## Nucleophilic substitution of halogen in 4-halo derivatives of glutamic acid 3.\* High pressure effect on the stereochemical result of the reaction

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Reactions of diastereomeric dialkyl N-phthaloyl-4-haloglutamates with para-anisidine were studied at high pressure, and an additional confirmation of the exact  $S_N^2$  mechanism of the reactions was obtained. Quantitative parameters of the relative reactivity of the diastereomers were found in various solvents, which made it possible to perform the desired synthesis of products of diastereomeric substitution.

Key words: glutamic acid, diastereoselectivity, nucleophilic substitution, reaction rate constant, high pressure.

Reactions of dimethyl N-phthaloyl-4-bromoglutamates (1) with arylamines are diastereoselective, and the yield of the *threo*-isomeric substitution product is threeto fivefold higher than that of the *erythro*-isomer.<sup>2</sup>

A kinetics model of the process was suggested and the reaction rate constants of diastereoisomeric dialkyl N-phthaloyl-4-bromo- (and 4-iodo-) glutamates 1-3were determined.<sup>3</sup> Substitution of halogen occurs via a mechanism close to the exact  $S_N^2$  reaction. A model for interpretation of the stereoselectivity of the reactions of these conformationally mobile substrates was suggested.<sup>3</sup>



3: 
$$X = Br, Alk = Et$$

Phth is phthaloyl,  $R = n - CH_3O - C_6H_4 - C_6H_4$ 

## a are threo-, b are erythro-isomers

Similar reactions strongly depend on the conditions (solvent, temperature, and pressure).<sup>4</sup> Therefore, the effect of high pressure on the diastereoselectivity of the

\* For Part 2, see Ref. 1.

substitution of halogen in compounds 1-3 under the action of *para*-anisidine in various solvents was studied in this work.

Mixtures of dialkyl (2S,4R)- and (2S,4S)-N-phthaloyl-4-bromo- (or 4-iodo)-glutamates (1b-3b or 1a-3a, respectively) were used. Their initial concentrations in EtOH, MeCN, or C<sub>6</sub>H<sub>6</sub> were 0.0325 mol L<sup>-1</sup>. A twelvefold excess of arylamine was taken.

Current concentrations of the reagents were determined by HPLC. The reaction kinetics was studied at 5 kbar and 68 °C in C<sub>6</sub>H<sub>6</sub> and at 53 °C in EtOH and MeCN. The calculation of the volume of the solvents mentioned at 5 kbar by the Tait equation<sup>5</sup> shows that the effect of different compressibilities on  $k_3$  and  $k_4$ values can be neglected. Rate constants of pseudo-first reactions  $k_3$  and  $k_4$  as well as parameter S ( $S = k_4/k_3$ ) were calculated by the method described previously.<sup>2</sup>

When the pressure increases from normal to 5 kbar, the  $k_3$  and  $k_4$  values increase more than 1000 times for compound 1 in C<sub>6</sub>H<sub>6</sub>, while they increase approximately by 20 times in EtOH and MeCN (Table 1).

The experimental data show that in EtOH and  $C_6H_6$ the sum of the concentrations of compounds **1a** and **1b** at any moment is equal to the initial concentration of **1a** 

**Table 1.** Effect of pressure on diastereoselectivity ( $S = k_4/k_3$ ) of the reaction of dimethyl (2S, 4RS)-N-phthaloyl-4-bromoglutamic acid with *para*-anisidine

T/°C	Solvent	<i>p</i> /kbar	$k_3 \cdot 10^5/s^{-1}$	$k_4 \cdot 10^5/s^{-1}$	S
68	C <sub>6</sub> H <sub>6</sub>	0.001 5.000	0.12 153.00	0.48 527.00	4.0 3.4
53	EtOH	0.001 5.000	0.79 15.80	4.12 67.70	5.2 4.3
53	MeCN	0.001 5.000	0.70 16.20	3.11 51.90	4.4 3.2

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within accuracy of measurements. By analogy, the sum of the concentrations of compounds **1b** and **4a** is equal to the initial concentration of the bromo-substituted derivative of **1b**. This means that the rate of mutual transformation of the isomers of compound **1** is considerably lower than that of nucleophilic substitution. Therefore, according to the model described,<sup>2</sup> the  $k_1$  and  $k_2$ values were accepted equal to zero for calculations of S in these solvents. The  $k_1$  and  $k_2$  values in MeCN are almost the same as those at normal pressure ( $k_1 =$  $3.6 \cdot 10^{-4}$  L (mol s)<sup>-1</sup> and  $k_2 = 3.7 \cdot 10^{-4}$  L (mol s)<sup>-1</sup>) and, as mentioned previously,<sup>2</sup> are effective, because they include the degree of dissociation of *para*-anisidine hydrohalide, the activity of the bromide ion, *etc.* 

Considerable acceleration of the substitution under the action of pressure testifies to the Winstein substitution mechanism without pre-ionization,  $^{6}$  *i.e.*, exact  $S_{N2}$  substitution. The S value changes insignificantly, somewhat decreasing in both  $C_6H_6$  and polar solvents. Since steric hindrance is usually associated with a lower volume than that occupied by the sterically nonhindered stereoisomer.<sup>7</sup> a more sterically strained transition state (from threoisomer) has a lower volume, *i.e.*, the activation volume for reaction 1a ---- 4b is somewhat more negative than that for reaction 1b ---- 4a, and the acceleration of the latter upon pressure is weaker. As a result, the diastereoselectivity of the process decreases as the pressure increases. However, changes in the S parameter of the reactions are insignificant in all solvents. It is likely that an increase in pressure results in similar changes in structures of transition states of parallel reactions.

An increase in pressure results in a decrease in the diastereometric ratio of threo- and erythro-products (R)in the mixture obtained by the reaction of the diastereoisomers of compound 1 (content of 1a in the initial mixture was 67.0 %) (Table 2), which can be caused by a relative decrease in the rate of mutual transformation of the diastereomers of halo-substituted derivatives compared to substitution reactions. Relative retardation of epimerization under pressure allows one to obtain mixtures of isomeric products, which are more enriched in the stereoisomer with the inverted configuration of the C(4) atom than in those obtained at normal pressure from individual diastereoisomers of halo-substituted derivatives. For example, a mixture of products 5 containing 72.4 % of 5b was obtained from individual isomer 3a in 1 h in  $C_6H_6$  at 7.5 kbar, while a mixture containing 70 % of product 4a was obtained from isomer 2b under the same conditions. Therefore, a mixture of products enriched with derivatives of erythro-isomers of 4-arylaminoglutamic acid, which were difficultly accessible previously, can be obtained at high pressure.

Thus, the diastereoselectivity of halogen substitution in the derivatives of 4-haloglutamic acid decreases insignificantly as the pressure increases, which indirectly confirms the conformational nature of diastereodifferentiation. Stereoisomers of derivatives of 4-arylaminoglutamic acid with a higher diastereomeric purity can be

Table 🛛	2. Degri	ee of c	onversi	on and	ratio d	of isomers	of pr	oducts
R = 1/	A1/[B]*	with	various	solvents	and	pressures	at 68	°C

Subst- rate	A (%)	Solvent	<i>p</i> /kbar	Reaction time min	Degree of con- version (%)	R
1	67.0	MeCN	0.001	360	63.5	2.97
			2.5	60	45.9	2.31
			5.0	60	90.4	2.34
			7.5	60	98.9	1.94
2	1.9	C <sub>6</sub> H <sub>6</sub>	7.5	60	100	5.58
3	98.0	C <sub>6</sub> H <sub>6</sub>	7.5	60	99.0	0.155

• A and B are the contents of *threo-* and *erythro-*isomers, respectively.

synthesized under high pressure, using individual isomers of 4-haloglutamates as initial compounds and benzene as a solvent.

## Experimental

Stereoisomers 1-3 <sup>8</sup> and 4,5 <sup>2</sup> were prepared as described previously. A barostat with a 1.5-mL tube was used. To study the kinetics, a weighed sample of a mixture of halo-substituted derivatives 1a and 1b (0.065 mol) was dissolved in 1.0 mL of a solvent. Freshly sublimed amine (0.782 mmol) in 1.0 mL of the solvent was added to the mixture. The mixture was placed in a Teflon tube, which was arranged in a plug of the barostat. The plug was preliminarily heated to the necessary temperature (53 °C in the case of EtOH and MeCN, 68 °C in the case of  $C_6H_6$ ). The mixture was kept for 5 min at this temperature, and the pressure was raised. The temperature was maintained with a thermostat. The reaction mass was stored for 20, 40, and 60 min at 5 kbar. The composition of the mixture was determined as previously by HPLC<sup>2</sup> on a Milikhrom macrocolumn chromatograph (column 64×3 mm, Silasorb 600 as sorbent). The kinetics at normal pressure was studied as described previously.3

## References

- V. P. Krasnov, M. A. Korolev, N. G. Evstigneeva, and I. A. Nizova, *Izv. Akad. Nauk, Ser. Khim.*, 1995, 656 [*Russ. Chem. Bull.*, 1995, 44, 635 (Engl. Transl.)].
- A. Nizova, V. P. Krasnov, O. V. Korotkovskikh, and L. V. Alekseeva, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1989, 2781 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1989, 38, 2545 (Engl. Transl.)].
- V. P. Krasnov and M. A. Korolev, *Izv. Akad. Nauk, Ser. Khim.*, 1995, 652 [*Russ. Chem. Bull.*, 1995, 44, 631 (Engl. Transl.)].
- Y. Izumi and A. Tai, Stereodifferentiating Reactions. The Nature of Asymmetric Reactions, Academic Press, Tokyo, 1979.
- 5. N. S. Isaaks, Liquid Phase High Pressure Chemistry, Wiley, Chichester-New York-Brisbane-Toronto, 1981, 187.
- 6. A. R. Katritzky and B. E. Brycky, J. Phys. Org. Chem., 1988, 1, 1.
- 7. N. S. Isaaks, Liquid Phase High Pressure Chemistry, Wiley, Chichester-New York-Brisbane-Toronto, 1981, 261.
- V. P. Krasnov, I. M. Bukrina, E. A. Zhdanova, M. I. Kodess, and M. A. Koroleva, Synthesis, 1994, 961.

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