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Abstract

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THE INFLUENCE OF SOLVENT ON THE ROTATORY DISPERSION OF ACYLAMINO ACIDS

In 1960, using the benzoyl derivative of (−)-α-phenylethylamine as an example, we for the first time observed a strong influence of the solvent on the course of the optical rotatory dispersion curves (ORD curves) of amides (^1). Subsequently this "solvent effect" was studied in a number of examples (^2). Analysis of the accumulated experimental material made it possible to propose an interpretation of this phenomenon as a consequence of a shift in the mesomeric state of the amide group under the influence of the solvent (^3):

$$\underset{\text{(Ia)}}{\mathrm{R^{*}-NH-C(=O)-C_6H_5}} \quad \rightleftarrows \quad \underset{\text{(Ib)}}{\mathrm{R^{*}-\overset{\oplus}{N}H=C(-\overset{\ominus}{O})-C_6H_5}}$$

As is known, optical rotatory dispersion is one of the principal methods for studying the conformation of polypeptide chains. Changes in rotation under the influence of a solvent are in this case associated with changes in the conformation of polypeptide chains, in particular with the formation or destruction of a helical conformation. Since we observed strong changes in rotation under the influence of solvents in monomeric amides (in which, naturally, there can be no question of the "formation or destruction of helices"), the question arose: is it permissible to relate analogous changes in polyamides (polypeptides and proteins) exclusively to conformational changes in the polymer chain? Obviously, an attempt to answer such a question required first of all the study of the rotatory dispersion of monomeric units closest to polypeptides, i.e. acylated amino acids. This idea formed the basis of the present work.

In order to make it possible to prepare solutions both in polar and in nonpolar solvents, we chose acyl derivatives of amino acid esters as the object of study. It turned out that the course of the ORD curves of the benzoyl and

acetyl derivatives of most amino acids in benzene and methanol solutions is opposite. A similar "solvent effect" was found by us for the benzoyl derivatives of α-aminobutyric acid, norvaline, valine, leucine, asparagine, glutamic acid, methionine, phenylalanine, tyrosine, histidine, and also for the acetyl derivatives of valine, norvaline, asparagine and glutamic acid, and methionine. No solvent effect was observed for the acetyl derivatives of tyrosine, phenylalanine, and phenylglycine. Somewhat unexpectedly, benzoylphenylglycine—the closest analog of benzoyl-α-phenylethylamine, in which the solvent effect was first discovered by us—behaves similarly. However, if our suggestion is correct that reversal of the ORD curve under the influence of a polar solvent is a consequence of a shift in the mesomeric state of the amide group toward the bipolar limiting structure Ib, then the absence of the ef-

Table 1

Moffitt constants b_0 for esters of acylamino acids

Substance	Solvent	b_0
Dimethyl ester of acetyl-L-glutamic acid	Benzene	+30
Dimethyl ester of acetyl-L-glutamic acid	Methanol	+30
Methyl ester of benzoyl-L-leucine	Benzene	+120
Methyl ester of benzoyl-L-leucine	Methanol	+130
Methyl ester of benzoyl-L-leucine	Acetic acid	+110
Methyl ester of benzoyl-L-phenylalanine	Benzene	+240
Methyl ester of benzoyl-L-phenylalanine	Dioxane	+70
Methyl ester of benzoyl-L-phenylalanine	Acetone	+30
Methyl ester of benzoyl-L-phenylalanine	Methanol	−50
Methyl ester of benzoyl-L-histidine	Dioxane	+230
Methyl ester of benzoyl-L-histidine	Methanol	+20
Methyl ester of benzoyl-L-histidine	Acetic acid	−100
L-alanyl-L-histidine	80% dioxane	+230
L-alanyl-L-histidine	Water	+120
L-alanyl-L-histidine	Acetic acid	+260

The solvent effect in benzoylphenylglycine can be associated with the fact that the above-mentioned shift is counteracted by the electron-acceptor action of two substituents—the phenyl and the carboxyl. A portion of the rotatory-dispersion curves measured by us is given in Fig. 1.

The modern approach to the use of rotatory dispersion for determining the conformation of polypeptide chains is based on the equation proposed by Moffitt ([4]). In this connection, the data we obtained on the rotatory dispersion of esters of acylamino acids were used to calculate Moffitt' s "helical constant" b_0. Some of the constants obtained are presented in Table 1.

As is seen from the data in Table 1, in acyl derivatives of glutamic acid and leucine the constant b_0 is practically independent of the solvent. According

Fig. 1. Rotatory-dispersion curves of the optical rotation of methyl benzoyl-L-phenylalaninate (A) and methyl benzoyl-L-leucinate (B). 1—in benzene, 2—in dioxane, 3—in methanol

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to preliminary data, derivatives of alanine, α-aminobutyric acid, valine, and norvaline behave similarly; in derivatives of aspartic acid the changes in b_0 are small and may be connected only with experimental errors. It should be noted that Tenford ([5]), who studied the rotatory dispersion of acetyl derivatives of amides of a series of aliphatic amino acids, likewise did not find a dependence of b_0 on the solvent.

Fig. 1. Curves of the dispersion of optical rotation of methyl benzoyl-L-phenylalaninate (A) and methyl benzoyl-L-leucinate (B). 1—in benzene, 2—in dioxane, 3—in methanol.

The situation is different for benzoyl derivatives of phenylalanine and histidine, and also for L-alanyl-L-histidine: here we observed a substantial dependence of b_0 on the solvent, far exceeding the possible experimental errors. According to preliminary data, derivatives of tyrosine and tryptophan behave similarly. It is noteworthy that all these are derivatives of amino acids with a chromophore at the β-carbon atom, which in general have a different character of rotatory-dispersion curves than amino acids of the simplest type ([6]).

Thus, from our data it follows that the parameter b_0, which according to Moffitt is a measure of the helicity of polypeptides, depends on the solvo-

···solvent and in some monomeric acylamino acids. In this case the changes in b_0 have no apparent relation to helicity, but one cannot exclude the possibility that the true primary cause of the influence of solvents on the rotatory dispersion of monomeric and polymeric amides is the same. It may be that the shift of mesomerism toward one of the limiting forms, which we assume, ultimately affects the rotatory-dispersion curves because such a shift leads to the predominance of a definite conformation of the amide molecule or of the monomeric unit of a polyamide.

Whatever the theoretical explanation may be, the results obtained by us compel one to treat with a certain caution the interpretation of b_0 exclusively from the positions accepted at present, since it may be thought that the dependence of b_0 on the solvent, outside a direct connection with helicity, may manifest itself in proteins or polypeptides containing a significant percentage of amino acids with a chromophore at the β-carbon atom.

Experimental Part

Starting amino acids. Optically active tyrosine, norvaline, glutamic acid, asparagine, histidine, and methionine were commercial preparations. (−)-Phenylalanine was obtained through the ethyl ester by resolution with dibenzoyltartaric acid ([7]); para-methoxyphenylalanine, by methylation of acetyltyrosine with dimethyl sulfate ([8]). Aminobutyric acid was obtained by amination of α-bromobutyric acid ([9]) and resolved through the formyl derivative with brucine ([10]). Valine was obtained by the described procedure ([11]) and resolved as the ethyl ester with dibenzoyltartaric acid ([7]). Leucine was obtained analogously ([12]) and resolved ([13]).

Acyl derivatives were obtained from the corresponding optically active amino acids by known procedures and were then converted into methyl esters by the action of diazomethane or into ethyl esters by esterification in the presence of hydrogen chloride.

Measurements of rotatory dispersion were carried out in the region 589-280 mμ on the photoelectric spectropolarimeter described earlier ([14]); part of the measurements was repeated on a new serial semiautomatic spectropolarimeter of VNIIEKIprodmash. The constant b_0 in the Moffitt equation

$$[\alpha]' = [\alpha]\frac{3}{n^2+2} = a_0\frac{\lambda_0^2}{\lambda^2-\lambda_0^2} + b_0\frac{\lambda_0^4}{(\lambda^2-\lambda_0^2)^2}$$

was calculated from the rotatory-dispersion data as the slope of a straight line plotted in the coordinates $(\lambda^2-\lambda_0^2)^{-1}\cdot 10^6$ and $[\alpha]'(\lambda^2-\lambda_0^2)\cdot 10^{-6}$. The calculation was made with $\lambda_0 = 212$ mμ, except for L-alanyl-L-histidine, for which linearity is best observed at $\lambda_0 = 195$ mμ. The values of the specific rotation in calculating b_0 were corrected for the refractive index of the solvent (with the exception of the calculation for L-alanyl-L-histidine).

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Note: Figure translations are in progress. See original paper for figures.