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THE INFLUENCE OF THE SOLVENT ON THE AMIDE CONFORMATION

Ignacy Z.Siemion
Department of Biochemistry,Medical School,Wrocław
Chałubińskiego 10,Poland

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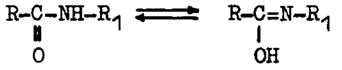
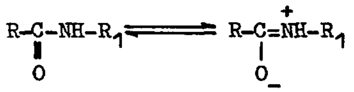
A few years ago Potapov and Terent'ev showed[1] that the rotatory dispersion curve of amide is related to the polarity of the solvent./In benzene the curve is positive and in methanol negative./ This solvent effect was interpreted as the demonstration of tautomerism:



$$R\text{-}\underset{\substack{\| \\ O}}{C}\text{-}NH\text{-}R_1 \rightleftharpoons R\text{-}\underset{\substack{| \\ OH}}{C}{=}N\text{-}R_1$$

However,in the light of Skulski's[2] NMR-measurements such an equilibrium is rather impossible.The Soviet investigators[3] are now inclined to think that mesomerism rather than tautomerism is manifested in the ORD curves of the amide:



$$R\text{-}\underset{\substack{\| \\ O}}{C}\text{-}NH\text{-}R_1 \rightleftharpoons R\text{-}\underset{\substack{| \\ O_-}}{C}{=}\overset{+}{N}H\text{-}R_1$$

Another hypothesis was discussed in Skulski's work.According to this author the differences of shape of ORD curves can be best explained by the different position of cis-trans equilibrium of the amide in different solvents.According to our experiments this hypothesis finds some support in the amino acids chemistry.

In our experiments we have performed ORD measurements for three leucine derivatives /ethyl esters of benzoyl-leucine, acetyl-leucine and formyl-leucine/ in three different solvents /benzene,dichloromethane and methanol/.The results of these measurements are shown in Table I.

Table I

OPTICAL ROTATORY DISPERSION OF LEUCINE DERIVATIVES

λ mμ	$[M]_\lambda$ of								
	Bz-Leu-OEt			Ac-Leu-OEt			For-Le-OEt		
	in benzene	in dichloro methane	in methanol	in benzene	in dichloro methane	in methanol	in benzene	in dichloro methane	in methanol
578	+ 55.6	+ 36.3	-51.2	-11.3	- 9.7	- 85.8	-12.2	-12.1	- 85.4
546	+ 67.4	+ 42.4	-58.0	-12.1	-10.4	- 99.9	-12.2	-12.1	- 96.6
435	+123.5	+ 90.0	-88.5	-11.3	- 8.4	-166.1	-14.7	-12.1	-163.6
405	+176.4	+117.7	-95.6	- 6.4	- 4.3	-200.3	-10.4	- 9.4	-195.6
365				+ 9.5	+11.8	-259.3	+ 2.2	+ 2.6	-252.7

The ORD curves in benzene and dichloromethane for each of all three leucine derivatives are very similar.Bz-Leu-OEt gives in both solvents positive,normal curves,whereas for Ac-Leu-OEt and For-Leu-OEt anomalous ones,crossing the zero value of optical rotation curves are obtained.It is interesting that only the curves of Bz-Leu-OEt in benzene and dichloromethane and those of Ac-Leu-OEt and For-Leu-OEt in methanol can be described by one-term Drude equation.This suggested that in these cases only one isomeric form of amide exists in the solvent.

The anomalous curves of Ac-Leu-OEt and For-Leu-OEt in benzene and dichloromethane can be described as the sum of two component curves:the experimental ORD-curve in methanol and the complementary curve,which can be calculated from the differences between the values of rotation of acylamino acid ester in benzene and in methanol /Fig.1./.

It is very interesting to note,that the complementary curve calculated in this way runs parallel to the curve of Bz-Leu-OEt in benzene and is also described by a one-term Drude equation.

For example,in the case of Ac-Leu-OEt,the experimental ORD-curve in benzene can be with good agreement described by the equation:

$$[M]_{\lambda} = \frac{22.6}{\lambda^2 - 0.046} - \frac{28.0}{\lambda^2 - 0.022} \qquad /1/$$

In this equation the second term represents the curve in methanol and the first the complementary curve.The value of λ_0 of the complementary curve is 215 mμ,which is very close to the value of λ_0 of proteins in random-coil conformation /212 mμ/.The values of optical rotation calculated according to our equation are in good correspondence with those,which were found experimentally /Table II/.

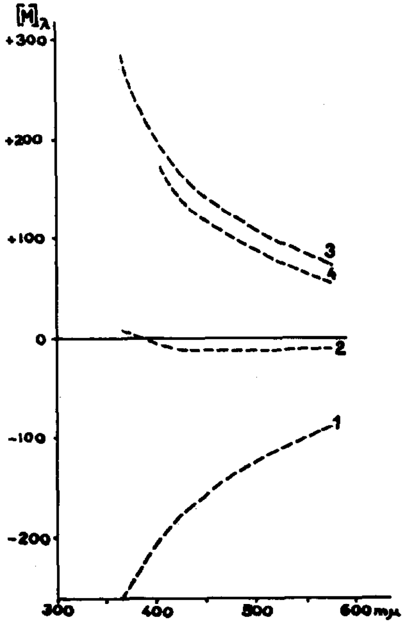


Fig.1.ORD CURVES OF LEUCINE DERIVATIVES: 1.Ac-Leu-OEt in methanol 2.Ac-Leu-OEt in benzene 3.Complementary curve for Ac-Leu-OEt in benzene 4.Bz-Leu-OEt in benzene

Table II

COMPARISON OF EXPERIMENTAL AND THEORETICAL VALUES OF $[M]_\lambda$ OF Ac-Leu-OEt IN BENZENE

mμ	Experimental values	Values acc. to equation /1/
578	-11.3	-10.9
546	-12.1	-11.8
435	-11.3	- 9.6
405	- 6.4	- 5.7
365	+ 9.5	+ 7.5

This analysis suggests that in the case of Bz-Leu-OEt only one isomeric form of amide exists in benzene,but in the cases of Ac-Leu-OEt and For-Leu-OEt there is the equilibrium of two isomeric forms.

Some evidence from the peptide chemistry permits to identify these forms as cis and trans conformational izomers of the amide. Thus,it was found by Young[4] that the degree of racemisation during peptides synthesis diminishes in the series of Bz-Leu,Ac-Leu and For-Leu.For the carbodiimide method with dichloromethane as solvent the amounts of L-peptide were 54 %,70 % and 94 %,and for the carbonic mixed anhydride method with tetrahydrofuran as solvent, the corresponding yields of L-peptide were 20 %,60 % and 86 %.

Thus,the pure isomeric form of Bz-Leu racemises considerably easier than the mixture of two forms in the cases of Ac-Leu and For-Leu.

Racemisation during peptide synthesis is evoked by collateral azlactone formation.It can be seen from the Stuart models of molecules that the azlactone formation is possible only in the case of trans conformation of the amide bond.Thus,it is very probable that in the case of Bz-Leu in benzene and in dichloromethane we have the pure trans conformation of the amide,and in the remaining cases there is an equilibrium of cis and trans isomers. It is natural that the steric hindrance for the change of conformation of amide must be greater in Bz-Leu than in Ac-Leu and For-Leu.

Negative curves observed for Ac-Leu and For-Leu derivatives in methanol solution can be thus interpreted as a manifestation of pure cis isomers.

Acknowledgment

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