cerning the formation and reactions of **1** are currently in progress.

Acknowledgment. This research was supported by Grant GM 18357 from the National Institutes of Health. R.E. and S.Z.G. gratefully acknowledge the donors of the Petroleum Research Fund, administered by the American Chemical Society, in partial support of this research.

Supplementary Material Available. A table of distances and angles will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D.C. 20036. Remit check or money order for $4.00 for photocopy or $2.50 for microfiche, referring to code number JACS-75-1961.

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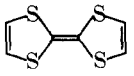
Received October 21, 1974

A New Approach to the Preparation of Tetrathiafulvalenium Salts

Sir:

Salts of 1,4,5,8-tetrathiafulvalene (TTF) exhibit unusual temperature dependent electric[1-3] and magnetic[4-6] properties. These salts were prepared by direct oxidation of TTF (**1**) by an acceptor (e.g., Cl_2,[1] I_2,[1] TCNQ,[3] TCM,[7] TNAP[8]). Such an approach precludes the preparation of TTF salts containing anions which are not derived from strong oxidizing agents (e.g., SCN^-). A logical approach to a more general preparation of TTF salts can be based on the metathetical reaction



1

$$TTFX + MZ \longrightarrow TTFZ + MX \quad (1)$$

Table I[a]

Compound	% Yield	$R(\Omega)$[b]	$\sigma_\parallel$[i] (Ω^{-1} cm^{-1})
$(TTF)_3(BF_4)_2$	60	$>10^6$	
$(TTF)_{15}(NCS)_8$[c]	70	2–6	250 (310)[j]
$(TTF)_{15}(NCSe)_8$[c]	45	7	15
$(TTF)_{11}I_8$[c,d]	28	0.5	365
$(TTF)_{24}I_{63}$[c,e]	37	4.5	
$(TTF)_8I_{15}$[c,f]	75	55	
$(TTF)_2Pt(CN)_4$	92	$>10^6$	
$(TTF)_2Cu(Mnt)_2$[g]	60	$>10^6$	
$(TTF)_2Co(Mnt)_2$[g]	69	$>10^6$	
$(TTF)_2Ni(Mnt)_2$[g]	70	$>10^6$	
$(TTF)_2Pt(Mnt)_2$[g]	70	$>10^6$	
TTF $Pt(Mnt)_2$[g,h]	94	$>10^6$	

[a] All elemental analyses based on C, H, and N.[10] [b] Determined at room temperature on ca. 0.1 mg compressed in a glass capillary between two steel pistons of 2 mm diameter. [c] Corresponds to "$(TTF)_2(NCS)$". This and other compounds below exhibit "nonstoichiometric" elemental analyses which are best described (within 0.1–0.05% of experimental) by the formulas given in the table. [d] This compound is also known as "TTF_3I_2" it was prepared from $(TTF)_3(BF_4)_2$ and $Bu_4N^+I_3^-$ and forms hollow needles. [e] Corresponds to $TTF_2{-}^2/_3I_7$. Prepared from $(TTF)_3(BF_4)_2$ and $Bu_4N^+I_3^-$. It has the appearance of silver wool. [f] Corresponds exactly to TTF_8I_{15}. Also prepared from $Bu_4N^+I_3^-$ and $(TTF)_3(BF_4)_2$. [g] Prepared from $(TTF)_3(BF_4)_2$ and $(Bu_4N)_2M(mnt)_2$, where mnt = maleonitriledithiolato ($N{\equiv}CC(S^-){=}{=}C(S^-)C{\equiv}N$) and M = Cu, Co, Ni, Pt, etc. [h] Prepared from $Bu_4NPt(mnt)_2$ and $(TTF)_3(BF_4)_2$. [i] $\sigma_\parallel$ = conductivity determined on the long axis of the crystal via a four-probe technique.[3] [j] $\sigma_\parallel$ at 220°K.

provided, of course, TTFX, MZ, and MX are soluble in a particular solvent and TTFZ is not.

We expected TTF salts of BF_4^-, PF_6^-, SbF_6^-, and Ph_4B^- to be soluble in solvents such as tetrahydrofuran or acetonitrile. Here we describe an efficient preparation of a fluoroborate salt and its use in metathetical syntheses.

At first we tried to prepare the fluoroborate salt from silver fluoroborate and TTF but could not separate the product efficiently from colloidal silver. We discovered reaction 2 to be a convenient method for the preparation of a soluble TTF salt.[9]

$$3TTF + 2HBF_4 + H_2O_2 \xrightarrow{CH_3CN} \underset{I}{TTF_3(BF_4)_2} + 2H_2O \quad (2)$$

The fluoroborate I is a purple, crystalline solid,[10] soluble in warm acetonitrile, but sparingly soluble in cold acetonitrile, acetone, methyl acetate. As shown in Table I, it is quite useful in the synthesis of new TTF salts.[11] These preparations were surprisingly simple. High dilutions were necessary to obtain large single crystals. When more concentrated solutions were employed, higher yields of microcrystalline powders were obtained.

Previously, a number of "onium" salts of TCNQ were prepared via metathesis.[12] We found $Et_3NH(TCNQ)_2$ to be best suited for metathesis in acetonitrile. The TTF(TCNQ) thus obtained consisted of small, poorly defined crystals. It appears that in this case the direct, redox synthesis affords the largest crystals.

When an excess of tetrabutylammonium selenocyanate was used in the above metathesis, the reaction mixture was bleached to light orange color. When this solution was allowed to stand at room temperature overnight, black needles of "$(TTF)_2(SeCN)$" formed. One may infer from this that reversible redox of TTF^+ and $SeCN^-$ may be occurring.

Fluoride and tetraphenylboride (as the Et_4N^+ and Na^+ salts, respectively) react irreversibly (bleaching) with

$(TTF)_3BF_4$. The products of these reactions were not identified.

The single-crystal electrical conductivities and ESR spectra of these and other TTF salts are currently being determined[13] and will be the subject of future publications.

Acknowledgment. I thank A. M. Trozzolo and E. A. Chandross for fruitful conversations. Thanks go to M. L. Kaplan for preparation of starting materials.

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(10) Correct elemental analysis was obtained.
(11) A dilute solution of $(TTF)_3(BF_4)_2$ in hot acetonitrile was filtered and to it was added an acetonitrile solution of the required anion as its tetrabutylammonium salt. Storage at room temperature overnight afforded crystals of the desired TTF salt.
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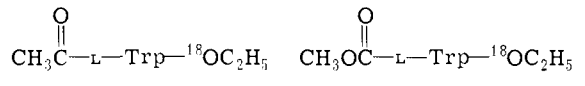
Kinetic Isotope Effects for the Chymotrypsin Catalyzed Hydrolysis of Ethoxyl-^{18}O Labeled Specific Ester Substrates[1]

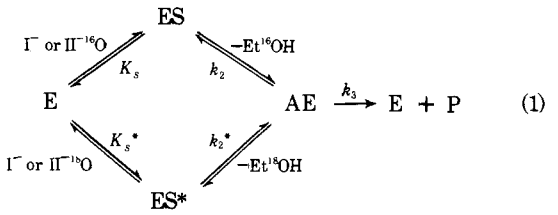
Sir:

We wish to report the results of oxygen-18 kinetic isotope effect measurements for the chymotrypsin-catalyzed hydrolysis of two esters, *N*-acetyl-L-tryptophan ethyl ester-*ethoxyl*-^{18}O (I) and *N*-carbomethoxy-L-tryptophan ethyl ester-*ethoxyl*-^{18}O (II). Kinetic isotope effect studies utilizing elements other than hydrogen are a relatively little used tool for the elucidation of enzyme mechanisms[2a] and yet offer unique insights into the nature of the transition state of many reactions. In a previous investigation with chymotrypsin, for example, O'Leary has determined a ^{15}N kinetic isotope effect of 1.006–1.010 for the chymotrypsin catalyzed hydrolysis *N*-acetyl-L-tryptophanamide, similar to the value 1.004–1.006 observed for the alkaline hydrolysis of amides.[2b]



I II

The accepted mechanism[3] for the chymotrypsin-catalyzed hydrolysis of esters proceeds by the initial rapid equilibrium formation of the Michaelis complex, followed by acylation of the enzyme with release of alcohol, and finally by deacylation to give the *N*-acylamino acid and the free enzyme. This pathway, when applied to a mixture of the ^{18}O- and ^{16}O-labeled forms of I or II is shown in eq 1, where ES and ES* are the Michaelis complexes with unlabeled and labeled substrate, AE is the acyl enzyme, and P is the *N*-acylamino acid. The kinetic isotope effect arising



(1)

from this mechanism in a competitive experiment is determined solely by the relative rates of formation of the acyl enzyme, even though the rate determining step is deacylation, a step not involving the isotope. With the assumption

$$\Delta = \frac{v}{v^*} = \frac{k_2 K_s^*}{k_2^* K_s}$$

that the binding constant, K_s, is the same for ^{18}O and ^{16}O substrates, $\Delta = k_2/k_2^*$.[4]

Ethanol-^{18}O was prepared as previously described.[5] L-Tryptophan ethyl ester hydrochloride-*ethoxyl*-^{18}O was prepared by the reaction of L-tryptophanyl chloride hydrochloride[6] with ethanol-^{18}O (65 atom %) in glyme, and N-acylated (in ethyl acetate over aqueous sodium carbonate) with acetic anhydride to give I, or with methyl chloroformate to give II. Racemization, as determined by measuring the unreacted substrate after chymotryptic hydrolysis, was less than 0.1%.

Enzymatic hydrolyses were done at pH 6.8 in potassium phosphate buffer, 0.05 *M* (or 0.01 *M* when $[S_0]$ = 0.1 m*M*), at 25°. The reaction was followed spectrophotometrically at 298 nm (or 265 nm when $[S_0]$ = 0.1 m*M*). Substrates used contained 10 or 25 atom % ^{18}O in the ethoxyl position. Aliquots were taken at preselected fractions of the complete reaction and quenched by extraction with methylene chloride. The substrate recovered from the organic layer was purified by preparative TLC on silica (ethyl acetate). For isotopic analysis, a substrate sample of 1–5 mg

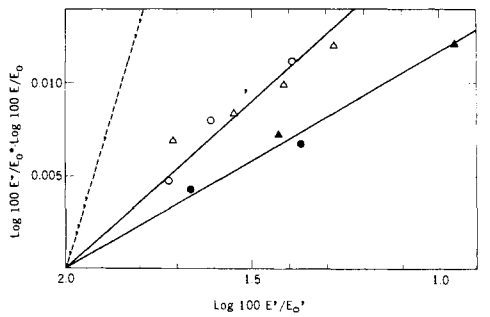


Figure 1. Oxygen-18 kinetic isotope effects for the chymotrypsin-catalyzed hydrolysis of ethoxyl-labeled *N*-acetyl-L-tryptophan ethyl ester: (○), (I) at S_0 = 0.1 m*M*, pH 6.8 in 0.01 *M* potassium phosphate buffer (△), (I) S_0 = 1.0 m*M*, pH 6.8 in 0.05 *M* potassium phosphate buffer; (●, ▲) (II) at S_0 = 0.5 m*M*, separate experiments at pH 6.8 in 0.05 *M* potassium phosphate buffer. The data are plotted according to eq 2, where the slope is $1 - (k_2/k_2^*)$. A horizontal line, therefore is indicative of no kinetic isotope effect, and the dashed line, given for reference, represents the isotope effect of 1.066 observed for hydrazinolysis of both esters under conditions of rate-determining breakdown of the tetrahedral intermediate, corresponding to a very late transition state with respect to the scission of the acyl–ethoxyl bond.