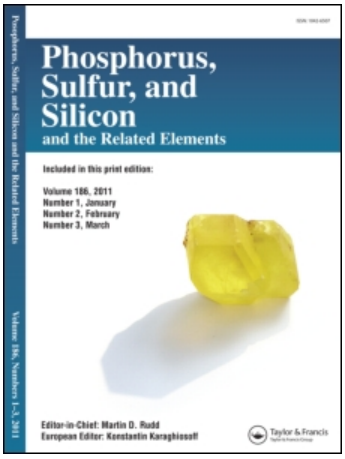

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ASYMMETRIC REDUCTION OF S-ALKYL-S-ARYL-N-*p*-TOSYLSULFILIMINES WITH L(-)CYSTEINE

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ASYMMETRIC REDUCTION OF S-ALKYL-S-ARYL-N-*p*-TOSYLSULFILIMINES WITH L(−)CYSTEINE

by

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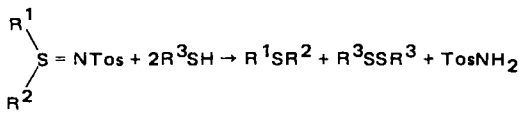
ABSTRACT

Partial reduction of racemic mixture of S-alkyl-S-aryl-*p*-tosyl sulfilimines with L(−)cysteine affords optically active recovered sulfilimine. In the case of S-methyl-S-*p*-tolyl-N-*p*-tosylsuifilimine the absolute configuration and the optical yield were determined.

We have previously found that aromatic[1] and aliphatic[2] thiols reduce S-alkyl-S-aryl-N-*p*-tosylsulfilimines (**1**) in methanol solution in almost quantitative yield affording sulfide, disulfide, and sulfonamide.



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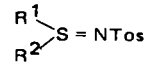
The widespread interest developed in recent years[3–8] in the determination of the stereochemical course of nucleophilic substitution reactions at the sulfur center and the convenient conditions under which the reaction mentioned occurs, prompted us to investigate the reduction of sulfilimines with optically active thiols in an attempt to observe asymmetric reduction.

In this note some preliminary results on the partial asymmetric reduction of racemic mixture of sulfilimines with L(−)cysteine are reported.

The sulfilimine (0.03 mol) dissolved in 150 ml of methanol/water (3:1) was added to a solution of L(−)cysteine (0.03 mol) dissolved in 150 ml of the same solvent. The solution was allowed to stand at room temperature for 3 days. The white precipitate (cystine and traces of *p*-toluensulfonamide) was filtered off. The solvent was then removed by evaporation under reduced pressure. The resulting residue was extracted with two 100 ml portions of hot $CHCl_3$, and

TABLE

Optical activity of the unreacted sulfilimines



	R^1	R^2	$[\alpha]^{25}_{546}$
1a	CH_3	C_6H_5	+4.20
1b	CH_3	$C_6H_4CH_3(p)$	+5.40[a]
1c	CH_3	$C_6H_4Cl(p)$	+5.94
1d	C_2H_5	C_6H_5	−5.16

[a] The mixture was assumed to be enriched in (+) S-Alkyl-S-aryl-N-*p*-tosylsulfilimines on the base of the literature data.[5] As the specific activity of the (−)-(S)-enantiomer of this sulfilimine is measured[5] only in acetone, to calculate the optical yield we prepared[5] the (−)-(S) sulfilimine enantiomer and measured its optical activity in $CHCl_3$: $[\alpha]^{25}_{546}$ −415.81 (c2). Therefore the optical yield of tested reaction is *ca.* 1.30.

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the solution obtained was concentrated and chromatographed on 150 g of silica gel with elution by $CHCl_3$/ether (3:1). In this way the sulfilimine was easily separated from the other components, weighed, and identified by analytical data, mp, ir, and ^{1}H-nmr spectra (0.015 mol of unreacted sulfilimine were collected in all the cases).

The optical activity of the unreacted sulfilimine was then measured (c2, $CHCl_3$) with a Perkin-Elmer 141 photopolarimeter, and the obtained specific rotations are reported in the Table. As it emerges from the Table in all the cases the unreacted sulfilimine was found to be optically active indicating therefore, that L(−)-cysteine reduces the enantiomeric sulfilimines with different rate.

In the case of S-methyl-S-*p*-tolyl-N-*p*-tosylsulfilimine, since the optical activity and the absolute configuration of one enantiomer is known,[5] it was possible to determine the optical yield and the absolute configuration of the sulfilimine unreacted. From the Table it results that L(−)cysteine reduces the (−)-(S) enantiomer of S-methyl-S-*p*-tolyl-N-*p*-tosylsulfilimine more easily than the (+)-(R) enantiomer with an optical yield of *ca.* 1.30.

It is known that sulfoxides are reduced to sulfides[9] when treated with aliphatic or aromatic thiols although more drastic conditions as compared to sulfilimine are generally required. A comparison of the data concerning the reduction of the sulfilimine (**1a**) and methylphenylsulfoxide[4] with L(−)cysteine in the same conditions indicates that asymmetric reduction occurs solely in the former and not in the latter case. This suggests a larger steric control in the reduction of sulfilimine as compared to the corresponding sulfoxides. However, the low optical yield obtained in the title reaction suggests no strong difference in the stability of the diastereoisomeric transition state; actually this fact was expected since in the tested thiol the SH group is not directly bonded to the asymmetric center.

Research with other asymmetric thiols is in progress in order to improve the optical yield.

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Conformational Properties of Sulfur-containing Homo-oligopeptides. Oligo-L-methionines[1]

Sir:

In previous papers we reported evidence of β-associated structure formation in trifluoroethanol and trifluoroethanol/water mixtures for homo-oligopeptides derived from amino acids with hydrocarbon side chains.[2-4] In this communication we wish to discuss the conformational properties of the sulfur-containing homologous series BOC(L-Met)$_n$-OMe[5] (n = 2-7) in the same solvent systems using circular dichroism.

Poly-L-methionine has been shown to assume the right-handed α-helical conformation in the solid state[6-7] and in non-denaturing organic solvents,[6,8-13] its stability being lower only to poly-L-alanine and poly-L-leucine.[6] Methionine was also found among the strongest structure-forming residues in proteins (total helical and β-regions).[14] Conversely, it has often experimentally been shown that the more stable conformation for oligopeptides derived from amino acids, whose homo-polymers assume the α-helical structure, is the β-conformation.[3,4,15-17]

The methionine oligopeptides have been synthesized *via* the dicyclohexylcarbodiimide and acid azide coupling methods as previously described for isoleucine,[18] valine,[4] and phenylalanine[19] oligopeptides. These methods are known to give products of high chemical and optical purity in good yields. The linearity of the plot of total molar rotation values at sodium D line of methionine oligomers *vs.* n[20] in hexafluoroacetone sesquihydrate (a denaturing solvent for the secondary structures of oligopeptides)[4,18] confirms the absence of racemization in the various synthetic steps.

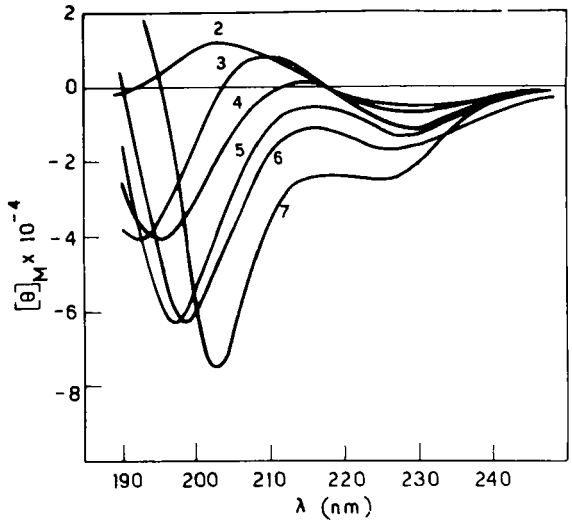

FIGURE I

Circular Dichroism Spectra of BOC-(L-Met)$_n$-OMe in Trifluoroethanol at 25°C (conc = 3 x 10^{-4} M).

The circular dichroism spectra (obtained with a Cary model 60 spectropolarimeter modified with a Cary model 6001 CD attachment) of the oligo-L-methionines in trifluoroethanol (conc 3 x 10^{-4} M) are illustrated in Figure I. In going from dimer to heptamer, the long-wavelength negative dichroic band increases in intensity and exhibits a blue shift to 225 nm; the positive band at 202 nm in the dimer undergoes a red shift to 214 nm in the tetramer while decreasing in intensity and finally disappearing (at the pentamer), and the negative short-wavelength band shifts gradually to the red while becoming more intense. The spectrum of the heptamer (negative Cotton effects at 225 and 202.5 nm) changes neither in the concentration range 3 x 10^{-3} M – 3 x 10^{-5} M nor on increasing the temperature to

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70°C (only a small blue shift to 200 nm of the more intense Cotton effect has been observed at higher temperatures). We suggest that all methionine oligomers (to $n = 7$) exist predominantly in unordered conformation in trifluoroethanol. In any case the results reported here allow us to conclude that the heptamer does not form β-aggregates in this solvent in contrast to the behavior of heptamers derived from L-isoleucine[2,18] and L-valine.[4]

Since proteins function primarily in water, it is important to investigate peptide model compounds in aqueous solution. Unfortunately these oligomers are insoluble in water. Nevertheless, we did examine their circular dichroic properties in trifluoroethanol/water mixtures. The addition of 80% water (v/v) to a solution of hepta-L-methionine in trifluoroethanol causes a dramatic change in the dichroic pattern (Figure II), a negative band at 223 nm and a positive stronger band at 198 nm clearly suggesting the presence of a high content of β-structure.[2,4,6] We have examined all the peptide series in this solvent mixture (Figure II). The spectral properties typical of the β-form appear at the pentamer. This confirms that the β-conformation has a critical chain length[2-4,15,18] analogous to the critical size necessary for α-helix formation.[6,21,22]

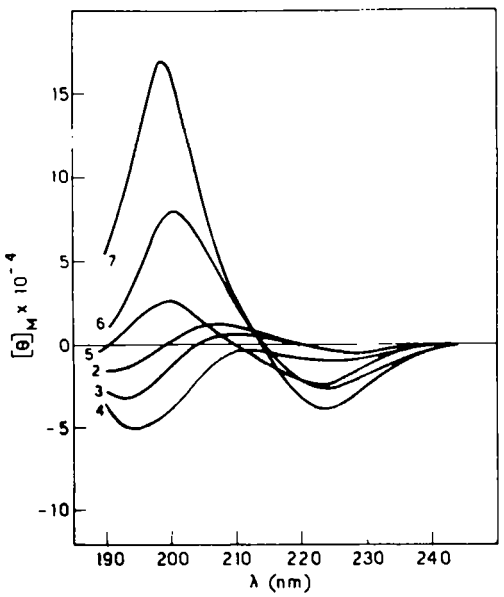

FIGURE II

Circular Dichroism Spectra of BOC-(L-Met-)$_n$OMe in Trifluoroethanol-Water (20:80, v/v) at 25°C (conc = 3×10^{-4} M).

The present findings demonstrate that the β-conformation is the preferred structure for oligo-L-methionines in water as for other oligopeptides derived from aliphatic and aromatic amino acids.[2-4,15,18] They also show the greater tendency of water when compared to trifluoroethanol in supporting the β-structure of oligo-α-amino acids with saturated side chains.[2,4,15] In this context, the higher tendency of isoleucine[2] and valine[4] with respect to methionine (and leucine)[4] in assuming the β-structure points to the relevant contribution of β-branching in determining peptide conformations;[2,4,6] in addition, the comparable conformational behavior of methionine and leucine[4] oligopeptides in trifluoroethanol-water mixtures suggests similarity in structural role of $-CH_2-CH_2-S-CH_3$ and $-CH_2-CH(CH_3)_2$ groups.[14] Finally, since the dichroic spectra shown in the Figures are similar to those exhibited by oligo-L-leucines in the same experimental conditions,[4] the influence of the thioether chromophore upon the chirospectroscopic properties of methionine derivatives is confirmed to be minor.[23]

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