amide was added and the mixture was allowed to stir for 1.5 hr at −25° and overnight at 4°. The mixture, after removal of insoluble triethylamine hydrochloride, was evaporated to dryness *in vacuo*. The residue was treated with 15 ml of water and 25 ml of ethyl acetate. An organic phase was separated, washed with water containing sodium bicarbonate, dried (Na_2SO_4), and evaporated. The residue was triturated with ether to give 0.462 g (64%) of the pure product. The combined aqueous phase was shaken with three 20-ml portions of ethyl acetate. The combined ethyl acetate extract was dried (Na_2SO_4) and evaporated. Trituration of the residue with ether afforded 0.096 g (13%) of the slightly contaminated product, which was not pooled with the original batch.

For analysis a small amount of the first product was recrystallized from methanol–ether, mp 140–142°; $[\alpha]^{20}D$ −21° (*c* 0.3, dimethylformamide); R_f 0.62.[14]

Anal. Calcd for $C_{69}H_{102}O_{20}N_{17}F_6 \cdot 2H_2O$: C, 50.54; H, 6.47; N, 14.53; F, 6.97. Found: C, 50.34; H, 6.27; N, 14.24; F, 7.37.

Hydrolysis of *t*-Butyloxycarbonyl-ε-trifluoroacetyllysyl-ε-trifluoroacetyllysylglycylleucylglycylglycine Ethyl Ester (IV) with Thermolysin. To 4.5 ml of water in a reaction vessel kept at 37°, a solution of 8.8 mg (10 μmol) of IV dissolved in 0.5 ml of ethanol was added, followed by 0.25 ml of 0.1 *M* $CaCl_2$. The pH of the solution was adjusted to 6.5 and 5 μl of thermolysin solution (50 mg of the enzyme/ml) was added. The hydrolysis was followed by titration with 0.025 *N* NaOH by using a pH stat. When alkali uptake had ceased, the solution was acidified to pH 3.0 with citric acid solution and extracted with two 5-ml portions of ethyl acetate. The combined ethyl acetate extract was dried and evaporated to dryness to give a crystalline residue (*ca.* 4 mg). Thin-layer chromatography showed a single spot with R_f 0.85.[15] Amino acid analysis gave the molar ratio, Lys 2.0 and Gly 1.0.

Hydrolysis of *t*-Butyloxycarbonylprolyl-ε-trifluoroacetyllysyl-ε-trifluoroacetyllysylglycylleucylglycylglycine Ethyl Ester (V) with Thermolysin. Hydrolysis of 9.6 mg (10 μmol) of V with thermolysin was carried out by the same procedure as described in the preceding paragraph. When the titration was complete, the solution was brought to pH 3.5 by addition of citric acid solution and shaken with two 4-ml portions of ethyl acetate. The combined ethyl acetate extract was dried and evaporated to dryness to give 5.5 mg of crystalline residue (single spot on thin-layer chromatography, R_f 0.88[15]). Amino acid analysis gave the ratio: Pro 1.0, Lys 2.0, and Gly 1.0. Thin-layer chromatography of an aqueous phase showed a single spot with the same R_f value (0.87[15]) as leucylglycylglycine ethyl ester.

Synthesis of *t*-Butyloxycarbonylglutaminylthreonyl-ε-benzyloxycarbonyllysylhistidylprolyl-ε-trifluoroacetyllysyl-ε-trifluoroacetyllysylglycine (XIV) by Hydrolysis of XIII with Thermolysin. To 26.5 ml of 0.01 *M* $CaCl_2$, a solution of 70 mg of XIII in 3 ml of ethanol was added and the pH was adjusted to 7.4. To this, 30 μl of thermolysin solution (5.0 mg/0.2 ml) was added and the hydrolysis (at room temperature) was followed by titration with 0.05 *N* NaOH at pH 7.4 using a pH stat. After completion of the reaction, the solution was brought to pH 3.5 and shaken with ethyl acetate in order to remove a trace of unhydrolyzed undecapeptide derivative (XIII). The aqueous phase was lyophilized and the dried material was subjected to countercurrent distribution involving 60 transfers using *sec*-butyl alcohol–0.05 *M* pyridinium acetate buffer (pH 6.5) (upper phase 10 ml, lower phase 10 ml). An aliquot of each tube was treated by the method of Lowry, *et al.*[22] The optical densities at 750 mμ were measured. The fractions 48–59 (K = 9.0, tube number of maximum optical density = 54) were pooled and lyophilized. The dried material was dissolved in methanol and a small amount of insoluble material was filtered off. After evaporation of the filtrate, the residue was crystallized with ether, 37 mg, mp 173–175° dec; $[\alpha]^{20}D$ −38° (*c* 0.11, dimethylformamide); R_f 0.43.[14] Amino acid analysis gave the molar ratio: Glu 0.9, Thr 0.7 (uncorrected for acid destruction), Pro 1.0, Gly 1.2, Lys 3.1, and His 1.3.

Anal. of an air-dried sample. Calcd for $C_{57}H_{81}O_{17}N_{14}F_6 \cdot 6H_2O$: C, 47.00; H, 6.43; N, 13.46. Found: C, 46.78; H, 6.50; N, 13.78.

Into a solution of 6 mg of XIV in 2 ml of trifluoroacetic acid, a stream of HBr was bubbled for 1.5 hr at 0° and then for 0.5 hr at room temperature. The solution was evaporated *in vacuo*, the residue was dissolved in 2 ml of 1 *M* piperidine, and the solution was allowed to stand for 2 hr at 0° and lyophilized. Paper electrophoresis (2000 V/60 cm) of the deprotected peptide (XV), using 0.05 *M* acetic acid–pyridine buffer (pH 3.7), showed a single band positive to the ninhydrin and Pauly reactions (in addition to the band due to the remaining piperidine). Amino acid analysis of XV gave the ratios: Glu 1.1, Thr 0.9, Pro 0.9, Gly 1.1, Lys 3.0, and His 1.1.

XV was hydrolyzed by leucine aminopeptidase M[1], and amino acid analysis of an aliquot of the hydrolysate yielded the following results (expressed in μmoles): Gln, 0.25; Thr, 0.25; Lys, 0.40; His, 0.10; Pro, 0.08; Gly, 0.04. If we assume that the first lysine residue in the octapeptide was liberated in stoichiometric amounts, the results suggest that the exopeptidase was unable to digest beyond the His–Pro bond with full efficiency.

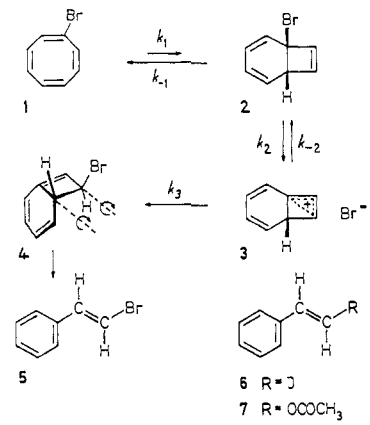
(22) O. H. Lowry, N. J. Rosebrough, A. L. Farr, and R. J. Randall, *J. Biol. Chem.*, 193, 265 (1951).

Communications to the Editor

Kinetics and Mechanism of the Rearrangement of Bromocyclooctatetraene to *trans*-β-Bromostyrene

Sir:

Cope and Burg[1] have described the conversion of bromocyclooctatetraene (**1**) at 100° to β-bromostyrene (**5**). Bromo- and chlorocyclooctatetraene recently became readily accessible by *cis* addition of halogen to cyclooctatetraene in dichloromethane at −55°[2,3] with subsequent *in situ* elimination of hydrogen halide by potassium *t*-butoxide.[4] We have now established the reaction path by which bromocyclooctatetraene rearranges to β-bromostyrene. Thus, valence tautomerization of **1** to 1-bromobicyclo[4.2.0]octatriene (**2**) is followed by ionization to the homocyclopropenium salt **3**. Ion recombination produces the cyclo-



(1) A. C. Cope and M. Burg, *J. Amer. Chem. Soc.*, 74, 168 (1952).
(2) R. Huisgen and G. Boche, *Tetrahedron Lett.*, 1769 (1965).
(3) R. Huisgen, G. Boche, W. Hechtl, and H. Huber, *Angew. Chem., Int. Ed. Engl.*, 5, 585 (1966); R. Huisgen, G. Boche, and H. Huber, *J. Amer. Chem. Soc.*, 89, 3345 (1967).
(4) G. E. Gream and R. Huisgen, unpublished.

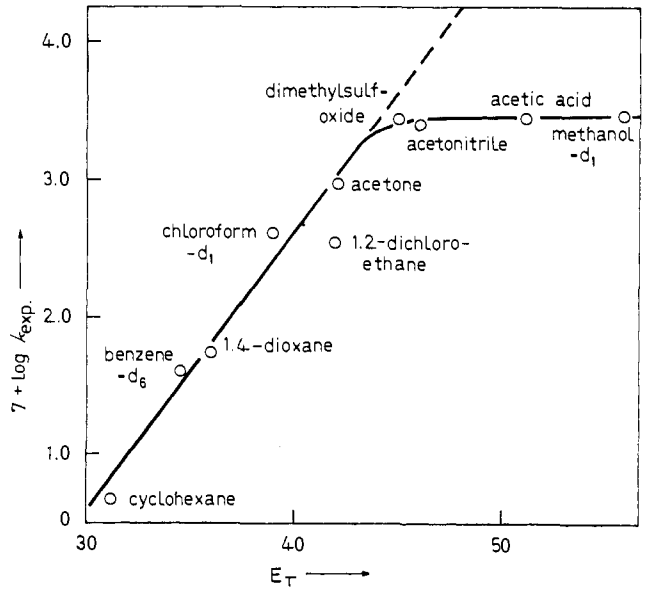


Figure 1. Kinetics of the rearrangement **1** → **5** at 79.5°. Correlation of log k_{exp} with solvent polarity E_T.[5]

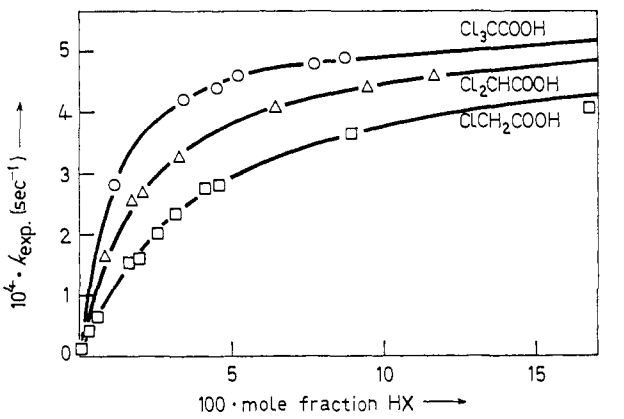


Figure 2. Kinetics of the acid-catalyzed rearrangement **1** → **5** in the neat state at 79.5°. Dependence of the rate constant k_{exp} on the mole fraction of acid.

butene derivative **4**, which upon conrotatory ring opening leads to *trans*-β-bromostyrene (**5**).

According to nmr and glpc analysis, the thermal conversion **1** → **5** at 80° is virtually quantitative and highly stereoselective, the *trans* isomer **5** being accompanied by only a small amount of *cis*-β-bromostyrene: 1.3% in benzene, 2.0% in cyclohexane, 2.1% in acetonitrile, and 3.0% in 1,2-dichloroethane; nmr of **5** ($CDCl_3$) olefinic AB spectrum τ 3.03 and 3.40, J = 14.1 Hz; nmr of *cis*-β-bromostyrene ($CDCl_3$) τ 3.00 and 3.64, J = 8.4 Hz.

Rearrangement of **1** in the presence of lithium iodide in acetone at 80° yields *trans*-β-iodostyrene (**6**) in addition to **5**; **5** does not exchange halogen under these conditions. In methanol at 80°, **1** is converted to **5** (64%), phenylacetaldehyde dimethylacetal (27%), and acetophenone (9%); in the presence of 1 equiv each of $LiClO_4$ and Li_2CO_3, methoxycyclooctatetraene (36%) is formed in addition to **5** (52%), the aforementioned acetal (9%), and acetophenone (3%). Heating of **1** with silver acetate in acetic acid for 3 hr at 80° produces acetoxycyclooctatetraene (50%, bp 60–63°(0.001 mm), $n^{25}D$ 1.5269, nmr ($CDCl_3$) CH_3, s, τ 7.99), **5** (25%), and *trans*-β-acetoxystyrene (**7**, 19%, AB spectrum, τ 2.16 and 3.67, J = 12.9 Hz).

These exchange experiments indicate the presence of a reversible ionization step in the reaction sequence. That this ionization is involved in the rate-determining step is established by the solvent dependence of rate. First-order kinetics for the conversion **1** → **5** were observed by nmr spectroscopic measurements, the process being 600 times faster in acetonitrile than in cyclohexane. Log k_{exp} is a linear function of the empirical solvent polarity parameter, E_T[5] (Figure 1); interestingly, log k_{exp} reaches a plateau at high E_T values.

The suspicion that another step becomes rate determining at high solvent polarity was substantiated by acid-catalysis measurements. The rearrangement, **1** → **5**, is accelerated by Lewis and Brønsted acids,[6] the rate constant being enhanced 50-fold by 2.7 mol % $ClCH_2CO_2H$ or by 0.9 mol % Cl_3CCO_2H. On plotting k_{exp} *vs.* the mole fraction of the three chloroacetic acids, nonlinear functions were obtained which approach a plateau value (Figure 2).

This kinetic phenomenon is compatible with an equilibrium **1** ⇌ X preceding the ionization step; X is interpreted in the above scheme as the valence-tautomeric *t*-bromide **2**. Using the steady-state approximation

$$\frac{d[2]}{dt} = k_i[1] - k_{-i}[2] - k_i[2] = 0 \qquad (1)$$

one obtains

$$\frac{d[5]}{dt} = k_{exp}[1] = k_i[2] = \frac{k_1 k_i[1]}{k_{-1} + k_i} \qquad (2)$$

where k_i is the part of the ionization reaction which goes to products, *i.e.*, $k_i = k_2k_3/(k_{-2} + k_3)$. For acid catalysis by HX we must define

$$k_i' = k_i + k_a[HX] \qquad (3)$$

Neglecting the uncatalyzed ionization (k_i), we substitute into eq 2 for the acid-catalyzed reaction

$$k_{exp} = \frac{k_1 k_a[HX]}{k_{-1} + k_a[HX]} \qquad (4)$$

At low acidity the intermediate **2** is partitioned between reversion to **1** (k_{-1}) and ionization to **3** (k_a[HX]). At high acidities the extreme value is approached and k_1 alone becomes rate determining. Equation 4 can be converted to the linear eq 5. On plotting the k_{exp}

$$k_{exp} = k_1 - \frac{k_{-1}}{k_a}\frac{k_{exp}}{[HX]} \qquad (5)$$

values of Figure 2 *vs.* k_{exp}/[HX], straight lines are the result (Figure 3) with the common intercept, k_1 = 5.5 × 10^{-4} (sec^{-1}), and the slopes, $100k_{-1}/k_a$ = 4.2, 2.2, and 1.1 (mol l.$^{-1}$), for mono-, di-, and trichloroacetic acids, respectively. With these data the solid lines of Figure 2 were calculated according to eq 4.

From the values of k_{exp} for **1** → **5** in acetic acid, which were measured over a range of 50°, Eyring parameters were evaluated: $\Delta H^{\pm}$ = 23.1 ± 0.5 kcal/

(5) C. Reichardt, *Angew. Chem., Int. Ed. Engl.*, 4, 29 (1965).

(6) First experiments carried out by Dr. G. E. Gream, Munich, 1966.

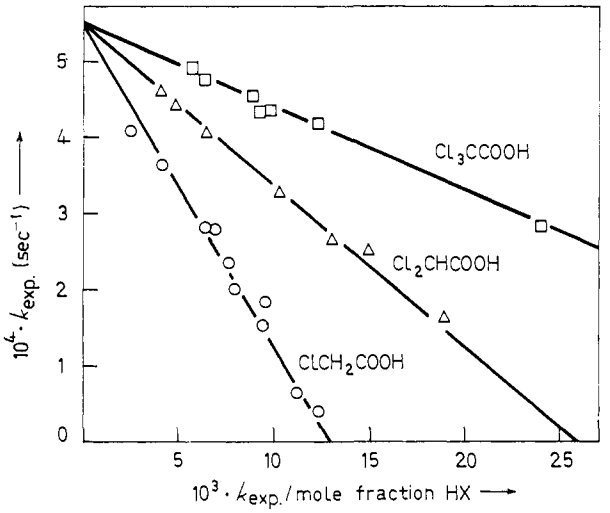


Figure 3. Plot of the rate constants of Figure 2 using eq 5.

mol, $\Delta S^{\pm} = -9.5 \pm 1.5$ eu. These data correspond to the barrier of valence isomerization, **1** → **2**, because acetic acid turned out to be a "plateau solvent" in Figure 1.

The mechanistic scheme above is plausible. It has been established that valence tautomerism of cyclooctatetraene leads to a 0.01% equilibrium concentration of bicyclo[4.2.0]octatriene (dioxane, 100°).[7,8] The ionization tendency of the 1-bromo derivative stems from the formation of a homocyclopropenium ion.[9] That ion recombination takes place on the same side of the four-membered ring, *i.e.*, to form **4**, may be due to an ion-pair phenomenon; it is also the least-hindered side for nucleophilic addition. The benzenoid character of **5** ensures the irreversibility of the *conrotatory* ring cleavage of **4**. The small amount of *cis*-β-bromostyrene in the product results probably not from a *disrotatory* ring opening of **4**, but rather from ion recombination on the opposite side of **3**, leading to the epimer of **4**.

Further evidence for this rearrangement mechanism—to our knowledge without precedence in cyclooctatetraene chemistry—is presented in the following communications. Criegee, *et al.*,[10] recently assumed an analogous reaction path by studying the thermal rearrangement of halobenzobicyclo[4.2.0]octatrienes.

(7) R. Huisgen and F. Mietzsch, *Angew. Chem., Int. Ed. Engl.*, **3**, 83 (1964).
(8) R. Huisgen, F. Mietzsch, G. Boche, and H. Seidl, *Chem. Soc., Spec. Publ.*, **19**, 3 (1965).
(9) T. J. Katz and E. H. Gold, *J. Amer. Chem. Soc.*, **86**, 1600 (1964).
(10) R. Criegee, C. Schweickhardt, and H. Knoche, *Chem. Ber.*, **103**, 960 (1970).

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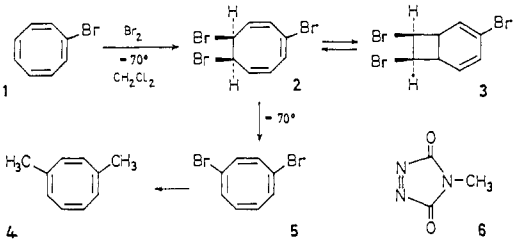
Further Contributions to the Mechanism of the Halocyclooctatetraene Rearrangement

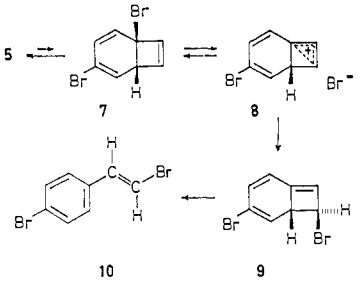
Sir:

On viewing the mechanistic path proposed for the conversion of bromocyclooctatetraene (**1**) to *trans*-β-bromostyrene,[1] one becomes aware of the fact that the bromine in the product is no longer attached to the original carbon atom but has undergone a 1,3 migration.

By the bromination of **1**, we obtained, *via* **2**, the 1,4-dibromo compound **5** in ≥92% purity. Evidence for the intermediacy of **2** came from the nmr spectra



of the Diels–Alder adducts of the bicyclic tautomer **3** with tetracyanoethylene or **6**. Elimination of HBr to give **5** was effected by potassium *t*-butoxide in dichloromethane. To establish the position of the two bromine atoms, **5** was converted to 1,4-dimethylcyclooctatetraene (**4**, 95%, bp 60–62°(12mm); n^{25}D, 1.5206°; nmr ($CDCl_3$) $2CH_3$, s, τ 8.30) by lithium dimethylcopper.[2] Catalytic hydrogenation of **4** gave 1,4-dimethylcyclooctane (nmr ($CDCl_3$) $2CH_3$, d, τ 9.11, J = 6.4 Hz), which was identical with a specimen prepared by the hydrogenation of 1,6-dimethylcycloocta-1,3,5-triene.[3]



On injecting **5** onto a glpc column (Apiezon L, 2 m, 180°, 30 lb/in.^{2} of N_2), one observed, besides three minor components, up to 92% of *p*-β-dibromostyrene (**10**). Preparative glpc made possible the isolation of **10**, its characterization (mp 67–68°; uv (methanol) 265 mμ, log ε 4.40; nmr ($CDCl_3$) olefinic AB spectrum, τ 2.99 and 3.24, J = 14.2 Hz), and its oxidation to *p*-bromobenzoic acid. The aforementioned facts were supplemented by the independent synthesis of **10**. Thus, the expected shift of bromine is established by the 1,6 positions of the bromine atoms in **10**.

Cope and Burg[4] obtained β-chlorostyrene from chlorocyclooctatetraene (**11**) at 200° and assigned the *cis* configuration to it. The nmr (AB τ 3.23 and 3.42, J = 13.8 Hz), however, leaves no doubt that it is *trans*-β-chlorostyrene (**13**) that is formed. As in the case of bromocyclooctatetraene,[1] the conversion, **11** → **13**, is strongly catalyzed by Lewis and Brønsted acids; rearrangement in the presence of D_2O or DOAc does not lead to deuterium incorporation in **13**. Also here the rate of rearrangement depends on solvent polarity. The rate constant at 120° in the neat state

(1) R. Huisgen and W. E. Konz, *J. Amer. Chem. Soc.*, **92**, 4102 (1970).
(2) E. J. Corey and G. H. Posner, *ibid.*, **89**, 3911 (1967).
(3) We gratefully acknowledge an authentic specimen obtained from Professor E. Vogel, Köln.
(4) A. C. Cope and M. Burg, *J. Amer. Chem. Soc.*, **74**, 168 (1952).