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.\(^1\)

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 SN2.

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.

* Part 1, see Ref. 1.
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.

### Table 1. Effective rate constants of substitution for threo- (k₃) and erythro-substrates (k₄) 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)

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Nucleophile</th>
<th>Ethanol</th>
<th>Acetonitrile</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>R¹</td>
<td>R²</td>
<td>k₃ · 10⁵/s⁻¹</td>
</tr>
<tr>
<td>R¹</td>
<td>R²</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 p-OMe</td>
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<td>Me</td>
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<tr>
<td>2 p-Cl</td>
<td>H</td>
<td>0.24</td>
<td>1.17</td>
</tr>
</tbody>
</table>