67.6 ± 2.4 kcal/mole, respectively. For D(Br—Br) and D(H—Br) we have used the values 46.1 ± 0.03 and 87.6 ± 0.13 kcal/mole. The heat of reaction calculated from this data is $+14.6 \pm 3.5$ kcal/mole.

The heat of formation of norbornyl bromide could now be obtained from eq. [3]

$$[3]\quad \Delta H_f(C_7H_{12})_{gas} + \Delta H_f(Br_2)_{gas} = \Delta H_f(C_7H_{11}Br)_{gas} + \Delta H_f{}^0(HBr)_{gas} + \Delta H_{reaction}$$

For $\Delta H_f(Br_2)_{gas}$ and $\Delta H_f{}^0$(HBr) we have used the established values of $+7.34 \pm 0.18$ kcal/mole and -8.66 ± 0.33 kcal/mole (8), and for ΔH_f of bicyclo[2,2,1]heptane and the heat of reaction we have used the quantities calculated above. From this data we have calculated ΔH_f(norbornyl bromide) $= -9.63 \pm 6.66$ kcal/mole.

Using this last value in eq. [1] gives ΔH_f (norbornyl ion)$_{gas} = +200 \pm 7.9$ kcal/mole. The agreement between this value and the values calculated by Klopman is excellent and seems to support the validity of the method and assumptions used by him in the quantum mechanical treatment. We understand that the value for the heat of formation of the "classical" norbornyl cation has recently been recalculated using different C—C bond lengths and revised (9), and because of the relatively large errors attendant upon this method of deriving the experimental heat of formation, it is, unfortunately, not possible to conclude that there is significantly better agreement with the quantum mechanically calculated value of the heat of formation for any one particular formulation of the norbornyl ion.

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Esterification of ε-*N*-carbobenzoxy-L-lysine with boron trifluoride – alcohol[1]

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The esterification of ε-*N*-carbobenzoxy-L-lysine with various boron trifluoride – alcohol mixtures at 80 °C leads to some deprotection, which increases as the chain length of the alcohol increases. A convenient synthesis of ε-*N*-carbobenzoxy-L-lysine methyl ester in 58% yield from ε-*N*-carbobenzoxy-L-lysine and boron trifluoride – methanol has been developed.

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ε-*N*-Carbobenzoxy-L-lysine esters are usually prepared from ε-*N*-carbobenzoxy-L-lysine α-*N*-carboxy anhydride and the pertinent alcohol (1). Our dissatisfaction with the use of this method for preparing the methyl ester (1, 2) has prompted an investigation of the feasibility of obtaining this ester directly from ε-*N*-carbobenzoxy-L-lysine. The latter has been achieved (3) using the thionyl chloride method (4), however the product obtained had a melting point 4° lower than that previously reported (1, 2).

This paper presents the results of a study of the esterification of ε-*N*-carbobenzoxy and other mono-*N*-substituted lysines with boron trifluoride – alcohol mixtures which are reagents used for the synthesis of aliphatic (5) and aromatic (6)

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TABLE 1

Esterification of ε-*N*-substituted-L-lysines*

Reactants		Yield of products (%)				
R	R_1	H·Lys(R)·OH	H·Lys(R)·OR_1	H·Lys·OH	H·Lys·OR_1	Total
Z†	methyl	4.8	92.0	0.4	5.8	103.0
Z	ethyl	28.8	66.5	2.4	5.3	103.0
Z	propyl	13.9	67.5	3.2	15.0	99.6
Z	butyl	6.7	48.4	5.9	27.0	88.0
Z	benzyl	15.7	32.3	24.6	16.0	88.6
Z‡	methyl	1.4	94.3	<0.1	1.2	96.9
Ac	methyl	12.4	76.3	1.6	9.1	99.4
For	methyl	0	0	2.7	93.3	96.0
Z	*iso*-propyl	81.8	12.7	6.8	1.2	102.5
Bz	*tert*-butyl	83.9	5.9	0.2	0	90.0

*H · Lys (R) · OH (2.5 mmoles) + $BF_3 \cdot O(C_2H_5)_2$ (12.5 mmoles) + R_1OH (25 ml) $\xrightarrow[24\ h]{80°}$ H · Lys (R) · OR_1.

†Z = carbobenzoxy; Ac = acetyl; For = formyl; Bz = benzoyl.
‡α-*N*-carbobenzoxy.

carboxylic acid esters, and describes a convenient synthesis of ε-*N*-carbobenzoxy-L-lysine methyl ester from ε-*N*-carbobenzoxy-L-lysine.

ε-*N*-Carbobenzoxy-L-lysine in excess methanol was heated in the presence of different amounts of boron trifluoride ethyl ether at 80 °C. Aliquots of the reaction mixtures were then analyzed for starting material, deprotected starting material, desired ester, and ester of the deprotected starting material. The time course of the reaction is illustrated in Fig. 1. In the presence of 5 moles of catalyst, the reaction was first order with respect to ε-*N*-carbobenzoxy-L-lysine and essentially complete after 24 h. When only 2 moles of catalyst were used, the reaction had proceeded to only 80% after 32 h. In a 16 h experiment, water (0.9% v/v) was added, with no apparent effect on the reaction.

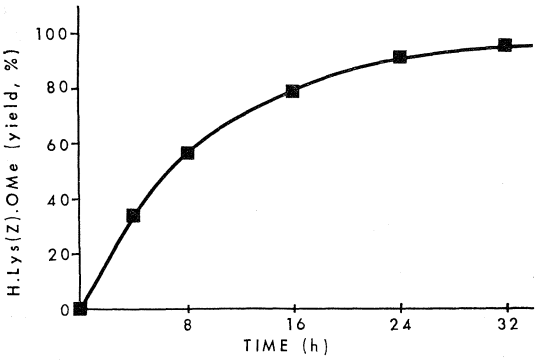

FIG. 1. Esterification of ε-*N*-carbobenzoxy-L-lysine in boron trifluoride – methanol at reflux temperature; 5 moles of $BF_3 \cdot O(C_2H_5)_2$ per mole of H·Lys(Z)·OH.

The results of the analyses for the different components when the mono-*N*-substituted lysines were heated at 80 °C in various boron trifluoride – alcohol mixtures for 24 h appear in Table 1. It is seen that the yields of esters of ε-*N*-carbobenzoxy-L-lysine decreased from 92 to 32% in going from the methyl to the butyl, and then the benzyl ester. This was accompanied by a parallel increase in the extent of cleavage of the carbobenzoxy group from about 6 to 40% (H·Lys·OH + H·Lys·OR_1). Since the same amount (5–15%) of starting material was recovered regardless of the primary alcohol used except for ethanol, and the extent of esterification (H·Lys(R)·OR_1 + H·Lys·OR_1) was over 70% in all cases except for the benzyl ester, the differences in the yields obtained reflect a difference in the susceptibility to cleavage of the urethane group by the various boron trifluoride – alcohol mixtures rather than a difference in the reactivity of the alcohols. The apparently anomolous result obtained with ethyl alcohol, when more starting material was recovered than in the other cases, was confirmed by a duplicate experiment.

The lack of esterification observed when *iso*-propyl and *tert*-butyl alcohol were used is in agreement with the demonstration that these alcohols are dehydrated to give water – boron trifluoride complex and the corresponding polyolefin in the presence of boron trifluoride (7). The resistance to cleavage of the *N*-acyl and *N*-carbobenzoxy groups to boron trifluoride etherate – methanol under our conditions stands

in striking contrast to the reported cleavage of amides to methyl esters by hot boron trifluoride – methanol (8, 9). That this apparent difference was not due to the fortuitous use by us of the etherate instead of gaseous boron trifluoride was demonstrated when results identical with those recorded in Table 1 were obtained for the esterification of ε-*N*-carbobenzoxy-L-lysine using boron trifluoride dissolved in methanol as the reagent.

In a preparative run, a yield of 58% of ε-*N*-carbobenzoxy-L-lysine methyl ester was obtained.[3] A simple and efficient purification of the product was achieved by the expedience of extracting it into an organic solvent from an aqueous solution at a p*H* (9.0) intermediate between the pK_a' of the α-amino group of the ester[4] and the much higher pK_a' of the ε-amino group of the lysine ester. At this p*H*, lysine, lysine methyl ester, and ε-*N*-carbobenzoxy-lysine remain in the aqueous phase, with most of the latter precipitating out. The product obtained with this procedure requires no recrystallization.

Experimental

Materials

Boron trifluoride ethyl ether (product No. 4272) was obtained from Distillation Product Industries, Rochester, New York, and was used without purification. ε-*N*-Carbobenzoxy-L-lysine was purchased from Pierce Chemical Company, Rockford, Illinois. Sources for the other lysine derivatives have been reported (10). The reagent grade alcohols were kept over anhydrous magnesium sulfate for 12 h, then over anhydrous calcium sulfate for 12 h, and filtered.

Method

A mixture of mono-*N*-substituted lysine (2.5 mmoles) and boron trifluoride ethyl ether (1.52 ml; 12.5 mmoles) in the alcohol (25 ml) was heated in an 80 °C oil-bath. The solution was made up to 50 ml with the alcohol (with ethanol for the butyl and benzyl esters) and a sample was diluted with p*H* 2.2 citrate buffer. An aliquot was placed on the 0.9 × 7 cm column of a Beckman model 120B amino acid analyzer and 0.35 *N* sodium citrate, p*H* 5.28, was pumped through for 40 min for the determination of lysine and starting material. The esters, which remained on the column, were then saponified by removing the buffer from the column head and forcing 0.2 *N* sodium hydroxide (1.3 ml) half-way down the resin column. After 20 min (at 57 °C) the column head was filled with sodium hydroxide (8.5 ml), the p*H* 5.28 buffer line was attached to the column, buffer was pumped through and the effluent from the column was collected for 20 min. The effluent was acidified, diluted to a known volume, and analyzed for lysine and mono-*N*-substituted derivative on the same column as described above. A control experiment had indicated that saponification of the methyl ester was complete without the 20 min delay period, but that it was required for complete saponification of the ethyl and benzyl esters. The *tert*-butyl esters were determined by difference after analyzing for the amino acid before and after cleavage of the ester with hydrogen bromide in acetic acid.

Preparation of ε-N-Carbobenzoxy-L-lysine Ester·HCl

A mixture of ε-*N*-carbobenzozy-L-lysine (7.0 g; 0.025 mole) and boron trifluoride ethyl ether (15.2 ml; 0.125 mole) in methanol (100 ml) in a flask fitted with a condenser was heated in a 80 °C oil-bath for 24 h. The cooled mixture was filtered through Celite, the solvent was removed *in vacuo* (bath temperature 40 °C), the residual oil was dissolved in water (50 ml) and extracted with ether (2 × 25 ml). 4 *N* NaOH was added to the cooled stirred solution until the p*H* was 9.0. The solution was saturated with NaCl, ethyl acetate (100 ml) was added, and the mixture was filtered to remove the ε-*N*-carbobenzoxy-L-lysine. The organic layer was separated and the aqueous layer was extracted again with ethyl acetate (2 × 100 ml). The combined extracts were dried ($MgSO_4$ followed by $CaSO_4$), the solvent was evaporated off, methanol (20 ml) was added to the residue, followed by 8 *N* HCl in methanol (3 ml). Ether (300 ml) was then added slowly while cooling the solution and ε-*N*-carbobenzoxy-L-lysine methyl ester·HCl (4.9 g; 58%) separated as white crystals with m.p. 117–118°, $[\alpha]_D^{25}$ +15.5° ±0.1° (*c*, 2 in H_2O), (lit. m.p. 117° (1); 117°, $[\alpha]_D^{21}$ +15.0° (2), 113–114°, sintered 111° (3)). On analysis with the amino acid analyzer the product was found to contain 0.1% of starting material, but no detectable amounts of lysine or lysine methyl ester.

[3]Carbobenzoxy-phenylalanine ester has been obtained in 70% yield from carbobenzoxy-phenylalanine, and phenylalanine ethyl ester in 40% yield from phenylalanine, using the same conditions.

[4]The pK_1' of lysine ethyl ester is 7.54. Unpublished results of J. H. Seely and N. L. Benoiton.

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