Study of the influence of the alkyl ester group in (*S*)-valinates on diastereoselectivity of their condensation with *N*-acetylphenylalanine by the mixed anhydride method

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The dynamic kinetic resolution in the synthesis of alkyl *N*-acetylphenylalanyl (*S*)-valinates was studied by the mixed anhydride method. The structure of the ester group of the amino component appeared to exert no substantial effect on the diastereoselectivity of the reaction.

Key words: dynamic kinetic resolution, diastereoselectivity, racemization, 5(4*H*)-oxazolones, amino acids, dipeptides.

The dynamic kinetic resolution (DKR) method has attracted increasing attention of researchers in the recent time. The *in situ* epimerization of a chiral substrate occurs during this method, which makes it possible to perform syntheses with high diastereoselectivity.[1—6] 5(4*H*)-Oxazolones are very convenient substrates in DKR processes, because they are rapidly racemized and react readily with nucleophiles. They are widely used for syntheses of modified α-amino acids and their derivatives.[7—10]

The synthesis of peptides by the mixed anhydride method is accompanied (under certain conditions) by substantial racemization, which proceeds mainly through the formation of 5(4*H*)-oxazolones.[11] The reaction of the latter with esters of amino acids affords a diastereomeric mixture of peptides. Diastereoselectivity in this process takes place when, along with the fast racemization of intermediate 5(4*H*)-oxazolone, one of its stereoisomers reacts with the amino component more rapidly than another.[7] Therefore, the formation of dipeptide is the DKR process. The determination of factors favoring an increase in differences in the rates of interaction of oxazolone stereoisomers with the amino component provides a possibility of diastereoselective synthesis of dipeptides.

In the previous work[12] we studied the influence of the nature of the side chain of the amino component on the diastereoselectivity of syntheses of dipeptides of *N*-acetyl-(*S*)-phenylalanine (**1**). It is found that the introduction of 20% excess triethylamine provides the fast racemization of intermediate 5(4*H*)-oxazolone. The (*R*)-isomer of 5(4*H*)-oxazolone **2″** reacts more rapidly with ethyl esters of (*S*)-amino acids (Ala, Phe, Val, Glu), which results in the predominant formation of (*R*,*S*)-diastereomers, whose content in the mixture is 61—90%. The main product of this DKR is dipeptide with the (*R*)-phenylalanine residue.

The purpose of the present work is to study the influence of the R substituent in the ester group of the amino component on the diastereoselectivity of condensation of alkyl (*S*)-valinates with *N*-acetyl-(*S*)-phenylalanine (**1**) (Scheme 1).

Scheme 1

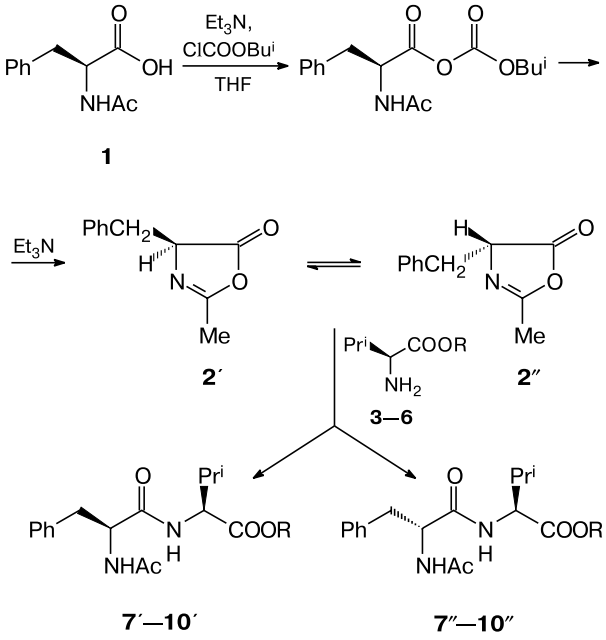

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Table 1. Selected physicochemical properties of stereoisomers **7′—10′** and **7″—10″**

Compound	M.p. /°C	HPLC data		
		Eluent	τ_R*/min	α**
7′	146—147	Hexane—Pr^{i}OH—MeOH	4.62	1.42
7″	—	(10 : 0.5 : 0.2)	6.54	
8′	119—121	Hexane—Pr^{i}OH—MeOH	3.97	1.22
8″	—	(10 : 0.5 : 0.2)	4.83	
9′	57—59	Hexane—Pr^{i}OH—MeOH	6.16	1.09
9″	—	(10 : 0.3 : 0.1)	6.73	
10′	136—138	Hexane—Pr^{i}OH—MeOH	6.11	1.10
10″	—	(15 : 0.6 : 0.1)	6.75	

* Retention time.
** Resolution coefficient.

Table 2. Diastereomeric compositions and yields of dipeptides **7′—10′** and **7″—10″**

Compound	R	Content of diastereomers (%)				Yield (%)
		HPLC		^{1}H NMR		
		S,*S*	*R*,*S*	*S*,*S*	*R*,*S*	
7′, **7″**	Me	22	78	25	75	76
8′, **8″**	Et	25	75	22	78	73
9′, **9″**	Bu^t	27	73	29	71	57
10′, **10″**	Bn	30	70	31	69	66

Results and Discussion

Dipeptides **7′—10′** and **7″—10″** were synthesized according to an earlier described procedure[12] in THF in the presence of 20% excess Et_3N. A solution of (*S*)-valinates **3—6**, which are formed by the neutralization of the corresponding salts with Et_3N, was added to oxazolone **2** obtained from isobutyl chloroformate and compound **1** (see Scheme 1).

The diastereomeric composition of the obtained mixtures of dipeptides **7—10** was analyzed by HPLC using systems of solvents (Table 1) and ^{1}H NMR spectroscopy. In the latter case, the methyl substituents of valine served as diagnostic groups (Table 2). The characteristic property of (*S*,*S*)- and (*R*,*S*)-diastereomers of the dipeptides under study is the difference of chemical shifts of nonequivalent protons of the β-CH_2 group of phenylala-

Table 3. ^{1}H NMR spectra of dipeptides **7′—10′** and **7″—10″** (δ, *J*/Hz)

Compound	Phe					Val				R	
	α-CH	β-CH_A	β-CH_B	NH (d)	Ac (s)	α-CH (dd)	β-CH (sept.d)	γ-Me (both d)	NH (d)	α-CH_n	β-CH_n
7′	4.76 (dt, *J* = 7.4, *J* = 7.2)	3.06 (d, *J* = 7.2)	3.06 (d, *J* = 7.2)	6.42 (*J* = 7.4)	1.97	4.42 (*J* = 8.5, *J* = 5.2)	2.09 (*J* = 6.9, *J* = 5.2)	0.83, 0.87 (*J* = 6.9)	6.52 (*J* = 8.5)	3.69 (s)	—
7″	4.82 (td, *J* = 8.0, *J* = 6.3)	3.10 (dd, *J* = 13.7, *J* = 6.5)	3.05 (dd, *J* = 13.7, *J* = 8.0)	6.43 (*J* = 8.0)	1.97	4.40 (*J* = 8.5, *J* = 4.9)	2.00 (*J* = 6.9, *J* = 4.9)	0.73, 0.75 (*J* = 6.9)	6.58 (*J* = 8.5)	3.69 (s)	—
8′	4.75 (dt, *J* = 7.6, *J* = 7.1)	3.06 (d, *J* = 7.1)	3.06 (d, *J* = 7.1)	6.39 (*J* = 7.6)	1.97	4.40 (*J* = 8.6, *J* = 5.1)	2.10 (*J* = 6.9, *J* = 5.1)	0.84, 0.88 (*J* = 6.9)	6.46 (*J* = 8.6)	4.16 (q, *J* = 7.2)	1.26 (t, *J* = 7.2)
8″	4.78 (ddd, *J* = 8.1, *J* = 7.9, *J* = 6.4)	3.11 (dd, *J* = 13.8, *J* = 6.4)	3.05 (dd, *J* = 13.8, *J* = 8.1)	6.37 (*J* = 7.9)	1.97	4.38 (*J* = 8.5, *J* = 4.7)	2.01 (*J* = 6.9, *J* = 4.7)	0.75, 0.76 (*J* = 6.9)	6.47 (*J* = 8.5)	4.17, 4.13 (both dq, *J* = 10.7, *J* = 7.1)	1.24 (t, *J* = 7.1)
9′	4.74 (dt, *J* = 7.8, *J* = 6.8)	3.09 (dd, *J* = 13.8, *J* = 6.8)	3.05 (dd, *J* = 13.8, *J* = 6.8)	6.38 (*J* = 7.8)	1.97	4.32 (*J* = 8.5, *J* = 4.7)	2.10 (*J* = 6.9, *J* = 4.7)	0.85, 0.87 (*J* = 6.9)	6.45 (*J* = 8.5)	—	1.46 (s)
9″	4.76 (td, *J* = 8.1, *J* = 6.2)	3.12 (dd, *J* = 13.7, *J* = 6.2)	3.04 (dd, *J* = 13.7, *J* = 8.1)	6.35 (*J* = 8.1)	1.98	4.30 (*J* = 8.7, *J* = 4.5)	1.99 (*J* = 6.8, *J* = 4.5)	0.73, 0.74 (*J* = 6.8)	6.32 (*J* = 8.7)	—	1.43 (s)
10′	4.74 (dt, *J* = 7.7, *J* = 7.0)	3.04 (d, *J* = 7.0)	3.04 (d, *J* = 7.0)	6.36 (*J* = 7.7)	1.95	4.47 (*J* = 8.5, *J* = 5.0)	2.11 (*J* = 6.9, *J* = 5.0)	0.80, 0.84 (*J* = 6.9)	6.51 (*J* = 8.5)	5.13 (s)	7.35 (m)
10″	4.79 (ddd, *J* = 8.1, *J* = 7.8, *J* = 6.5)	3.10 (dd, *J* = 13.8, *J* = 6.5)	3.04 (dd, *J* = 13.8, *J* = 8.1)	6.29 (*J* = 7.8)	1.93	4.44 (*J* = 8.5, *J* = 4.7)	2.02 (*J* = 6.9, *J* = 4.7)	0.70, 0.72 (*J* = 6.9)	6.52 (*J* = 8.5)	5.11, 5.18 (both d, *J* = 12.2)	7.31 (m)

nine (Δ_{AB}). The ratio $\Delta^{RS}_{AB} \gg \Delta^{SS}_{AB}$ is observed for all dipeptides of *N*-acetylphenylalanine. It should be noted that in the (*R*,*S*)-dipeptides the Δ^{RS}_{AB} value increases with an increase in the size of the R substituent in the COOR group of the valine fragment, whereas in the (*S*,*S*)-isomers the Δ^{SS}_{AB} value is almost zero (Table 3), *i.e.*, the β-CH_2 protons are equivalent (except for the case of R = Bu^t).

Individual diastereoisomers **7′—10′** synthesized by the method excluding racemization were used for assignment of the signals.[11]

It follows from the data presented in Table 2 that all mixtures obtained are enriched in (*R*,*S*)-diastereomers **7″—10″** (up to 69—78%) regardless of the structure of the R substituent in the ester group of peptides **7—10**. A tendency to some decrease in the diastereoselectivity with an increase in the size of the R substituent should also be mentioned. Thus, the structure of the ester group exerts a weak effect on the diastereoselectivity of the reaction, unlike, *e.g.*, the structure of the side chain of amino acids.[12] It is most likely that stereodifferentiation is determined by the interaction of the groups closest to the reaction centers.

Experimental

^{1}H NMR spectra were recorded on a Bruker DRX 400 spectrometer (400.13 MHz) using Me_4Si as internal standard. The synthesized compounds were analyzed by HPLC on a Milikhrom 4-UF chromatograph (Silasorb-60 as sorbent, column 64×2 mm, detection at 230 nm, elution rate 200 μL min^{-1}). Melting points were determined on a Boetius heating stage and used without correction.

Methyl and ethyl (*S*)-valinate hydrochlorides and benzyl (*S*)-valinate *p*-toluenesulfonate were synthesized as described previously.[13] *tert*-Butyl (*S*)-valinate acetate was synthesized according to a known procedure.[14]

Synthesis of alkyl *N*-acetyl-(*S*)-phenylalanyl and *N*-acetyl-(*R*)-phenylalanyl (*S*)-valinates 7′—10′ and 7″—10″ (general procedure). Triethylamine (0.61 mL, 4.34 mmol) and isobutyl chloroformate (0.48 mL, 3.62 mmol) were added dropwise with stirring to a solution of *N*-acetyl-(*S*)-phenylalanine (0.75 g, 3.62 mmol) in THF (17 mL) at −10—−15 °C. The reaction mixture was stirred for 30 min at −13 °C, and then a mixture obtained by stirring of the corresponding salt of (*S*)-valine ester (3.62 mmol) with Et_3N (0.51 mL, 3.62 mmol) in THF (9 mL) and cooled to −10 °C was added. The reaction mixture was stirred for 1 h at −10—−15 °C, for 1 h at 0 °C, and for 3 h at ~20 °C and then kept without stirring for ~16 h at ~20 °C. The precipitate was filtered off, and THF was removed *in vacuo*. The residue was dissolved in chloroform, and the solution was washed with a 5% solution of $NaHCO_3$, water, 5% HCl, with water again (to pH ~7), and dried with Na_2SO_4. The chloroformic solution was concentrated *in vacuo* to dryness. The residue was analyzed by ^{1}H NMR spectroscopy and HPLC.

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References

1. R. S. Ward, *Tetrahedron Asymmetry*, 1995, **6**, 1475.
2. R. Noyori, M. Tokunaga, and M. Kitamura, *Bull. Chem. Soc. Jpn*, 1995, **68**, 36.
3. S. Caddick and K. Jenkins, *Chem. Soc. Rev.*, 1996, **25**, 447.
4. H. Pellissier, *Tetrahedron*, 2003, **59**, 8291.
5. M. Calmes, C. Glot, T. Michel, M. Rolland, and J. Martinez, *Tetrahedron Asymmetry*, 2000, **11**, 737.
6. S. A. Brown, M.-C. Parker, and N. J. Turner, *Tetrahedron Asymmetry*, 2000, **11**, 1687.
7. N. L. Benoiton, K. Kuroda, and F. M. F. Chen, *Tetrahedron Lett.*, 1981, **22**, 3361.
8. H. S. Bevinakatti, R. V. Newadkar, and A. A. Banerji, *J. Chem. Soc., Chem. Commun.*, 1990, 1091.
9. J. Z. Crich, R. Brieva, P. Marquart, R.-L. Gu, S. Flemming, and C. J. Sih, *J. Org. Chem.*, 1993, **58**, 3253.
10. L. Xie, W. Hua, A. S. C. Chan, and Y.-C. Leung, *Tetrahedron Asymmetry*, 1999, **10**, 4715.
11. *The Peptides. Analysis, Synthesis, Biology. V. 1. Major Methods of Peptide Bond Formation*, Eds E. Gross and J. Meienhofer, Academic Press, New York—San Francisco—London, 1979.
12. V. P. Krasnov, E. A. Zhdanova, N. Z. Solieva, L. Sh. Sadretdinova, I. M. Bukrina, A. M. Demin, G. L. Levit, M. A. Ezhikova, and M. I. Kodess, *Izv. Akad. Nauk, Ser. Khim.*, 2004, 1278 [*Russ. Chem. Bull., Int. Ed.*, 2004, **53**, 1331].
13. A. A. Gershkovich and V. K. Kibirev, *Khimicheskii sintez peptidov* [*Chemical Synthesis of Peptides*], Naukova Dumka, Kiev, 1992, 360 pp. (in Russian).
14. V. P. Krasnov, G. L. Levit, I. M. Bukrina, A. M. Demin, O. N. Chupakhin, and Ii Uk Yoo, *Tetrahedron Asymmetry*, 2002, **13**, 1911.

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