Electroorganic Preparations

VII. Reduction of a Compound Containing a Trifluoromethyl Group

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Several compounds are reducible at the dropping mercury electrode due to an electrochemical fission of a carbon-halogen bond. The reductive splitting of such bonds have been studied by means of polarography and controlled potential reductions and in most cases the halogens have been iodine, bromine or chlorine. Apparently only in the reduction of one compound, [1] phenacyl fluoride, the electrochemical fission of an aliphatic carbon-fluorine bond has been reported. In this communication the polarography and reduction of a compound containing a trifluoromethyl group is investigated.

The trifluoromethyl group which has received considerable attention as a substituent in various drugs is not generally reducible at the dropping mercury electrode, as no reduction between 0 and -2.0 V *vs.* S.C.E. was observed for trifluoroacetic acid, trifluoromethylbenzene, 3-trifluoromethylaniline, or 3-trifluoromethyl-4-sulphamyl-aniline. However, the introduction of two sulphamyl groups in 3-trifluoromethylaniline renders the compound reducible. In Table 1 is reported

Table 1. Diffusion currents in μA and half-wave potentials *vs.* S.C.E. for 6-trifluoromethyl-7 - sulphamyl - 3,4 - dihydro - 1,2,4 - benzo-thiadiazine-1,1-dioxide. Concentration 0.60×10^{-3} M. 0.01 % gelatine added as maximum suppressor.

pH	i_d μA	$E_{\frac{1}{2}}$ V
6.28	8.4 *	1.67
7.35	7.7	1.67
8.30	7.1	1.67
8.80	7.0	1.67_5
9.75	6.7	1.70
10.50	6.6	1.75
10.75	6.5	1.78

* merges with the hydrogen wave.

the polarographic behaviour of 6-trifluoro-methyl-7-sulphamyl-3,4-dihydro-1,2,4-ben-zothiadiazine-1,1-dioxide (6-TFM).

The compound yields in the pH-interval 6 to 11 a well-defined, diffusion controlled, irreversible wave. By comparison of the wave height with that of 2,4-disulphamyl-5-bromo-aniline, which was assumed to be reduced in a two-electron reduction to 2,4-disulphamyl-aniline, it was found that the wave height of 6-TFM corresponded to a comsumption of $5-6$ electrons per molecule. As seen from Table 1 the half-wave potentials of 6-TFM are constant at pH-values lower than about 8.5, whereas they at higher pH-values become more negative. This pH-dependence of the half-wave potentials is connected with the presence of the two sulphamyl groups. Each sulphamyl group contains a weakly acidic hydrogen atom. The pK-values of the groups are 8.9 and 10.7. At pH-values lower than 8.5 the undissociated sulphamyl groups strongly attract electrons from the benzene ring and the trifluoromethyl group, thus making an attack of electrons more easy. At pH-values higher than 8.5 an increasing part of the sulphamyl groups are dissociated into anions which attract electrons much less than does the undissociated sulphamyl group. The potential required to promote an attack of electrons thus becomes more negative.

A similar dependence of the half-wave potentials upon pH has been found for many halogen compounds containing a dissociable group, such as α-halogenated acids [2,3], iodophenols [4], and iodoanilines [4]. A plot of the half-wave potentials of these compounds against pH normally yields an S-shaped curve with one pH-independent branch in acid solution and one in alkaline solution. The pK_a value of the acid is found in the rising part of the curve; the midpoint of the S-shaped curve is generally found at a pH somewhat higher than the pK_a of the acid. This is probably due to recombination of the anion with hydrogen ions at the electrode surface.

As the half-wave potential of both the acid and the anion are pH-independent one might have expected a pH-interval in which two waves were observed due to the reduction of the acid and of the anion, respectively. This is the case in the reduction of, *e. g.*, pyruvic acid [5]. The pH at which the wave due to the reduction of the acid is of equal height as that due to the reduction of the anion is somewhat higher than the pK_a of pyruvic acid and is determined by the rate of the recombination at

the electrode surface [5]. A difference between pyruvic acid and the halogenated acids lies in the fact that the reduction of the reducible group in pyruvic acid (the carbonyl group) generally is pH-dependent in acid solution, whereas the reduction of a carbon-halogen bond as such is pH-independent. It seems that the half-wave potentials of the halogen compounds by some as yet undetermined feature of the electrode process kinetics reflects the average electronic interaction between the dissociable group and the carbon atom, at which the fission of the carbon-halogen bonds takes place.

Controlled potential reduction of 6-TFM and its parent disulphonamide, 5-trifluoromethyl-2,4-disulphamyl-aniline, showed that the electrode reaction was a six-electron reduction and the methyl compounds, 6-methyl-7-sulphamyl - 3,4 - dihydro - 1,2,4 - benzothiadiazine-1,1-dioxide and 5-methyl-2,4-disulphamyl-aniline, respectively, were isolated from the reaction mixture. A photometric determination with zirconiumeriochrome cyanine of the fluoride ions produced showed the presence of about 95 % of the total original fluorine content as fluoride ion. The overall reaction thus is

$$R\text{—}CF_3 + 6e^- + 3\ H_2O \rightarrow$$
$$R\text{—}CH_3 + 3\ F^- + 3\ OH^-$$
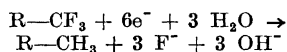
Although a stepwise reduction of a polyhalogenated carbon atom is the most common reaction path a few examples of polarographic waves due to a complete reduction of a polyhalogenated compound are reported. Chloral hydrate [6] thus produces a single wave which corresponds to a reduction to acetaldehyde.

Elving and Leone [1] point to the fact that the carbon-fluorine bonds in F_3CH are considerably shorter than in FCH_3, which is reflected in the greater stability of the polyfluoromethanes. They conclude that if this behaviour is generally true for the trifluoromethyl group, the stepwise fission of the carbon-halogen bonds would not be observed as in the case of trichloro- and tribromoacids, but all of the bonds would· probably be ruptured in a single step at a potential more negative than that at which the one carbon-fluorine bond in the monofluoro compound would be reduced. The results of the present investigation fully substantiate the conclusion of Elving and Leone.

As 6-TFM can be determined spectrophotometrically after alkaline hydrolysis, diazotization and coupling we have a means of determining in a solution both the concentration of the primary, aromatic amine and of trifluoromethyl groups bonded to a benzene ring containing two sulphamyl groups. This has been applied to the determination of 6-TFM in the urine from persons given 6-TFM perorally, and has shown that the concentrations of the amine and the trifluoromethyl compound found in the urine were the same, which strongly suggests that the trifluoromethyl group remains intact during the passage through the body.

Experimental. The polarograph was a recording polarograph Radiometer Type PO 3a. The capillary delivered 2.16 mg of mercury per second at a corrected mercury height of 48.5 cm. The drop time 3.90 sec (water, open circuit). The capillary constant $m^{2/3}t^{1/6} = 2.13$ $mg^{2/3}\ sec^{-\frac{1}{2}}$. The apparatus used for the controlled potential reductions was an electromechanical potentiostat of the Lingane-Jones type.

The buffer solutions used were below pH 8 sodium phosphate-citric acid buffers and from pH 8 to 11 sodium borate buffers. The medium employed was 40 % alcohol containing 1 M potassium chloride and 0.01 % gelatine. The pH-values were measured with a glass electrode; in the medium used they have only relative value.

Reduction of 6-trifluoromethyl-7-sulphamyl-3,4 - dihydro - 1,2,4 - benzothiadiazine - 1,1 - dioxide. A suspension of 1.0 g of 6-TFM in 180 ml 30 % aqueous methanol containing 20 g of potassium hydrogen carbonate was reduced at a cathode potential of —1.70 V vs. S.C.E.; the reduction was completed after the consumption of 6.3 electrons per molecule. Small amounts of hydrochloric acid were added during the electrolysis to compensate for the hydrogen ions used in the reduction; the consumption of hydrogen ions was calculated from the reading of the coulometer. After completion of the reduction the reaction mixture was extracted several times with ethyl acetate, which was evaporated. The residue was recrystallized from dilute methanol yielding 600 mg of a compound with an IR-spectrum identical with that of actual 6-methyl-7-sulphamyl-3,4 - dihydro - 1,2,4 - benzothiadiazine - 1,1 - dioxide. (Found: C 34.53; H 4.04; N 15.12; S 22.99. Calc. for $C_8H_{11}N_3O_4S_2$: C 34.64; H 3.99; N 15.16; S 23.13.)

From a similar reduction of 5-trifluoro-methyl-2,4-disulphamyl-aniline were isolated 650 mg of a compound with an IR-spectrum identical with that of 5-methyl-2,4-disulph-amyl-aniline. (Found: C 31.79; H 4.22; N 15.92; S 24.02. Calc. for $C_7H_{11}N_3O_4S_2$: C 31.69; H 4.18; N 15.84; S 24.17.)

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Separation of Hg^{++} from Active Carbon by Extraction with EDTA

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In the synthesis of vinyl chloride from acetylene and hydrogen chloride active carbon impregnated with mercuric chloride is used as a catalyst. The catalyst usually contains $8-10$ % by wt. of mercuric chloride. The mercuric chloride content of catalyst samples drawn from a reactor which has been in use for a certain length of time, varies between zero and a value higher than the original one.

A producer of vinyl chloride is of course highly interested in a rapid and fairly accurate method for the determination of the mercury content of the catalyst. The present work was initiated some 20 months ago, at which time no publications dealing with this special problem could be found in available literature.

In our first experiments we investigated several procedures based on initial oxidation of the carbon, e.g. combustion in a Parr bomb, oxidation with fuming sulphuric acid and potassium persulphate and the method described by Schöniger[1,2] where the sample is burned in a conical flask filled with oxygen. By all these methods, however, the recovery of mercury was too low. This was also the case when the catalyst was extracted with acetone, while extraction with nitric acid or a mixture of nitric and hydrochloric acid seemed more promising. Another possible way of separating the mercury from the carbon may be distillation in a quartz apparatus, a method worked out for the determination of mercury in organic matter.[3]

During our further work, however, we were led to the conclusion that the most convenient method would be direct extraction of the mercury by means of EDTA. Check analysis by the aqua regia/H_2O_2 extraction method described in Ref.[4] have shown that this extraction is complete also when applied on spent catalyst samples. In the extract the mercury content is easily determined photometrically as mercury dithizonate. For a more detailed description of the dithizone procedure, Ref.[5] may be consulted.

Experimental. All of the solutions are made up with glass distilled water.

Buffer solution, pH = 10. 70 g NH_4Cl and 610 ml 12 N NH_4OH, diluted to 1 000 ml.

EDTA-solution. Disodiumsalt of ethylene-diaminetetraacetic acid, 0.1 M.

Procedure. 20—30 mg of ground catalyst is transferred to a centrifuge tube together with 5 ml of EDTA-solution and 15 ml of buffer solution and extracted for 30 min with moderate shaking. The complexing of Hg^{++} with EDTA is considered a very rapid reaction and it therefore seems probable that complete extraction is achieved in considerably less than 30 min. The extraction is followed by settling of the carbon, which is most conveniently done by means of centrifuging. 5 ml of the supernatant liquid is pipetted into a volumetric flask and the volume is adjusted to 100 ml. An aliquot of this solution is used for the subsequent determination with dithizone.

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