Nucleophilic substitution of halogen in 4-halogenated derivatives of glutamic acid

2.* Structural effects of arylamine as nucleophile

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Kinetics of nucleophilic substitution of halogen in diastereomeric dimethyl 4-bromo- and 4-iodoglutamates with *ortho-*, *meta-*, and *para*-substituted anilines was studied by HPLC. The *threo*-diastereomers of the halogenated derivatives react 3—5 times faster than the *erythro* ones. The structure of the transition state is discussed.

Key words: glutamic acid; diastereoselectivity; nucleophilic substitution; rate constant; arylamine.

Previously, it was found that the reaction of dimethyl *N*-phthaloyl-4-bromoglutamate (**1**) with aniline derivatives proceeds diastereoselectively, affording the *threo*-isomer as the major product.[2]

Studying the factors determining the different reactivities of the diastereomers is of significant interest, because it might be useful for the synthesis of biologically active *C(*4)-derivatives of glutamic acid.[3] In addition, these compounds are used in mechanistic studies of enzymatic reactions.[4,5]

In relation to these needs, we investigated the nucleophilic substitution of a halogen in 4-halogenated derivatives of glutamic acid. In the previous communication,[1] we proposed a mathematical model of the process and determined the rate constants for the reactions of the diastereomers of bromide **1** with *p*-anisidine in various solvents. It was shown that the reactions proceeded with the inversion of the configuration of C(4), and the mechanism of the substitution was close to the classical S_N2.

In the present work, the relative reactivities of diastereomers of bromide **1** and iodide **2** (**a** is *threo*, and **b** is *erythro*) in reactions with substituted anilines is studied (Scheme 1).

Both the position of the substituent and its polarity were varied. The pseudo-first order rate constants k_3 and k_4 and the parameter of diastereoselectively $S = k_4/k_3$ of the reaction for diastereomers **1** and **2** were determined as previously described[1] in the presence of a 12-fold excess of the corresponding amine.

The effect of polarity of *para*-substituents on the stereoselectivity was investigated in the following series: *p*-chloroaniline, *p*-toluidine, *p*-anisidine. To elucidate the character of steric hindrances, the reaction was carried out with *o*-, *m*-, and *p*-toluidines, and also with *N*-methyl-*p*-anisidine.

The individual diastereomers **3**—**8** (racemates), which were necessary for identification of the reaction products, were obtained by the reactions of racemic compounds **1** (*RS*-**1**) with the corresponding amine followed by crystallization and column chromatography. The configurations of the diastereomers were determined on the basis of ^{1}H NMR (see Ref. 2, Table 1).

A hexane—THF (5 : 1) eluent (*cf.* Ref. 6) gave the best results in HPLC separation of the products of the reaction with toluidines.

The observed values of the rate constants of the parallel substitution reactions in the isomers and the *S* parameter are presented in Table 2.

The values of k_3 and k_4 decreased with a decrease in the +M-effect of the *para*-substituent, whereas the values of *S* for the reactions with *p*-chloroaniline, *p*-toluidine, and *p*-anisidine are practically equal.

The spatial inhibition of the reaction is characterized by a decrease in k_3 and k_4 and is accompanied by some increase in diastereoselectivity during the interaction of compounds **2** with *N*-methyl-*p*-anisidine *vs.* *p*-anisidine. In the series of *o*-, *m*-, and *p*-toluidines, the *S* value is higher for *m*- than for *p*-toluidine and it is minimum in all the series of the reactions for *o*-toluidine.

One can assume that in the transition state (TS) of the reaction of substitution of a halogen by amine, the C(2) and C(3) atoms are located approximately in one plane with C(4), C(5), and 4-H; this only minimally impedes the nucleophilic attack and the leaving of the halide ion.

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* Part 1, see Ref. 1.

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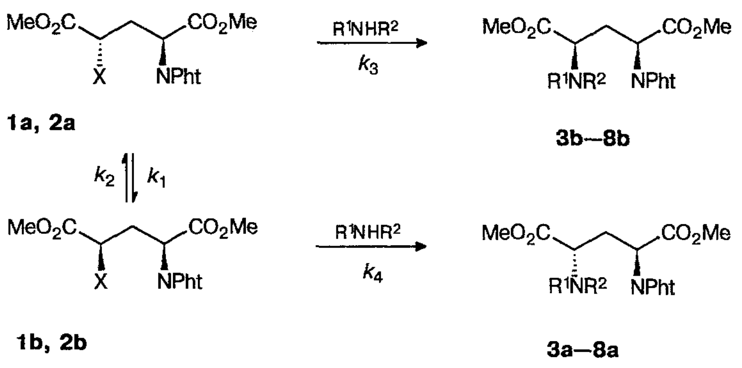
Scheme 1

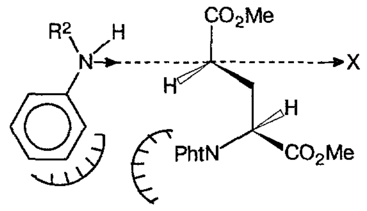


X = Br (**1**), I (**2**), Pht = phthaloyl
R^1 = *p*-$MeOC_6H_4$ (**3**, **5—8**); *m*-MeC_6H_4 (**6**); *o*-MeC_6H_4 (**7**);
R^2 = H (**3**, **5—8**); Me (**4**)

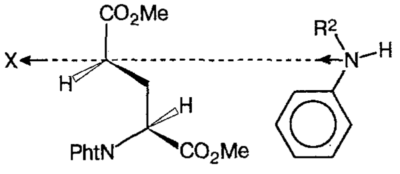
The reasons for the different reactivities of the diastereomers are apparently conformational, because the products of side reactions of carbonyl groups are absent, and, as has been shown previously,[1] the product with the retention of configuration was not observed, like it would be in the case of anchimeric assistance of the neighboring groups.[7] Therefore, the result of the reaction is determined only by the difference in steric hindrances generated by the most bulky substituents at C(2).

The *erythro*-diastereomers of compounds **1** and **2** react with the substituted anilines faster than the *threo*-isomers, so one can assume that in TS, the carbon chain of the substrate forms the conformations presented in Scheme 2. Simultaneously, the ester group at C(1) is maximally distant from C(5), and the carbon chain has the *trans-trans*-conformation, which has minimum repulsive interactions of the bulky functional groups, and the *N*-phthaloyl group in the *threo*-diastereomer shields the pathway for the nucleophile.

Scheme 2



TS formed from the *threo*-derivative (**a**)



TS formed from the *erythro*-derivative (**b**)

Table 1. Effective rate constants of substitution for *threo*- (k_3) and *erythro*-substrates (k_4) and the stereoselectivity *S* parameter for the reactions of compounds **1** and **2** with arylamines (68 °C, initial ratio of halogen derivative to amine is 1 : 12)

Substrate	Nucleophile		Solvent					
			Ethanol			Acetonitrile		
	R^1	R^2	$k_3 \cdot 10^5/s^{-1}$	$k_4 \cdot 10^5/s^{-1}$	*S*	$k_3 \cdot 10^5/s^{-1}$	$k_4 \cdot 10^5/s^{-1}$	*S*
1	*p*-OMe	H	2.1	10.2	4.9	1.7	7.0	4.1
1	*p*-Cl	H	0.17	0.88	5.2	—	—	—
2	*p*-OMe	H	2.9	12.7	4.3	2.9	10.1	3.4
2	*p*-OMe	Me	—	—	—	0.90	4.28	4.7
2	*p*-Me	Me	1.2	5.3	4.4	0.97	4.11	4.2
2	*m*-Me	H	—	—	—	0.69	3.49	5.0
2	*o*-Me	H	0.14	0.46	3.2	0.11	0.34	3.1
2	*p*-Cl	H	0.24	1.17	4.9	0.11	0.43	4.0

The kinetic data confirm this hypothesis. Thus, *S* is from 3.1 to 5.0 for the interaction of diastereomers **2a** and **2b** with arylamines (this fact also suggests the conformational nature of the diastereoselectivity).[8] In the case of *o*-toluidine, the rate constants for diastereomers **2a** and **2b** are approximately 10 times lower than those of *p*-anisidine. The ratio k_4/k_3 also decreases due to additional spatial hindrances, which are caused by the *ortho*-effect of the substituent. The character of this hindrances differs from those arising in the case of *para*-substituted anilines. On the contrary, *S* increases significantly for *m*-toluidine in comparison with the *para*-isomer, probably due to increases in the similar steric hindrances. This phenomenon probably arises because the interaction of the *meta*-methyl group with the *N*-phthaloyl ring in TS is stronger than that of the *ortho*-methyl. The increase in *S* in the case of *N*-methyl-*p*-anisidine in comparison with *p*-anisidine, probably results from the additional hindrances that arise when the nucleophile is approaching the reaction center, thus making the entropy requirements more rigorous, as occurs in the reaction in nucleophilic solvents.[1]

The diastereoselectivity of the reaction of arylamines with bromides **1a** and **1b** is higher than that of iodides **2a** and **2b** under the same conditions (either in ethanol or in acetonitrile). The apparent reason is that the bromide anion is harder than iodide. The former leaving group requires a closer approach of the nucleophile and, hence, creates stronger spatial hindrances, which cause significant differences in the reactivities of the diastereomers.

In spite of the lower diastereoselectivity of the reactions of arylamines with iodo derivative **2** *vs.* bromo derivative **1**, compound **2** was used for this study because its higher reactivity allows one to reduce significantly the time of an experiment.

Thus, the relative reactivities of diastereomeric halo derivatives of glutamic acid depend on the structure of both the nucleophile and the substrate. The diastereoselectivity depends on the non-bonding interactions between the nucleophile and the bulky functional groups of the substrate. Further investigations are needed to elucidate the details of this process.

Experimental

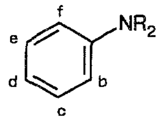
The ^1H NMR spectra were recorded with a Tesla BS-567A spectrometer (100 MHz) in $CDCl_3$ using tetramethylsilane as the internal standard. The IR spectra were obtained with a Specord 75-IR spectrometer in a thin film or in nujol, and the UV spectra were measured with a Specord UV-VIS spectrophotometer in ethanol. HPLC was carried out on a Millikhrom chromatograph, using a Silasorb C18 column (64×2 mm). Detection was carried out at 220 nm (hexane—2-propanol, 40 : 1, (A)) and at 230 nm (hexane—THF, 5 : 1 (B); hexane—THF, 7 : 1 (C)). The flow rate was 0.20 mL min^{-1}. The separation coefficient was 1.35 to 1.80. Silufol UV-254 standard plates were used for TLC, and the following eluents were used: chloroform—acetone, 4 : 1 (D); hexane—ethyl acetate, 85 : 15 (E); chloroform—benzene—acetone, 5 : 4 : 2 (F); hexane—toluene—acetone, 5 : 4 : 3 (G). Silica gel Chemapol L 100/250 was used for column chromatography.

Compounds **1a**, **1b**, **2a**, and **2b** were prepared using known procedures.[9] Compounds **3**, **5**, and **8** were obtained as de-

Table 2. ^1H NMR spectra of the prepared compounds

Compound	δ										
	CH_2 (m, 2 H)	Δδ	5-OMe (s, 3 H)	1-OMe (s, 3 H)	N–Me (s, 3 H)	C(4)–H (dd, 1 H)	C(2)–H (dd, 1 H)	PhtH (m, 4 H)	Protons of the arylamino group		
									Me (s, 3 H)	C_6H_4*	
4a	2.87	0.22	3.69	3.74	2.89	4.18	5.06	7.76	3.60	6.68	
4b	2.84	0.49	3.68	3.70	2.80	3.96	4.61	7.76	3.60	6.69	
										bdf (m, 3 H)	e (t, 1 H)
6a	2.56	0.17	3.67	3.73	—	4.08	5.20	7.80	2.17	6.45	6.95
6b	2.76	0.62	3.50	3.72	—	4.20	5.18	7.82	2.16	6.43	6.93
										ce (m, 2 H)	fd (m, 2 H)
7a	2.81	0.14	3.68	3.74	—	4.11	5.20	7.78	2.16	6.99	6.57
7b	2.88	0.46	3.49	3.62	—	4.44	4.86	7.81	2.21	6.98	6.55

* The positions of protons in the aromatic nucleus are given as shown:



scribed previously.[2] The ^{1}H NMR spectra of these compounds are in accordance with the published ones. The retention times in eluent B were 4.9 min for **1a**, 4.3 min for **1b**, 4.8 min for **2a**, and 4.1 min for **2b**. The solvents were purified and dried by standard procedures.[10]

General procedure of kinetic measurements. A mixture of diastereomers of halo derivatives **1a** and **1b** or **2a** and **2b** (0.065 mmol) was dissolved in ethanol or acetonitrile (1.0 mL), and a solution of freshly sublimated amine (0.782 mmol) in 1.0 mL of the same solvent was added and thermostatted in a sealed vessel at 68 °C (a UW-4 thermostat). In the cases of *p*-chloroaniline or *o*-toluidine, the reaction mixture was placed in sealed ampules, which were thermostatted and opened at definite time intervals. Aliquots ($V \approx 3$ μL) were taken with a micropipette, dissolved in 1 mL of a mixture of the eluent (see above) with benzene (20 : 5), and chromatographed. Average values of relative concentrations of reactants were taken for calculations.

Concentrations of reactants were calculated taking into account the extinction coefficients obtained by calibration using artificial mixtures with substrate : product ratios of 1 : 1, 1 : 2, and 2 : 1.

Dimethyl *threo*- and *erythro*-4-(*N*-methyl-*p*-anisidino)-*N*-phthaloylglutamates (*RS*-4a, *RS*-4b). A solution of a mixture of isomers of bromo derivative *RS*-**1** (1.4 g, 3.6 mmol) and *N*-methyl-*p*-anisidine (1.5 g, 11 mmol) in MeOH (9 mL) was refluxed for 32 h and evaporated *in vacuo*. The dark oily residue was precipitated from 50 % MeOH. The product *RS*-**4** (0.6 g, 38 %) was obtained as a slightly yellow oil, containing 83 % *threo*-isomer. R_f 0.63 (D). Found (%): C, 62.69; H, 5.39; N, 6.27. $C_{23}H_{24}N_2O_7$. Calculated (%): C, 62.72; H, 5.45; N, 6.36. IR (thin layer), ν/cm^{-1}: 3350 (NH); 1750 (C=O of phthaloyl group); 1700 (C=O of ester groups). UV, λ_{max}/nm: 210 sh. (arylamino group); 221, 301 (phthaloyl group). Mother liquor was evaporated *in vacuo*, and the residue was precipitated from 50 % ethanol. The slightly yellow oil contained a mixture of isomers *RS*-**4a** and *RS*-**4b** (0.65 g, 40 %) in the ratio of 1 : 1 (total yield of *RS*-**4** was 1.25 g (78 %)). Retention times (HPLC, B): isomer **4b** 7.50 min, isomer **4a** 8.23 min. The separation coefficient was 1.46.

Dimethyl *threo*- and *erythro*-4-(*m*-toluidino)-*N*-phthaloylglutamates (*RS*-6a, *RS*-6b). A solution of *RS*-**1** (6 g, 15 mmol) and *m*-toluidine (5.04 g, 46.8 mmol) in dry acetonitrile (5 mL) was stirred at 50 °C for 14 h. The precipitated amine hydrobromide was separated, and the solvent was removed *in vacuo*. The residue was crystallized from MeOH. *RS*-**6** (4.1 g, 64 %) was obtained as colorless crystals, m.p. 145—162 °C, R_f 0.57 (F) (the content of *RS*-**6a** was 61 %). Found (%): C, 63.98; H, 5.40; N, 6.96. $C_{22}H_{22}N_2O_6$. Calculated (%): C, 64.39; H, 5.66; N, 6.82. IR (nujol), ν/cm^{-1}: 3350 (NH); 1755 (C=O of phthaloyl group), 1720, 1700 (C=O of ester groups). UV, λ_{max}/nm: 210 (*m*-toluidino group), 220 sh., 294 (phthaloyl group). Separation of isomers was carried out on a silica gel column (eluents G, then F). Retention times (HPLC, B): isomer **6b** 5.25 min, isomer **6a** 6.00 min. The separation coefficient was 1.50.

Dimethyl *threo*- and *erythro*-4-(*o*-toluidino)-*N*-phthaloylglutamates (*RS*-7a, *RS*-7b). A solution of *RS*-**1** (5 g, 13 mmol) and *o*-toluidine (4.2 g, 39 mmol) in dry acetonitrile (5 mL) was stirred at 52 °C for 15 h. The precipitated amine hydrobromide was separated. The solvent was removed *in vacuo*. The residue was recrystallized from MeOH. *RS*-**7** (2.35 g, 44 %) was obtained as slightly yellow crystals, m.p. 119—122 °C, containing 56.5 % *RS*-**7a**, R_f 0.16 (D). Found (%): C, 64.24; H, 6.05; N, 6.88. $C_{22}H_{22}N_2O_6$. Calculated (%): C, 64.39; H, 5.66; N, 6.82. IR (nujol), ν/cm^{-1}: 3355 (NH); 1755 (C=O of phthaloyl group); 1700 (C=O of ester groups). UV, λ_{max}/nm: 211 (*o*-toluidino group), 221, 294 (phthaloyl group). After evaporation of the mother liquor, the separation of diastereomers was carried out on a silica gel column (G, then E). Retention times (HPLC, C): isomer **7b** 4.03 min, isomer **7a** 4.25 min. The separation coefficient was 1.35.

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