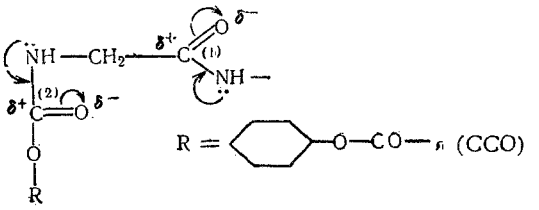
INFLUENCE OF THE NATURE OF THE AMIDE GROUP ON THE RATE OF SPLITTING OUT OF THE CARBOCYCLOHEXYLOXY PROTECTOR DURING HYDROBROMINOLYSIS

(UDC 547.466 + 542.938)

K. T. Poroshin, T. P. Chuvaeva, and V. A. Shibnev

Institute of Biological Physics, Academy of Sciences, USSR, and
V. I. Lenin Tadzhik State University
Translated from Izvestiya Akademii Nauk SSSR, Seriya Khimicheskaya, No. 8,
pp. 1548-1550, August, 1964
Original article submitted January 23, 1964

Under the action of HBr in glacial CH_3COOH on the carbocyclohexyloxy group (CCO), it was found that the rate of its splitting out depends on whether it is bonded to an amino acid or a peptide [1]. We proposed that such a difference should depend on the state of the electron density of the nitrogen of the amide group (scheme 1), which



in turn determines the greater or lesser electronegativity of the carbon of the carbonyl group (C_1), and this exerts its own influence on the different degree of compensation of the positive charge C_2 on account of the displacement of the electron density of the neighboring nitrogen atom. It was found that of the compounds obtained (Table 1), only CCO-gly-amide does not undergo the action of hydrobrominolysis even under rigorous conditions (boiling) and is an extreme case in comparison with the other amides (Fig. 1). Evidently the weaker the base, the more strongly the electron pair of nitrogen will be displaced toward the carbonyl group (C_1) possessing the C-effect. Hence, in the case of an amide of an acid which is a rather weak base [2], we should expect rather good compensation of the positive charge on the carbonyl carbon (C_2) of the urethan protector on account of displacement of the electrons of the neighboring nitrogen atom. The complete inertness of this compound with respect to HBr in glacial CH_3COOH is evidence in favor of this hypothesis. The splitting out of the CCO group in CCO-gly proceeds with great difficulty. Evidently, in this case the -OH group has less influence on the basicity of the carbonyl group at C_1 than does the -NH group. As we pass to CCO-gly-pro and the piperidide of CCO-gly, we can see that a certain kinship of these compounds on account of the tertiary nitrogen atom also leads to an approximately equivalent rate of splitting out of the CCO groups from these compounds. Although K_{base} of aniline is less than K_{base} of NH_3, and hence we should have expected a weaker splitting out of the CCO group from CCO-gly-anilide in comparison with CCO-gly-amide, nonetheless we observed an increase in the rate. This was due to the fact that the electron pair of the nitrogen of the amide bond is already found under the competitive influence of the benzene ring and the C-effect of the carbonyl group, which also leads to a certain intensification of the basic properties of the amide group; moreover, the rate of splitting out of the CCO group of CCO-gly-anilide becomes comparable with the rate of splitting out from CCO-gly-n-butylamide, in which n-butylamide, which forms the amide, is an incomparably stronger base than amonia [3].

The behavior of the methyl ester of CCO-gly-gly and that of CCO-gly-gly are of interest. According to the above, we should have expected that the rate of splitting out of the CCO group of these compounds should be very close to the rate of splitting out in the case of CCO-gly-pro or CCO-gly-pro-ala; in any case, it should not exceed the rate of splitting out of the CCO group in the n-butylamide of CCO-gly, as is detected experimentally. Obviously

TABLE 1

Compound	Gross formula	Mol. wt.	C, %	H, %	M. p., °C (solvent for crystallization)	Yield, %
CCO-gly	$C_9H_{15}NO_4$	201	–	–	98	
CCO-gly-gly-OCH_3	$C_{12}H_{20}N_2O_5$	272	52.74 52.21	7.44 7.36	83 Ethyl acetate	30.8
CCO-gly-anilide	$C_{15}H_{20}N_2O_3$	276	65.71 65.18	7.29 7.47	163 Ethanol	34
CCO-gly-n-butylamide	$C_{13}H_{24}N_2O_3$	256	60.33 60.68	10.67 9.3	70 Petroleum ether	26
CCO-gly-piperidide	$C_{14}H_{24}N_2O_3$	268	62.80 62.47	8.97 8.59	106 Methanol	36.5
CBZ-gly-piperidide	$C_{15}H_{20}N_2O_3$	276	–	–	109 Menthol	17
CCO-gly-amide	$C_9H_{16}N_2O_3$	200	54.0 53.85	8.00 8.00	340 With decomposition (methanol)	50
CCO-gly-gly	$C_{11}H_{18}N_2O_5$	258	51.25 51.00	6.98 6.83	38 Petroleum ether	30
CCO-gly-gly-O-CH_2	–	–	–	–	96 Methanol-water	47

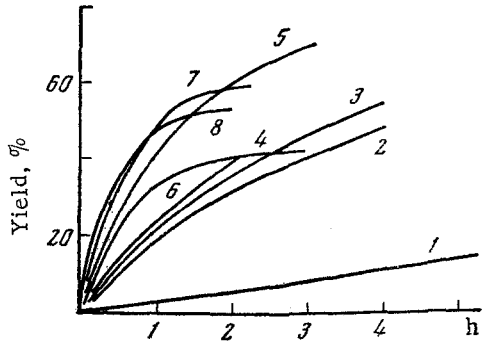


Fig. 1. Relative rate of splitting out of the CCO group from CCO-glycyl-amides in the presence of HBr in glacial CH_3COOH. 1) CCO-glycine; 2) CCO-glycyl-proline; 3) CCO-glycyl-prolyl-alanine; 4) CCO-glycyl-anilide; 5) CCO-glycyl-n-butylamide; 6) CCO-glycyl-piperidide; 7) methyl ester of CCO-glycyl-glycine; 8) CCO-glycyl-glycine.

this indicates that we must consider the nature of the amino acid residues, which can substantially change the stability of the CCO-protector with respect to the action of hydrobrominolysis during the process of use of the CCO-group, which opens up additional possibilities for the use of protection of the urethan type in peptide synthesis.

EXPERIMENTAL SECTION

CCO-gly-anilide. CCO-gly (6 g) was dissolved in 30 ml of dry $CHCl_3$, 3.72 ml of triethylamine was added, the solution was cooled to -15°, and 27 ml of ethyl chloroformiate was added. The reaction mixture was exposed at -15° for 1 h; the temperature was raised to 2°, the mixture exposed for 5 min, and then cooled again to -15°. Then 2.7 ml of aniline was added. The reaction mixture was exposed at 0° for 1 h, at ~20° for 2 h, and at 50° for 10 min. After cooling to room temperature, the solution was diluted twice with $CHCl_3$ and washed with water, 1 N HCl, 0.5 N $NaHCO_3$, and water. It was dried over anhydrous Na_2SO_4, and the solvent distilled off under vacuum. The CCO-gly-anilide obtained was recrystallized from alcohol, yield 3 g (34%), m.p. 163°. Found: C 65.71; H 7.47%. $C_{15}H_{20}N_2O_3$. Calculated: C 65.18; H 7.29%. The constants of the other CCO-gly-amides are presented in Table 1.

Hydrobromide of Glycyl-Anilide. CCO-gly-anilide (0.5 g) was suspended in 2 ml of 40% HBr in glacial CH_3COOH. The mixture was allowed to stand until complete solution of the precipitate. Dry ether was added to the reaction mixture, the precipitate that formed washed with ether, and dried over alkali under vacuum. Yield 0.22 g (52%), m.p. 198°; R_f 0.66. The constants of the remaining hydrobromides of amides of CCO-gly are presented in Table 2.

Hydrobrominolysis of CCO-glycyl-amides. To keep the HBr concentration constant during the reaction, hydrobrominolysis was conducted in sealed ampoules. The reaction temperature was 56° (vapors of boiling acetone). In all cases 0.02 g of the substance was used for the reaction, and this amount was dissolved in 1 ml of glacial CH_3COOH, containing 40% HBr (by weight). The solution was poured into six ampoules, which were sealed and placed in vapors

TABLE 2

Compound (hydrobromides)	R_f	M.p., °C	Yield, %	Compound (hydrobromides)	R_f	M.p., °C	Yield, %
Gly-anilide	0.66	198	52	Gly-piperidide	0.39	–	70
Gly-gly-OCH_3	0.36	94	52	Gly-gly	0.14	124	81
Gly-n-butylamide	0.76	54	66				

of boiling acetone. Samples were taken after 15, 30 min, 1, 2, 3, and 4 h. After the heating was stopped, the ampoules were frozen in an ice-salt mixture. Three spots were applied from each sample on an ascending chromatogram, using a pipette for quantitative application, accommodating 0.00525 ml of solution.

Chromatography and Colorimetry. Chromatography was conducted in the system butanol : water : CH_3COOH (4 : 5 : 1), on "Leningrad" paper, type "M," longitudinal. The chromatograms were run for 15 h. They were dried in air and developed with a 0.5% ninhydrin solution in 95% aqueous acetone and exposed at 20° for 18-20 h. The spots were eluted with 6 ml of 75% ethanol, containing 70 mg of $CuSO_4$ per 100 ml of solution. The elution was continued for 2-3 h. Colorimetry was performed on the FÉK-M instrument with l = 10 mm and at μ = 570 mμ (green filter). Each point in Fig. 1 represents an arithmetic mean of three measurements.

In conclusion, the authors would like to thank V. G. Debabov for his aid in the work.

CONCLUSIONS

1. A series of CCO-glycyl-amides was synthesized.

2. A pattern was detected in the rate of splitting out of the CCO group as a function of the basicity of the amine forming the amide bond.

LITERATURE CITED

1. V. G. Debabov and V. A. Shibnev, Izv. AN SSSR. Otd. Khim. N.,870 (1963).
2. R. Huisgen and H. Brade, Chem. Ber. 90, 1433 (1957).
3. H. Brown, H. Bartholomay, and M. Taylor, J. Amer. chem. Soc. 66, 435 (1944).