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

1. Solvent effect

V. P. Krasnov and M. A. Koroleva*

Institute of Organic Synthesis, Ural Branch of the Russian Academy of Sciences, 20 ul. S. Kovalevskoi, 620219 Ekaterinburg, Russian Federation. Fax: +7 (343 2) 440 458

The reaction of nucleophilic substitution of bromine by *p*-anisidine in dimethyl *(2S,4S)*- and *(2S,4R)*-*N*-phthaloyl-4-bromoglutamates proceeds according to the S_N2 mechanism. The relative reactivity of diastereomers in various solvents was studied.

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

Amino acids are widely used as optically active synthons.[1,2] If a new chiral center is introduced into an amino acid molecule, diastereomers are formed, as a rule, in unequal amounts.[3] If two chiral centers are present in the amino acid molecule, the configuration of a product in which one of them is modified depends on the structure of both centers.[4]

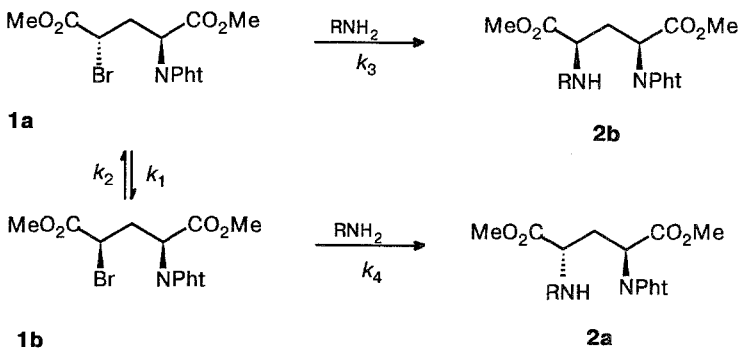
A similar phenomenon, resulting from different reactivities of diastereomers, is observed for haloamino acid derivatives used as chiral synthons. It has been shown previously that the reaction of dimethyl *N*-phthaloyl-4-bromoglutamate with aromatic amines proceeded diastereoselectively with the predominant formation of the *threo*-isomers,[5] which were used in the synthesis of (2*S*,4*S*)-4-arylaminopyrrolidones.[6]

The 4-haloglutamic acid derivatives are used for the preparation of *C*(4)-derivatives of glutamic acid,[7,8] therefore, it is interesting to study the factors that determine the yields and stereoisomeric composition of the products.

Results and Discussion

In the present work, the effect of the solvent on the rate and diastereoselectivity of the reaction of dimethyl (2*S*,4*RS*)-*N*-phthaloyl-4-bromoglutamate (**1**) with *p*-anisidine is studied. Compound **1** is a mixture of (2*S*,4*S*)- and (2*S*,4*R*)-diastereomers (**1a** and **1b**). A mixture of (2*S*,4*R*)- and (2*S*,4*S*)-isomers of dimethyl *N*-phthaloyl-4-(4'-methoxyphenylamino)-glutamate (**2b** and **2a**) is formed in the reaction (Scheme 1).

Scheme 1



R = *p*-$MeOC_6H_4$, Pht = phthaloyl

Translated from *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 4, pp. 652—655, April, 1995.

In kinetic studies of the reaction, the relative concentrations of compounds **1a**, **1b**, **2b**, and **2a** were determined by HPLC. The process was carried out at 68 °C in the presence of a 12-fold excess of *p*-anisidine.

It was established that when **2a** and **2b** were heated with *p*-anisidine hydrobromide, both reverse reactions and mutual transformations were absent. During heating of initial compounds **1a** and **1b** in various solvents, epimerization was observed, with rates increasing[9] in the following order: ethanol < acetonitrile < DMF.

It was shown in preliminary experiments that the starting compound **1** containing 60—70 % (2*S*,4*S*)-stereoisomer **1a**, gave a mixture of products containing 65—75 % (2*S*,4*S*)-stereoisomer **2a**. Hence one could assume that the nucleophilic substitution of bromine in compound **1** proceeds with retention of configuration. However, it was established that when individual stereoisomers **1a** and **1b** were used, only the starting compound and product having the inverted C(4) configuration were found in the reaction mixture in the initial period. Simultaneously, as a result of epimerization of halogenated derivative **1**, catalyzed by the bromide anion formed,[10] the second diastereomer of halogenated derivative **1** is accumulated in the reaction mixture, and is transformed into the second diastereomer of compound **2** with inversion of the configuration. Thus, the replacement of the halogen in compound **1** with *p*-anisidine is accompanied by inversion of the C(4) configuration.

The formation of stereoisomers **2b** and **2a** from **1a** and **1b** has practically the same reaction rate in ethanol in the presence of 1 eq. of LiBr. The absence of the common ion effect in conjunction with Walden inversion allows one to assume that the reaction of halogenated derivatives **1a** and **1b** with *p*-anisidine proceeds through a tight transition state without pre-ionization;[11] the mechanism of the reaction is similar to "rigorous" S_N2.

The data presented indicate the significant dependence of the concentrations of reaction products on the diastereomeric composition of the initial halogenated derivative, the nature of the solvent, and the rates of epimerization and nucleophilic substitution. Hence, these concentrations cannot be a measure of the diastereoselectivity of the S_N reaction. The ratio $S = k_4/k_3$ is usually used for this.[12]

This results allows one to propose the following system of differential equations to describe the changes in concentrations in the course of this pseudo-first order reaction:

$$d[\mathbf{1a}]/dt = -(k_1[\mathbf{1a}]-k_2[\mathbf{1b}])([\mathbf{2b}]+[\mathbf{2a}])-k_3[\mathbf{1a}] ,$$

$$d[\mathbf{1b}]/dt = (k_1[\mathbf{1a}]-k_2[\mathbf{1b}])([\mathbf{2b}]+[\mathbf{2a}])-k_4[\mathbf{1b}] ,$$

$$d[\mathbf{2b}]/dt = k_3[\mathbf{1a}] ,$$

$$d[\mathbf{2a}]/dt = k_4[\mathbf{1b}] ,$$

where [**1a**], [**1b**], [**2b**], [**2a**] are the current concentrations of reactants. The value ([**2b**]+[**2a**]) is equal to the concentration of the halide ion formed in the reaction.

The solution of the system of differential equations with the initial conditions [**1a**] = [$\mathbf{1a}_0$], [**1b**] = [$\mathbf{1b}_0$], [**2a**] = [**2b**] = 0 was performed by the numerical method. To calculate the time functions of the concentrations of the reactants and to see a graphical presentation of the results, a C-program for IBM PC/AT computers was written. The determination of k_1, k_2, k_3, k_4 was performed by the method of root mean square deviations for the experimental and calculated values of the current concentrations in each experiment with known initial conditions. (The relative error in the determinations of the constants for 4—6 measurements of concentrations did not exceed 15 % for k_1 and k_2, and 8 % for k_3 and k_4.) The minimization was carried out by the Hook—Jives method.[13]

The data presented in Figs. 1 and 2 indicate good agreement between the calculations and the experimental data. Simultaneously, the method has some limitations, because the system is not ideal and the law of mass action can be applied only to a certain extent. In particular, to accelerate the process and simplify calculations, a large excess of *p*-anisidine was used. The latter is not only a nucleophile, but it binds eliminated HBr.

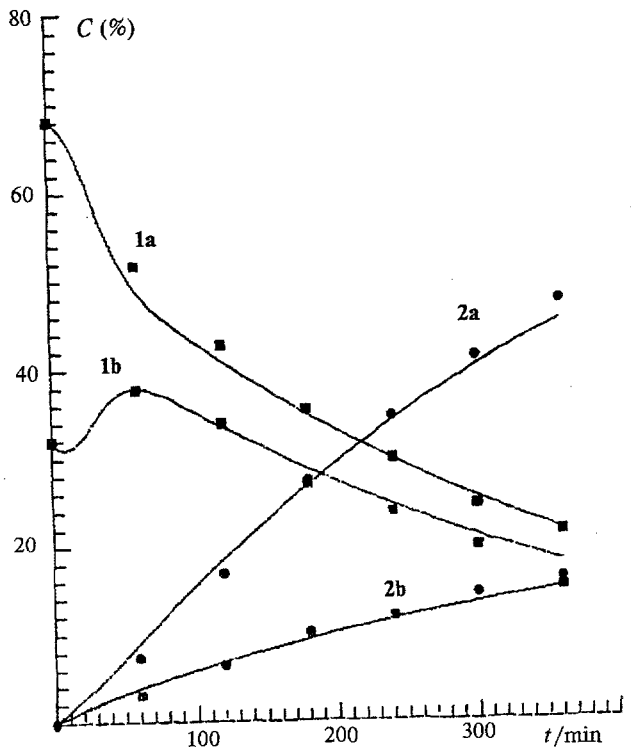


Fig. 1. Plots of the relative concentrations of reactants *vs.* time (acetonitrile, 68 °C). Experimental values are shown with circles, and calculated data are given with solid lines.

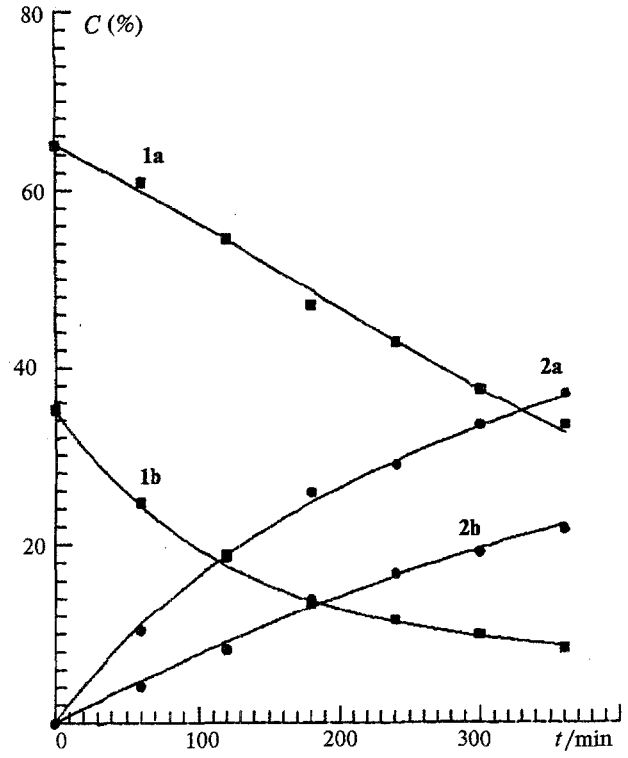


Fig. 2. Plots of the relative concentrations of reactants *vs.* time (ethanol, 68 °C). Experimental values are shown with circles, and calculated data are given with solid lines.

Both the degree of dissociation of the hydrobromide and the activity coefficient for bromide are included in the k_1 and k_2 values, so they are effective. However, in the mathematical model chosen, the accuracy of the determination of k_3 and k_4 practically depends only on the k_1/k_2 ratio, which is 1.0—1.3. The calculated k_3, k_4, and S values are presented in Table 1.

The striking increase in the rate of the S_N reaction during transfer from benzene to polar solvents is apparently due to greater polarization in the transition state than in the molecules of the initial compounds. The k_3 and k_4 values for polar protic and aprotic solvents differ slightly and increase with an increase in nucleophilicity of the solvent (according to Parker's order:[14] acetonitrile < ethanol ≈ *tert*-butanol < sulfolan << DMF); the phenomenon is characteristic for S_N2 reactions. The role of the nucleophilic solvent[15] is to assist in polarization of the C—Br bond. The S value, which characterizes the different reactivities of diastereoisomers **1a** and **1b**, increases slightly during the transfer from protic and aprotic solvents. This apparently indicates that the difference in the energy of transition states of diastereomers is proportional to the energies of the specific and non-specific interactions of the stereoisomers with a solvent. An increase in S for solvents of similar nature in parallel with the size of the solvent molecule was observed (ethanol < *tert*-butanol; acetonitrile < DMF < sulfolan). The largest S value was obtained for sulfolan, probably due to specific steric requirements for the orientation of a bulky solvent molecule in the tight transition state.

Table 1. Donor and acceptor numbers, k_3, k_4, and S values in different solvents at 68 °C

Solvent	Polarity of the medium, $\varkappa$	DN	AN	$k_3 \cdot 10^5$ /s^{-1}	$k_4 \cdot 10^5$ /s^{-1}	S
Benzene	0.232	0.4	8.3	0.22	1.1	5.0
tert-Butanol	0.441	—	34.1	1.3	6.7	5.1
Ethanol	0.469	31.5	31.5	2.1	10.2	4.9
Acetonitrile	0.480	14.1	18.9	1.7	7.0	4.1
DMF	0.479	26.6	16.0	6.8	35.3	5.2
Sulfolan	0.483	14.8	—	5.2	30.7	5.9

Note. For the donor and acceptor numbers of solvents see Refs. 12, 15—18.

The difference in the reactivity of the diastereomers has a significant influence on the reaction. Thus, the conversion of the mixture containing 65 % **1a** and 35 % **1b** after 3 h is 40 % in ethanol and 80 % in sulfolan. The ratio of diastereomers **2a** : **2b** in the first case is 1.6 : 1, and in the second case it is 3.1 : 1.

Experimental

Compounds **1a**, **1b** and **2a**, **2b** were prepared by known procedures.[5,9] A solution of freshly sublimated amine (0.782 mmol) in 1.0 mL of solvent was added to a mixture of halogenated derivatives **1a** and **1b** (0.065 mmol). The cell was sealed and thermostatted at 68 °C in a UW-4 thermostat. Aliquots ($V \approx 3$ μL) were taken periodically by a micropipette, dissolved in 1 mL of a mixture of eluent and benzene (20 : 5), and chromatographed on a Millikhrom instrument at 220 nm. A mixture of hexane and 2-propanol (40 : 1) was used as the eluent. The measurements were carried out three times in two parallel experiments. 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 the substrate : product ratios 1 : 1, 1 : 2, and 2 : 1.

The authors thank M. L. Gal'perin for assistance in designing the computer program for the calculations of the kinetic parameters.

References

1. G. M. Coppola and H. F. Schuster, *Asymmetric Synthesis. Construction of Chiral Molecules Using Amino Acids*, Wiley Interscience Publ. J. Wiley and Sons, New York—Chichester, 1987, 223.
2. *Studies in Natural Products Chemistry. Stereoselective Synthesis (Part A)*, Ed. Atta-ur-Rahman, Elsevier, New York, 1988, **1**, 331.
3. J. E. Baldwin, T. Miranda, M. Moloney, and T. Hokelek, *Tetrahedron*, 1989, **45**, 7459.

4. Y. Izumi and A. Tai, *Stereo-Differentiating Reactions. The Nature of Asymmetric Reactions*, Kodansha Ltd., Tokyo, Academic Press, New York—San Francisco, 1977.
5. I. A. Nizova, V. P. Krasnov, O. V. Korotovskikh, and L. V. Alekseeva, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1989, 2781 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1989, **39**, 2545 (Engl. Transl.)].
6. I. A. Nizova, V. P. Krasnov, T. A. Sinitsina, and N. V. Avdyukova, *Izv. Akad. Nauk, Ser. Khim.*, 1993, 2087 [*Russ. Chem. Bull.*, 1993, **42**, 2001 (Engl. Transl.)].
7. G. G. Vatulina, T. N. Tuzhilkova, T. V. Matveeva, V. P. Krasnov, N. L. Burde, and L. V. Alekseeva, *Khim. Farm. Zhurn.* [*Chem. Pharm. J.*], 1986, **20**, 1078 (in Russian).
8. C. Ducrocq, A. Righini-Tapie, R. Azerad, J. F. Green, P. A. Friedman, J.-P. Beaucourt, and B. Rousseau, *J. Chem. Soc., Perkin Trans. 1*, 1986, 1323.
9. V. P. Krasnov, I. M. Bukrina, E. A. Zhdanova, M. I. Kodess, and M. A. Korolyova, *Synthesis*, 1994, № 7.
10. C. K. Ingold, *Structure and Mechanism in Organic Chemistry*, Cornell Univ. Press, Ithaca and London, 1969.
11. A. R. Katritzky and B. E. Brycki, *J. Phys. Org. Chem.*, 1988, **1**, 1.
12. N. S. Isaacs, *Physical Organic Chemistry*, Longman Sci. and Tech., Belfast, 1987, 315.
13. B. Bandy, *Metody optimizatsii* [*Optimization Procedures*], Radio i Svyaz', Moscow, 1988, 37 pp. (in Russian).
14. L. P. Hammet, *Physical Organic Chemistry*, McGraw Hill Book Company, New York, 1970.
15. V. Gutmann, *Coord. Chem. Rev.*, 1976, **18**, 225.
16. W. R. Fawcett and T. M. Krygowski, *Can. J. Chem.*, 1976, **54**, 3283.
17. W. R. Fawcett and T. M. Krygowski, *J. Am. Chem. Soc.*, 1975, **97**, 2143.
18. V. Gutmann, *Electrochem. Acta*, 1976, **21**, 661.

Received July 4, 1994