, **18**, and **19** an additional short-wavelength CD band is observed at ca. 186 nm. This band probably originates from the $\sigma \rightarrow \pi^*$ transition of the amide group although this band was also attributed to the carbonyl $\pi \rightarrow \pi^*$ transitions.[21] However, the contribution of the substituent at the C(7) carbon atom (including the Si atom), which is the characteristic feature of compounds **13**, **15**, **18**, and **19**, may be responsible for the presence of this 186 nm band. It has to be added that the observed magnitude of the n → π^* CD band in compounds **6**−**34** is relatively strong.

The presence of the *exo* double bond at the position α to the carbonyl group in compounds **23**, **33**, and **34** constitutes an extension of the chromophore system. Such a change of the chromophore is normally manifested in a different shape of the spectrum. As can be seen in Table 1, compounds **23**, **33**, and **34** possess two additional CD bands occurring above 250 and below 190 nm.

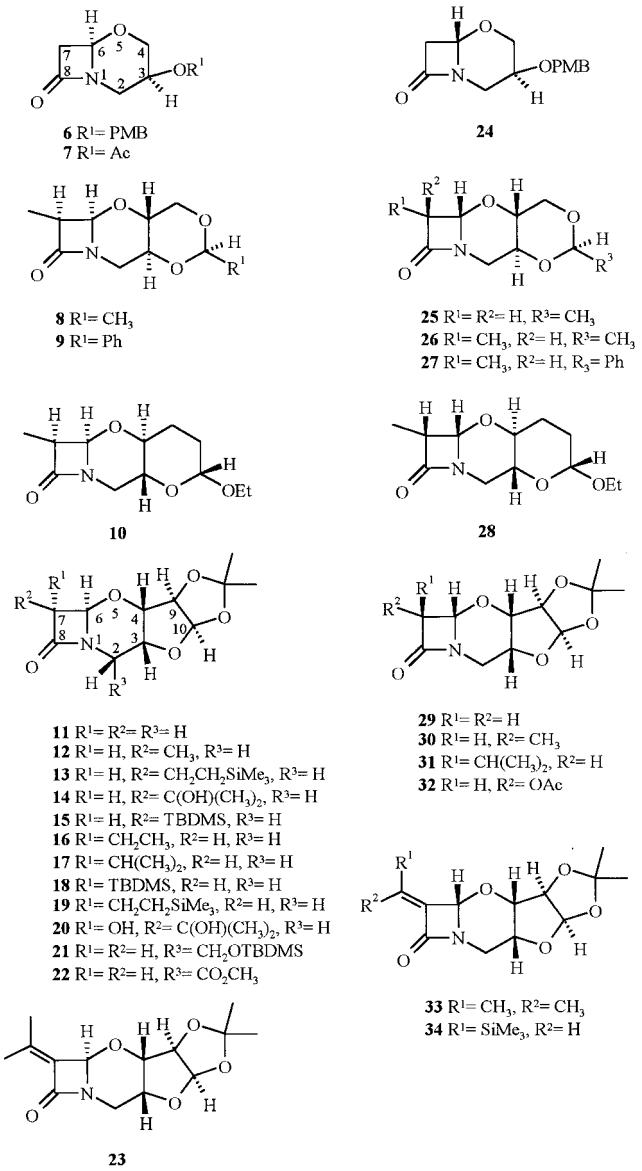

Figure 2. Investigated bi-, tri-, and tetracyclic oxacephams **6**−**34** (the numbering of atoms shown for compound **6** according to an IUPAC recommendation from 1999).

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Table 1. UV and CD Data of Compounds 6−34 Recorded in Acetonitrile[a]

compd	UV ϵ (λ_{max}), L mol^{-1} cm^{-1} (nm)		CD $\Delta\epsilon$ (λ_{max}), deg mol^{-1} cm^{-1} (nm)			
6	9800 (226)[b]	40100 (196)		−8.02 (192.0)	+10.67 (215.5)[b]	
7	580 (221^{sh})	2400 (199)		−2.81 (191.5)	+11.47 (215.5)	
8	300 (221^{sh})	2800 (198)		+2.90 (196.5)	+5.60 (220.0)	
9	280 (222^{sh})[b]	13100 (196^{sh})[c]		+13.17 (192.5)[d]	+5.91 (221.5)[b]	
10	340 (221^{sh})	5750 (197)		−6.42 (192.0)	+7.17 (219.0)	
11	420 (226^{sh})			−6.35 (194.0)	+14.67 (219.0)	
12	610 (221^{sh})			−11.53 (195.5)	+14.53 (222.0)	
13	340 (217^{sh})		+2.2 (185.0)	−8.68 (195.0)	+9.96 (225.0)	
14	420 (221^{sh})	2700 (200)		−3.06 (194.5)	+6.52 (222.0)	
15	330 (223^{sh})		+3.5 (187.0)	−0.60 (196.5)	+16.07 (219.5)	
16	460 (224^{sh})	8200 (195)		−6.00 (196.0)	+9.60 (223.5)	
17	530 (223^{sh})			−6.49 (196.5)	+10.05 (224.5)	
18	970 (222^{sh})	3300 (200)	+3.6 (187.0)	−0.31 (197.0)	+8.56 (220.5)	
19	780 (222^{sh})	9800(195)	+2.0 (184.0)	−7.49 (196.5)	+9.79 (225.0)	
20	540 (221^{sh})	3450 (201)		+7.90 (194.5)	+2.86 (234.5)	
21	300 (224^{sh})			1.24 (193.0)	+15.59 (220.5)	
22	330 (222^{sh})			*e* (196.0)	+10.36 (218.5)	
23	16850 (216)	6100 (247^{sh})	*f* (187.0)	−9.70 (203.5)	+8.69 (235.5)	−1.33 (271.0)
24	13900 (226)[b]	52500 (195)		−6.16 (198.0)	−11.68 (217.0)[b]	
25	400 (221^{sh})	7500 (196)		+14.97 (189.0)	−14.78 (216.5)	
26	600 (221^{sh})	5900 (196)		+8.66 (191.0)	−8.06 (219.0)	
27	740 (221^{sh})[b]	2100 (198)		−11.87 (191.5)	−15.69 (219.0)[b]	
28	480 (221^{sh})			−3.55 (198.5)	−4.61 (220.5)	
29	310 (221^{sh})			+7.62 (190.0)	−10.26 (215.0)	
30	400 (221^{sh})			+9.80 (191.5)	−9.38 (218.5)	
31	1020 (222.0)			+9.84 (192.0)	−8.98 (220.0)	
32	520 (222^{sh})	3300 (199)		+11.61 (190.5)	−7.10 (222.5)	
33	14900 (215)	4090 (245^{sh})	−1.9 (187.0)	+1.38 (204.0)	−3.57 (228.5)	+1.96 (253.0)
34	15300 (208)	5140 (241^{sh})	+3.0 (190.0)	−5.62 (214.0)	−5.69 (234.5)	+5.49 (269.5)

[a] UV and CD values are given as ϵ (L mol^{-1} cm^{-1}) and $\Delta\epsilon$ (deg mol^{-1} cm^{-1}), respectively. [b] An additional band at 260−270 nm is observed. [c] An additional band at ca. 205 nm is observed. [d] An additional positive CD band at ca. 209 nm is observed. [e] Positive minimum. [f] Negative minimum

In the UV spectra, the n → π* band at ca. 220 nm is not sufficiently separated and is observed as a shoulder of the second absorption band, most probably of the π → π* origin, with its maximum out of the measurement range, i.e., below 190 nm, in most cases. Compounds **6**, **9**, **24**, and **27** exhibit an additional weak absorption band at ca. 260 nm associated with the ^1L_b excitation of the aromatic group present in the molecule. This aromatic substitution also influences the remaining bands in the UV spectrum, as can be seen from Table 1. For the sake of simplicity, the CD and UV bands in the aromatic spectral range are only indicated in Table 1.

The data collected in Table 1 demonstrate that the investigated compounds fall under two different classes with respect to their CE (Cotton effect) sign of the n → π* transition. In the first class, consisting of compounds **6**−**23**, the sign of the long-wavelength CD band is positive, whereas in the second group, represented by compounds **24**−**34**, this band is negative. Except for compounds **8**, **9**, and **20** and **24**, **27**, **28**, and **34** from the first and second classes, respectively, the short-wavelength band located around 196 nm has a sign opposite that of the n → π* band.

With respect to their molecular structure, all compounds of the first group differ from the corresponding compounds of the second group by the configuration of the stereogenic center at C(6), which for both groups remains in the enantiomeric relationship. Following the stereochemical models of the [2 + 2] cycloaddition reaction, which, in many cases, proceeds with excellent stereoselectivity,[17,22] compounds **6**−**23** should be (6*R*)-isomers, while oxacephams **24**−**34** should be (6*S*)-isomers. These findings are additionally corroborated by the X-ray data obtained for the representative compounds of both groups, namely, compound **11** for the first group and compound **29** for the second group (Figure 3). Moreover, the X-ray data obtained previously for compounds **8**,[23] **20**,[20] **25** and **26**,[23] **33**,[13] and **34**[13] are in accordance with the above prediction. On this basis, it can be unambiguously established that the absolute configuration at C(6) is (*R*) in compounds **6**−**23** and (*S*) in the series **24**−**34**.

For compounds **8**, **20**, **25**, **26**, and **34**, with their structures and stereochemistry confirmed by X-ray analysis, the CD curves in the solid state were also measured (Table 2). The obtained results are in good agreement with the respective data recorded in solution, as can be seen from Tables 1 and 2, thus providing additional proof that the same molecular species are present in the solid state as well as in solution. This indicates that the solute−solvent interactions, which may affect the CD spectra considerably for both conformational and vicinal effects, are negligible in these cases and points out that the CD observed is largely a molecular property. Therefore, the analysis of the CD data for the purpose of determination of the absolute configuration of oxacephams **6**−**34** can be performed on the basis of chiroptical data obtained for solutions.

Comparison of the CD spectra presented in Table 1 indicates that oxacephams **6**−**23** and **24**−**34** give CD spectra with opposite signs of their n → π* CE; i.e., compounds of both groups represent local enantiomers. Thus, one can conclude that the stereochemistry at C(6) is responsible for the sign of the n → π* CD band. As can be seen from Table 1 and Figure 2, this statement holds independently of the kind and position of substituents

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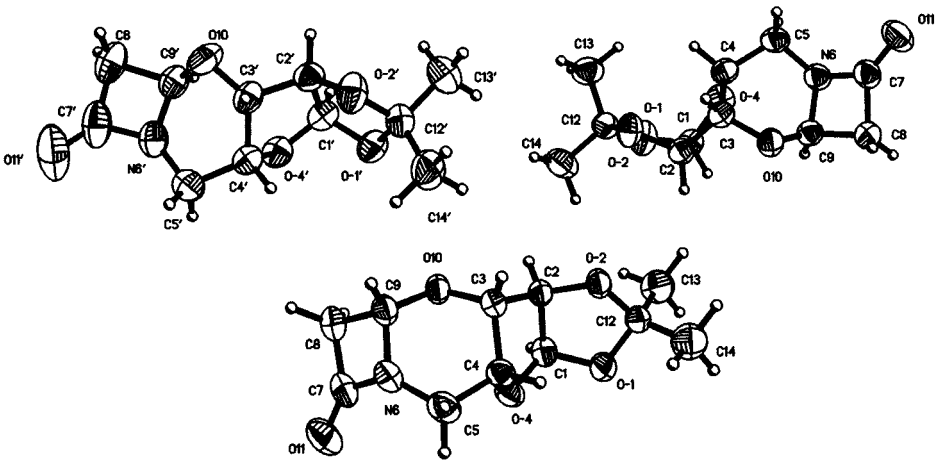

Figure 3. Crystal structures of compounds **11** (top) and **29** (bottom) with the crystallographic numbering scheme. Thermal ellipsoids are shown at the 30% probability level. In the case of compound **11** two independent molecules were found in the asymmetric unit.

Table 2. Solid-State CD Data of Compounds 8, 20, 25, 26, and 34 Measured in a KBr Matrix in the 200−350 nm Range and Given as Δε (deg mol^{-1} cm^{-1})[a]

compd	CD Δε (λ_{max}), deg mol^{-1} cm^{-1} (nm)	compd	CD Δε (λ_{max}), deg mol^{-1} cm^{-1} (nm)	
8[b]	+28.23 (233.0)	**26**	−6.86 (224.0)	
20	+3.68 (230.0)	**34**	−4.23 (244.0)	+3.96 (275.0)
25	−10.54 (217.0)			

[a] Δε values are approximately calculated on the basis of the density of KBr equal to 2.75 g cm^{-3}. [b] The spectrum was taken in a Nujol mull, and the CD value is given in millidegrees.

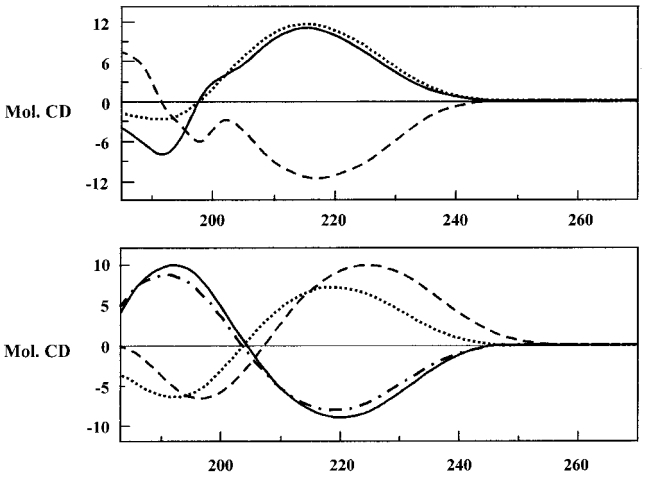

Figure 4. CD spectra of oxacephams **6** (—), **7** (···), and **24** (---) (top) and **10** (···), **17** (---), **26** (·-·), and **31** (—) (bottom) taken in acetonitrile.

present in the oxacepham moiety. However, the presence of substituents influences the intensity of individual CD bands. CD spectra of representative oxacephams are presented in Figure 4.

Compounds **23**, **33**, and **34**, with the C(7) *exo*-methylene group incorporated into the *β*-lactam ring, also conform to this prediction. It is worth mentioning that the comparison of the C(7)−C(8) bond lengths in the oxacepham **23** and compound **11** shows a difference of 2.4 pm. This shortening of the C(7)−C(8) bond in compound **23** indicates an interaction of the *exo* double bond with the *β*-lactam chromophore system. Therefore, the

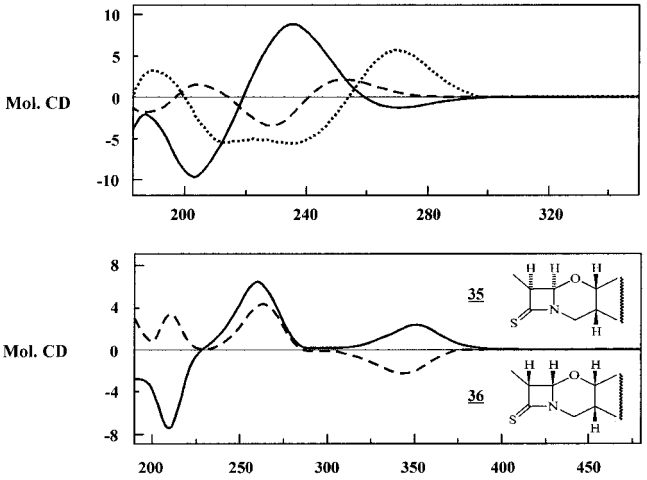

Figure 5. CD spectra of oxacephams **23** (—), **33** (---), and **34** (···) (top) and thionooxacephams **35** (—) and **36** (---) (bottom) recorded in acetonitrile.

shape of the CD curves for compound **23** as well as for **33** and **34** differs significantly compared to those found for compounds without an *exo* double bond. Due to the perturbing influence of the *exo* double bond, the position of the n → *π** CD band is bathochromically shifted around 10 nm in comparison with those of compounds **6**−**22** and **24**−**32**. However, the sign of the CD band at ca. 230 nm remains in a mirror image relationship depending upon the configuration at C(6), as can be seen for compound **23** with an (*R*)-configuration at the C(6) carbon atom versus compounds **33** and **34**, both with an (*S*)-configuration at the same carbon atom (Figure 5). Moreover, this is also in agreement with the sign of the 220 nm band displayed by oxacephams with the same configuration but without the *exo*-methylene group. Thus, compounds **23**, **33**, and **34** also conform to the discussed regularity.

To achieve a better resolution of the CD bands and, consequently, a better understanding of the *β*-lactam chromophore in the oxacephams in question, oxacephams **12** and **30** were converted to their respective thiono equivalents **35** and **36**, by thionation reaction with Lawesson's reagent.[24] As demonstrated in Figures 3 and 6 and Table 4, the structural features including the

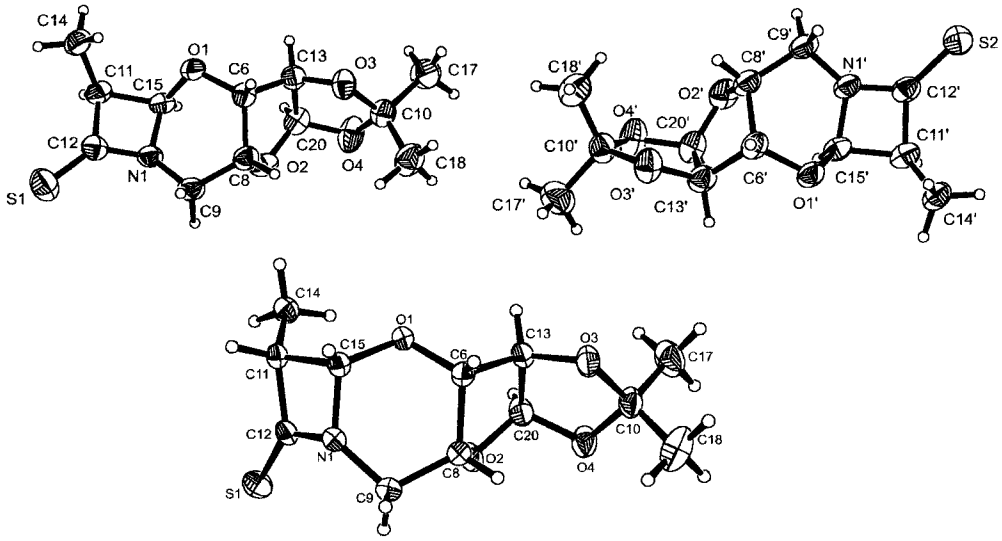

Figure 6. Crystal structures of compounds **35** (top) and **36** (bottom) with the crystallographic numbering scheme. Thermal ellipsoids are shown at the 30% probability level. In the case of compound **35** two independent molecules were found in the asymmetric unit.

Table 3. UV and CD Data of Compounds 35 and 36 Recorded in Acetonitrile[a]

compd	UV ϵ (λ_{max}), L mol^{-1} cm^{-1} (nm)			CD $\Delta\epsilon$ (λ_{max}), deg mol^{-1} cm^{-1} (nm)		
35	10030 (200)	26800 (262)	130 (338)	−7.53 (210.0)	+6.28 (260.0)	+2.23 (351.5)
36	4900 (202)	17100 (262)	47 (337)	+3.23 (210.5)	+4.19 (263.5)	−2.27 (344.0)

[a] UV and CD values are given as ϵ (L mol^{-1} cm^{-1}) and $\Delta\epsilon$ (deg mol^{-1} cm^{-1}), respectively.

crystal packing of thiono-β-lactams **35** and **36** are very similar to those of the original β-lactams studied.

It is well-known that in thiocarbonyl compounds, in general, the UV and CD bands are shifted appreciably to the red.[25] The sign of the n $\rightarrow \pi^*$ band for carbonyls and thiocarbonyls is, however, the same provided that their chiral environment remains identical. The UV spectra of compounds **35** and **36** show a weak low-energy band around 340 nm corresponding to the n $\rightarrow \pi^*$ transition, the intense band at 262 nm arising from the $\pi \rightarrow \pi^*$ excitation, and a moderately intense band at 200 nm (Table 3).[25−27] The polarization direction of this short-wavelength transition, most probably of $n_\sigma \rightarrow \pi^*$ origin,[25] is nearly orthogonal to the polarization direction of the $\pi \rightarrow \pi^*$ band.

The CD spectra of thionocephams **35** and **36**, presented in Table 3 and Figure 5, show the presence of three well-developed bands in the 450−200 nm range. These bands correspond nicely with the absorption bands. Inspection of the data shown in Tables 1 and 3 indicates that thiono-β-lactams **35** and **36** exhibit the same CE sign for the n $\rightarrow \pi^*$ transition as the parent β-lactams **12** and **30**, respectively. On the other hand, the 260 nm band, of $\pi \rightarrow \pi^*$ origin, has the same sign for both thionocephams. The third, short-wavelength CD band located at 200 nm is of opposite sign for compounds **35** and **36**. This band, however, is absent in the spectra of the parent oxacephams. Therefore, it seems to be justified to use the principal transition of amide n $\rightarrow \pi^*$ character for the purpose of correlation of the CD signs and molecular geometry in oxacephams **6**−**34**. Moreover, the transition, easily observed in the CD spectrum, is accurately described by the theoretical methods and should be diagnostic for the amide chromophore.[28−30] Therefore, the rules developed for the amide chromophore evaluate only the bands of n $\rightarrow \pi^*$ excitation.[28,31−35]

There are several sector and helicity rules established for the correlation between the structure and CE signs of the n $\rightarrow \pi^*$ transition, e.g., the β-lactam octant rule,[31−33] Weigang's sector rule,[28] and Ogura's[35] and Wolf's helicity rules.[36] Application of these rules to the correlation of the spatial arrangement of the studied oxacephams with the sign of the n $\rightarrow \pi^*$ CE indicates a disagreement between observed and predicted CE signs. Since compounds **6**−**34** with rigid or extremely rigid bi-, tri-, and tetracyclic skeletons are restricted in their conformational mobility, factors other than the presence of different conformers in the solution have to be responsible for this inconsistency. The conformational restric-

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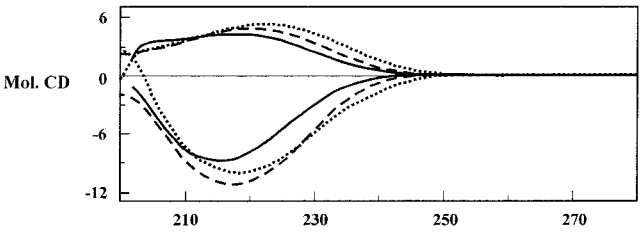
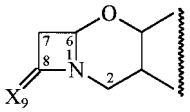


Figure 7. Solvent dependence of representative oxacephams **8** (top) and **24** (bottom) recorded in acetonitrile (---), ethanol (—), and methylcyclohexane (···).

Table 4. Selected Torsional Angles (deg) and Pyramid Height (pm) for the N Atom Determined by the X-ray Diffraction Method[a]



compd	7−8−1−6	9−8−1−2	9−8−1−6	7−8−1−2	pyramid height
8	7.4(1)	−24.1(5)	−170.8(2)	153.6(2)	25.0(2)
11	5.1(2)	−26.6(4)	−172.3(3)	150.9(2)	24.3(2)
25	−8.5(2)	27.0(4)	171.3(3)	−152.8(2)	25.6(2)
26	−10.6(2)	24.1(5)	167.9(3)	−154.4(3)	26.0(3)
29	−2.5(2)	23.9(4)	−178.0(3)	−156.6(2)	17.3(2)
33	−4.9(6)	24.0(1)	176.0(1)	−157.2(7)	18.0(3)
34	−8.2(5)	20.7(1)	169.3(7)	−156.8(6)	21.7(6)
35	4.5(3)	−23.5(6)	−172.8(3)	153.5(4)	22.0(2)
36	−7.2(2)	15.0(4)	170.7(2)	−162.9(1)	16.2(2)

[a] For compounds **8**, **11**, **25**, **26**, **29**, **33**, and **34** X = O, whereas for **35** and **36** X = S.

tions are reflected by the absence of a solvent effect, as shown for the representative oxacephams **8** and **24** in Figure 7.

Examination of the X-ray data should provide more information about the geometry of the chromophore which is necessary for the proper analysis of the chiroptical data of the studied oxacephams, and thus it should help to explain the discrepancy in the observed and predicted CE signs. The values of the torsional angles of the β-lactam ring, shown in Table 4, indicate a significant degree of deviation from the planarity of the azetidinone chromophore in the analyzed oxacephams, as evident, for example, from the values of the torsional angle O═C(8)—N—C(6) (Table 4). Furthermore, a pyramidal configuration of the N atoms is found with the smallest pyramid height of 17.3 pm and the highest of 26.0 pm for β-lactams **29** and **26**, respectively.

The loss of planarity causes an intrinsic dissymmetry of the analyzed system. Since the torsional angles of O−C(8)−N−C(6) and O−C(8)−N−C(2) structural units are different from 180° and 360° (or 0°), these units represent two skewed systems which can be treated as inherent dissymmetric chromophores, both contributing to the CD. The inherent dissymmetric chromophores, in general, give strong contributions to the CEs. This is in accordance with the experimental data presented in Table 1, which shows relatively strong magnitudes for both the n → π* and π → π* bands. Thus, the observed magnitude of the n → π* CE in oxacephams **6**−**34** is a consequence of the inherent dissymmetry of the chromophore. Contributions from other rings and substituents (chiral second and third spheres, according to Snatzke[34]) should also be considered, but the sign-determining factor for the n → π* band is the helicity of the chromophore (chiral first sphere[34]).

The nonplanarity of the chromophore excludes the possibility of application of the sector rules for the prediction of the n → π* CE sign, since these rules were developed for the planar amide chromophores only. In such cases a helicity rule should in principle be able to correlate the chiroptical properties and structure. However, for oxacephams **6**−**34** a breakdown of Ogura's[35] and Wolf's[36] helicity rules was found. Therefore, some other relation between the CD spectra and geometry should be established to accomplish a valid stereochemical assignment. It is noteworthy that both helicity rules were developed for the monocyclic β-lactams, which are known to prefer an sp^2 nitrogen, and some limitations of the applicability of these rules to the bicyclic β-lactams can be found in the literature.[37]

Recently, a "spiral rule" based mostly on the CD results obtained for the nonplanar α-lactams and monocyclic β-lactams was proposed.[38] This rule correlates the positive torsional angle O═C—N—C with a negative n → π* CE. The opposite relation is observed for a negative torsional angle; i.e., in this case a positive CE is observed. This spiral rule, in general, is valid for oxacephams **6**−**34** (see Tables 1 and 4). On the other hand, the helicity of the lactam moiety in the discussed oxacephams is controlled by the stereochemistry at the C(6) carbon atom, as was shown above. Therefore, it appears to be possible to directly correlate this structural parameter and the sign of the n → π* CE. Experimental data presented in Table 4 indicate that oxacephams **8** and **11** show a negative value of the torsional angle O(9)−C(8)−N(1)−C(6), whereas oxacephams **25**, **26**, **33**, and **34** show a positive value of the torsional angle for the same structural unit. Thus, it can be concluded that oxacephams with a negative O(9)−C(8)−N(1)−C(6) torsional angle make a positive contribution to the CD of the n → π* transition whereas oxacephams with a positive O(9)−C(8)−N(1)−C(6) torsional angle make a negative one. This statement can be extended to all investigated oxacephams **6**−**34**. It is worth noting that thionolactams **35** and **36** possessing a nonplanar chromophore, similarly to β-lactams **6**−**34** (Table 4), undergo the same regularity. Among the oxacephams listed in Table 4, an exceptional behavior was displayed by the oxacepham **29** with its negative n → π* CD band and the negative torsional angle O(9)−C(8)−N(1)−C(6). As indicated by the values of torsional angles O(9)−C(8)−N(1)−C(6) and C(7)−C(8)−N(1)−C(6), which are equal to −178.0° and −2.5°, respectively, the four-membered β-lactam ring in oxacepham **29** is nearly planar. The inherent dissymmetry of the chromophore is due to the skewness of the β-lactam unit as indicated by the positive torsional angle O(9)−C(8)−N(1)−C(2) amounting to 23.9°. In this case the negative sign of the n → π* band correlates with the positive torsional angle O(9)−C(8)−N(1)−C(2) only and not with both O(9)−C(8)−N(1)−C(2) and O(9)−C(8)−N(1)−C(6) (Table 4).

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Conclusions

The molecular structures and chiroptical properties of 2-, 3-, 4-, and 7-substituted 5-dethia-5-oxacephams **6**−**34** were investigated by means of X-ray diffraction and circular dichroism, respectively. The most important feature of the molecular structure of oxacephams is the nonplanarity of the amide chromophore and the pyramidal configuration of the N atoms. The latter feature may also have a predictive value in relation to the biological activity of the studied oxacephams, since, according to the literature,[39] the pyramidal hybridization at the β-lactam nitrogen has been found to be one of the factors that may increase the activity of β-lactam antibiotics.

The nonplanarity of the β-lactam chromophore system causes its intrinsic dissymmetry and is expressed in a right or left helicity depending upon the absolute configuration at the C(6) carbon atom. This means that the sense of chirality of the chromophore is controlled by the (6*R*) or (6*S*) absolute configuration and is also the sign-determining factor for the n → π* CD band. On this basis, a rule for the prediction of the n → π* CE sign for policyclic β-lactam derivatives possessing a nonplanar amide chromophore can be formulated as follows: a positive (negative) O=C(8)−N(1)−C(6) torsional angle of the β-lactam subunit correlates with a negative (positive) sign of the n → π* CE.

The applicability of the rule was also checked for other classes of biologically important cyclic β-lactam derivatives such as clavams, penicillins, and cephalosporins. Our results obtained for clavams are in accordance with the rule.[12] Moreover, the stereochemistry of penicillins[21] and cephalosporins,[40] predicted using the proposed rule on the basis of experimental chirooptical data, appears to be in accordance with appropriate X-ray data, available from the Cambridge Crystallographic Data Centre. This finding validates the proposed rule for those classes of compounds also. Therefore, it can be concluded that the proposed rule is obeyed by a large variety of cyclic β-lactam derivatives. For the sake of nomenclature clarity, we suggest to call this rule "the helicity rule" instead of "the spiral rule" because a spiral in the strict mathematical sense is a plane curve.[41]

Experimental Section

General Methods. Melting points were determined on a Boetius hot-stage apparatus with a microscope and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on Varian Gemini AC-200 and Brucker Avance 500 spectrometers at ambient temperature. Chemical shifts (δ) are reported in parts per million, using residual solvents as internal standard. Optical rotations were measured using a JASCO P 2010 polarimeter at ambient temperature. IR spectra were recorded on a Perkin-Elmer FT-IR Spectrum 2000 spectrophotometer. Mass spectra were determined with an AMD 604 Inectra GmbH spectrometer. UV spectra were measured on a Cary 100 spectrophotometer in acetonitrile. CD spectra were recorded between 180 and 400 nm at room temperature with a JASCO J-715 spectropolarimeter using acetonitrile solutions. Solutions with concentrations in the range 0.8×10^{-4} to 1.2×10^{-3} mol·dm^{-3} were examined in cells with path length 0.1 or 1 cm. In some cases CD and UV spectra were taken in methylcyclohexane and ethanol solutions. For solid-state CD measurements a crystalline compound (1−3 mg) and KBr (280−300 mg) were ground and formed into a disk which was rotated around the optical axis during the entire measurement using original JASCO equipment for this purpose.

Merck silica gel 60 (230−400 mesh) was used for flash chromatography, and analytical thin-layer chromatography was performed on Merck percolated silica gel 60-F_{254} plates.

Source of Compounds. Compounds **6**,[9] **8**,[23] **11**,[43] **12** and **13**,[19] **14**,[20] **15**,[18] **16**,[44] **17**,[20] **18**,[18] **19**,[19] **20**,[20] **21** and **22**,[45] **23**,[13] **24**,[9] **25** and **26**,[23] **29**,[43] **30**,[19] **31** and **32**,[20] and **33** and **34**[13] were obtained according to literature data.

Diastereomers **9** and **27** were obtained by the standard method[23] involving [2 + 2] cycloaddition of chlorosulfonyl isocyanate and 1,3-*O*-benzylidene-5-*O*-prop-1′-enyl-4-*O*-mesyl-L-erythrotetritol followed by the intramolecular alkylation of the β-lactam nitrogen atom in the cycloadduct, and chromatographical separation of the resulting diastereomers. Full experimental procedures and analytical and spectroscopic details will be published elsewhere.[42]

Diastereomers **10** and **28** were obtained by the standard method[43−45] involving [2 + 2] cycloaddition of chlorosulfonyl isocyanate and ethyl 1,3-dideoxy-6-*O*-mesyl-4-*O*-prop-1′-enyl-α-D-erythrohexopyranoside followed by the intramolecular alkylation of the β-lactam nitrogen atom in the cycloadduct, and chromatographical separation of the resulting diastereomers. Full experimental procedures and analytical and spectroscopic details will be provided elsewhere.[42]

Preparation of (3*S*,6*R*)-3-*O*-Acetoxy-5-oxacepham (7). To a suspension of anhydrous $SnCl_2$ (2 mg, 0.011 mmol), **6**[9] (29 mg, 0.11 mmol), and anisole (18 μL, 0.165 mmol) in CH_2Cl_2 (1 mL) was added TMSCl (41 μL, 0.33 mmol) at room temperature.[46] The reaction mixture was stirred for 1 h at room temperature, and quenched with saturated $NaHCO_3$ solution (1 mL). The organic material was extracted with AcOEt, dried (Na_2SO_4), and evaporated. The crude product was purified by flash chromatography (5% MeOH in AcOEt) to give 0.012 g (77%) of suitable alcohol as an oil, which was characterized as the 3-*O*-acetate **7** (76%): mp 82−85 °C (from AcOEt/hexane); $[\alpha]^{22}_D$ +95.8 (*c* 0.15, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.98 (d, 1H, J = 3.0 Hz, H-6), 4.70 (m, 1H, H-3), 4.17 (dt, 1H, J = 2.3 and 13.2 Hz, H-2a), 3.93 (ddd, 1H, J = 1.3, 2.2 and 14.9 Hz, H-4a), 3.83 (dd, 1H, J = 1.2 and 13.2 Hz, H-2b), 3.21 (m, 2H, H-4b, H-7a), 2.93 (d, 1H, J = 15.2 Hz, H-7b), 2.12 (s, 3H, Ac); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 170.60, 167.90, 76.93, 66.72, 64.09, 45.97, 42.18, 21.05; IR (film, CH_2Cl_2) 1756, 1732 cm^{-1}; HRMS (LSIMS) *m*/*z* $(M + H)^+$ calcd for $C_8H_{12}O_4N$ 186.07663, found 186.07825. Anal. Calcd for $C_8H_{11}O_4N$ (185.184): C, 51.89; H, 5.98; N, 7.56. Found: C, 52.07; H, 6.05; N, 7.48.

Preparation of (3′*S*,4′R)-5-Deoxy-1,2-*O*-isopropylidene-3-*O*:5-*C*-(3′-methylazetidin-2′-thion-1′,4′-diyl)-α-D-xylofuranose (35). The β-lactam **12** (0.15 g, 0.59 mmol) and Lawesson's reagent (0.16 g, 0.4 mmol) were refluxed in toluene (3 mL) for 1.5 h under a N_2 atmosphere. After evaporation of the solvent, the crude product was purified by flash column chromatography on silica gel (AcOEt/toluene/hexane, 1.5:1.0:7.5, v/v/v) to give **35** (0.048 g, 30%) as colorless crystals: mp 128−132 °C (from AcOEt/hexane); $[\alpha]^{22}_D$ +129.6 (*c* 0.41, CH_2Cl_2); ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.96 (d, 1H, J = 3.8 Hz, H-10), 5.35 (d, 1H, J = 3.3 Hz, H-6), 4.64 (d, 1H, J = 3.8 Hz, H-9), 4.50 (ddd, 1H, J = 1.5, 3.0 and 4.3 Hz, H-3), 4.36 (d, 1H,

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J = 3.0 Hz, H-4), 3.97 (dd, 1H, J = 4.3 and 14.5 Hz, H-2b), 3.67−3.79 (m, 1H, H-2a), 3.19−3.35 (m, 1H, H-7), 1.50, 1.33 (2s, 6H, 2•Me), 1.23 (d, 3H, J = 7.5 Hz, CH_3-7); ^{13}C NMR (50 MHz, $CDCl_3$) δ 211.41, 112.13, 104.29, 85.26, 81.64, 77.84, 71.25, 52.35, 41.21, 26.55, 26.06, 9.35; IR (film, CH_2Cl_2) 1472, 1440, 1070 cm^{-1}; HRMS (EI) m/z M^+ calcd for $C_{12}H_{17}O_4SN$ 271.08783, found 271.08547. Anal. Calcd for $C_{12}H_{17}O_4SN$ (271.34): C, 53.12; H, 6.31. Found: C, 52.98; H, 6.49.

Preparation of (3′*R*,4′*S*)-5-Deoxy-1,2-*O*-isopropylidene-3-*O*:5-*C*-(3′-methylazetidin-2′-thion-1′,4′-diyl)-α-D-xylofuranose (36). The thiono-β-lactam **36** was obtained from **30** according to the above procedure (64%): mp 162−163.5 °C (from AcOEt/hexane); $[\alpha]^{22}_D$ −5.0 (c 0.32, CH_2Cl_2); ^{1}H NMR (500 MHz, benzene-d_6) δ 5.60 (d, 1H, J = 3.7 Hz, H-9), 4.23 (d, 1H, J = 14.8 Hz, H-2b), 4.20 (d, 1H, J = 3.4 Hz, H-6), 4.11 (d, 1H, J = 3.7 Hz, H-10), 3.64 (m, 1H, H-3), 3.47 (m, 1H, H-4), 2.78 (dddd, 1H, J = 2.3, 3.4, 7.4 and 14.8 Hz, H-7), 2.45 (ddd, 1H, J = 2.3, 4.0 and 14.8 Hz, H-2a), 1.34 (s, 3H, Me), 1.18 (d, 3H, J = 7.4 Hz, CH_3-7), 1.00 (s, 3H, Me); ^{13}C NMR (125.8 MHz, benzene-d_6) δ 111.64, 105.35, 96.44, 83.59, 82.76, 77.58, 70.96, 52.23, 40.10, 26.68, 26.02, 9.77; IR (CH_2Cl_2) 1485, 1111, 1074 cm^{-1}; HRMS (EI) m/z M^+ calcd for $C_{12}H_{17}O_4SN$ 271.08783, found 271.08854. Anal. Calcd for $C_{12}H_{17}O_4SN$ (271.34): C, 53.12; H, 6.31. Found: C, 53.09; H, 6.49.

X-ray Crystallography. Single crystals of compounds **11**, **29**, **35**, and **36** suitable for X-ray structure analysis were obtained by slow evaporation of the ethyl acetate/hexane mixture.

X-ray diffraction experiments for monocrystals of compounds **11**, **29**, **35**, and **36** were performed at room temperature on the MACH3 diffractometer. Cu Kα radiation and the $\omega\angle 2\theta$ scanning mode were used. Three standard reflections showed no significant intensity fluctuation (ca. 0.6%) throughout the experiments. The structures were solved by direct methods using SHELXS97[47] and refined against F^2 with the SHELXL97 program.[48]

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(48) Sheldrick, G. M. *SHELXL97, Program for the Refinement of Crystal Structures*; University of Göttingen, Göttingen, Germany, 1997.

Table 5. Crystallographic Data for Compounds 11, 29, 35, and 36

	11	29	35	36
empirical formula	$C_{11}H_{15}NO_5$	$C_{11}H_{15}NO_5$	$C_{12}H_{17}NO_4S$	$C_{12}H_{17}NO_4S$
fw	241.24	241.24	271.33	271.33
a, Å	8.6857(4)	8.2001(4)	9.2601(9)	12.7254(7)
b, Å	11.9422(5)	11.6091(5)	12.5495(5)	8.9427(5)
c, Å	11.5043(10)	11.9503(6)	23.082(3)	11.6801(3)
β, deg	106.261(5)			
V, Å^3	1145.56(12)	1137.62(9)	2682.3(5)	1329.2(1)
Z	4	4	8	4
cryst syst	monoclinic	orthorhombic	orthorhombic	orthorhombic
space group	$P2_1$	$P2_12_12_1$	$P2_12_12_1$	$P2_12_12_1$
ρ, g cm^{-3}	1.399	1.409	1.344	1.356
T, °C	22(2)	22(2)	22(2)	22(2)
λ, Å	1.54178	1.54178	1.54178	1.54178
μ, mm^{-1}	0.940	0.946	2.222	2.242
R1 (obsd data)	0.0355	0.0359	0.0379	0.0347
wR2 (all data, F^2)	0.1031	0.1067	0.1172	0.1058
Flack parameter	0.04(16)	0.0(2)	0.05(3)	0.01(3)

Hydrogen atoms were added geometrically and refined with the riding model. Details of the data collection and structure solution and refinement are shown in Table 5.

Crystallographic data for structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC 166716 (for **11**), CCDC 166717 (for **29)**, CCDC 166718 (for **35)**, and CCDC 166719 (for **36)**.

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