

PROFESSORIAL LECTURE

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# Synthesis of sugar functionalized tetrathiafulvalene

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*The synthesis and chemistry of the water soluble sugar functionalized tetrathiafulvalenes are discussed. The use of a suitable protecting group for the coupling between oxone and thiones is given along with deprotection and subsequent nucleophilic substitution with halosugars. The potential applications of these promising sugar derivatized tetrathiafulvalenes are hereby enumerated.*

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A pleasant afternoon to everybody. Allow me to thank all of you for coming to my first professorial lecture for this century. The title of my lecture is "Synthesis of Sugar Functionalized Tetrathiafulvalene".

Alan Heeger and his colleagues at the University of Pennsylvania first discovered the conducting property of tetrathiafulvalene or TTF in 1973. They prepared a charge transfer salt of TTF and 7,7,8,8-tetracyano-p-quinodimethane(TCNQ) which at a temperature of  $-220\text{ }^{\circ}\text{C}$  has a conductivity approaching that of copper<sup>1</sup>. Since then numerous derivatives and analogues thereof have been synthesized with the sole purpose of improving its conductivity or perhaps even for it to exhibit superconductivity.

For the past several years, my working group and I have focused much of our effort on the synthesis of novel sugar functionalized TTF. We speculated that if we could attach sugar units to the TTF structure, such system would have better solubility. This property would make TTF easier to handle and work with. Furthermore, with the combination of sugar and TTF

units in a single structure, we envision to open the following new frontiers in TTF and sugar chemistry research:

## New Structures for Drug Design

We have thoroughly search the literature for reports on the possible biological activity of TTF and its derivatives. Unfortunately, we found no publication dealing with such investigation. Obviously, the poor solubility of TTF and its derivatives had made this class of compound non-ideal for biological testing. The synthesis of a more soluble form of TTF derivatives could provide new materials for pharmaceutical applications.

## Better Electrochemically Active Materials

The presence of a polyfunctional moiety such as sugar bonded to a TTF structure could provide more functionalization sites. This will greatly improve synthetic strategy and molecular designs and architecture for better fine- tuning of TTF's redox and

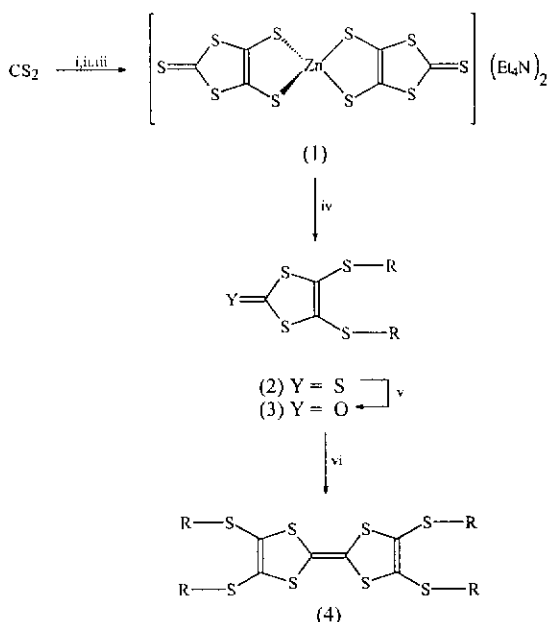
electrochemical behavior for the purpose of producing sensors, batteries, conductors, molecular switches and modified electrode materials<sup>2</sup>.

### Materials for Molecular Recognition Experiments and Catalysis

Macrocycles have long been studied because of its ability to display molecular recognition ability on various kinds of substrate<sup>3</sup>. Novel macrocycles containing TTF and sugar units may prove to be very interesting compounds. This is due to the fact that sugars possess a number of chiral centers, which can greatly enhance high selectivity on guest molecule. The presence of TTF structure on the other hand, can make the macrocycle electro active thereby making the cavity a potential site for electrochemical reactions.

### Novel Metal Complexes

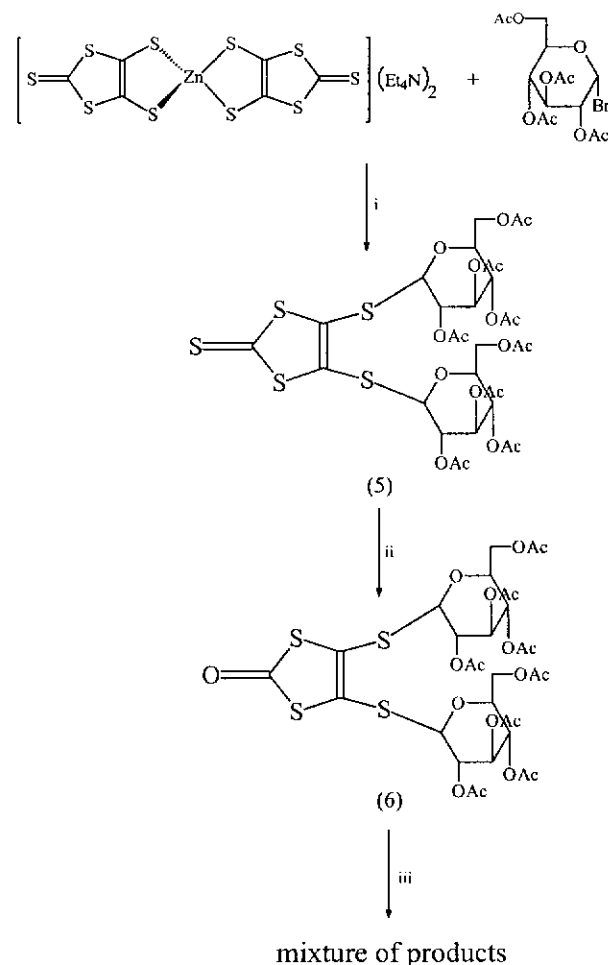
The binding of carbohydrates with metals have been known to be a fundamental importance in many



**Scheme 1** Reagents and Conditions: i. Na, DMF, ii.  $\text{ZnCl}_2$ , MeOH, iii.  $\text{Et}_4\text{NBr}$ ; iv.  $\text{R-X}$  ( $\text{X}=\text{Cl}$ ,  $\text{Br}$  or  $\text{I}$ ) in DMF or MeCN; v.  $\text{Hg}(\text{OAc})_2$ , AcOH,  $\text{CHCl}_3$ ; vi.  $\text{P}(\text{OEt})_3$ , toluene.

biochemical processes such as the transport and storage of metals<sup>5,6</sup>, the function and mechanism of metalloenzymes, the mechanism of action of metal-containing pharmaceuticals, and toxic metal metabolism<sup>7</sup>. Hence, from the standpoint of developing novel metal complexes<sup>8-10</sup>, a sugar functionalized TTF-metal complexes may prove useful for the above mentioned importance.

However, when we started with this work, little is known regarding the chemistry of bonding sugar to TTF structures. With a bit of perseverance and patience, we were able to prepare the first sugar



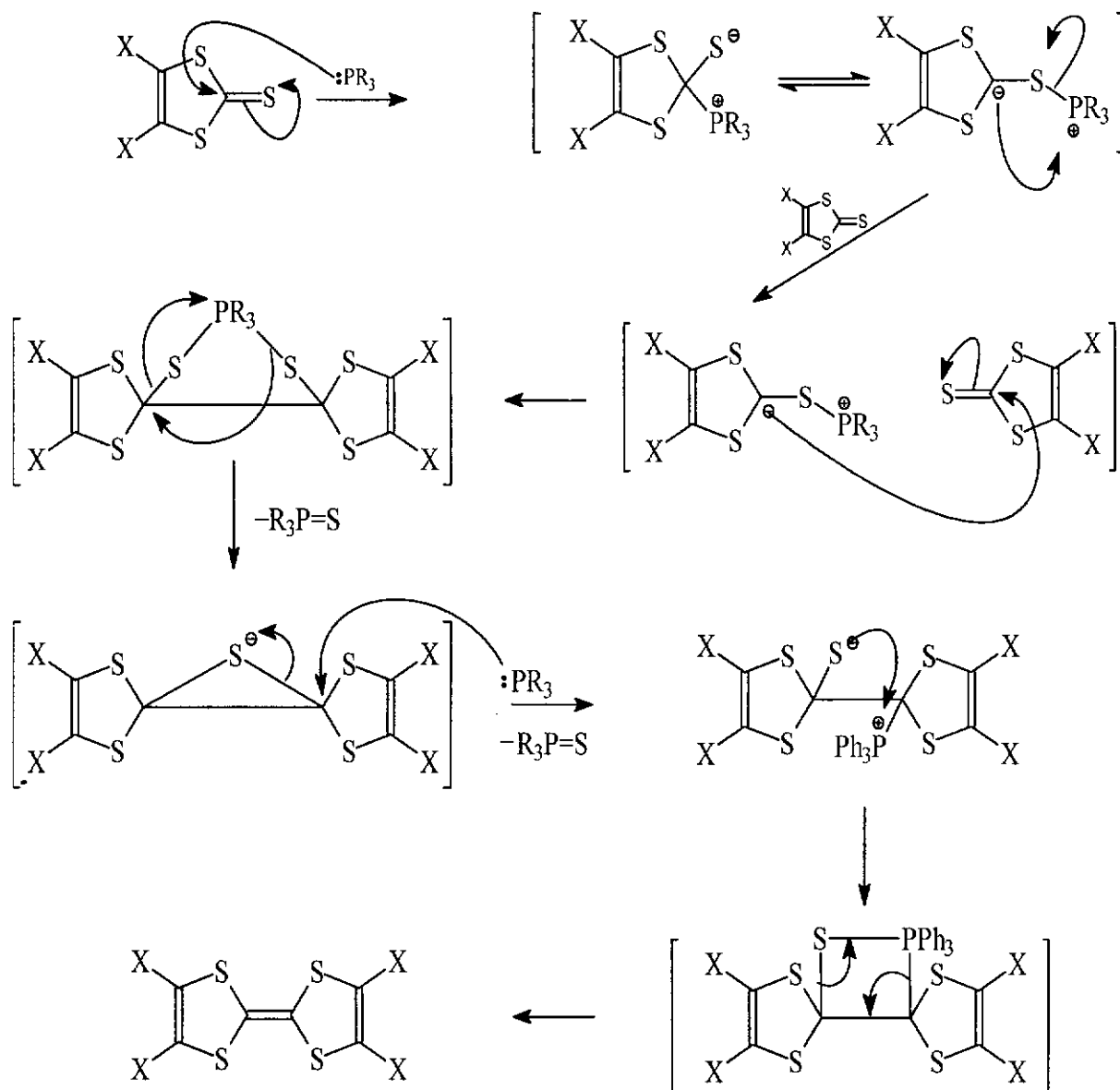
**Scheme 2** Reagents and Conditions: i. 4.4 equivalents of glucosyl bromide; ii.  $\text{Hg}(\text{OAc})_2$ , AcOH,  $\text{CHCl}_3$ ; iii.  $\text{P}(\text{OEt})_3$ , toluene.

functionalized TTFs that are water soluble.

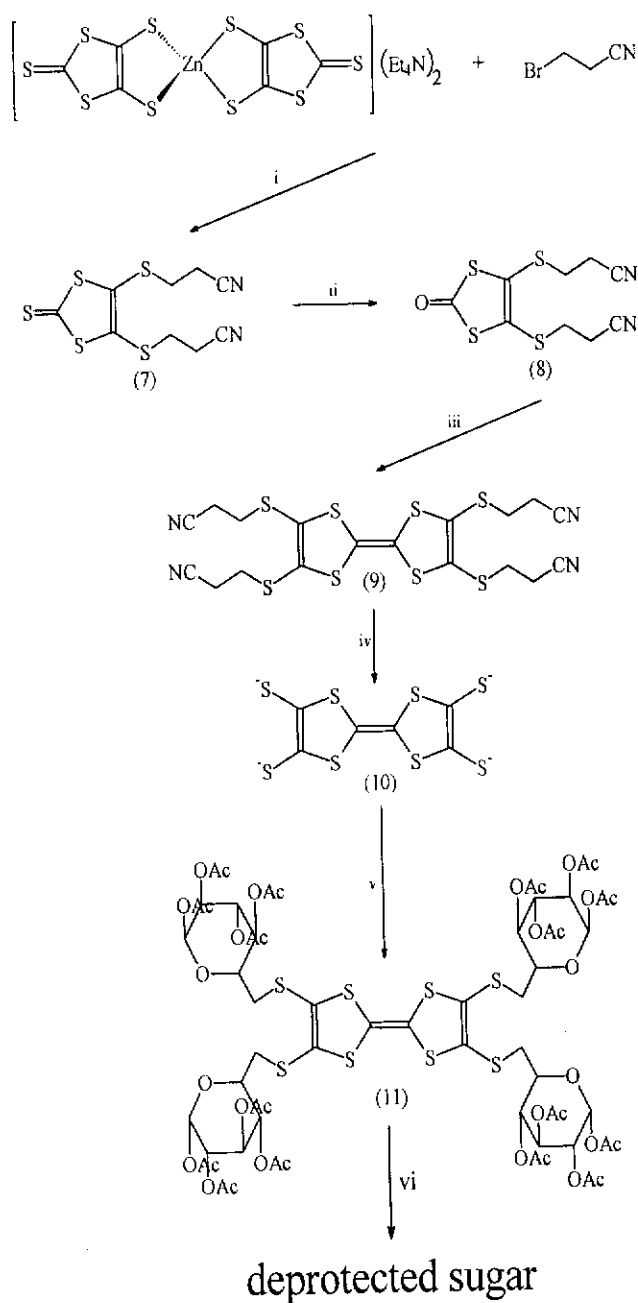
The approach that we utilized for our work was the coupling of two molecular units of the precursor 4,5-dithio-1,3-dithiole-2-thione derivatives using triethyl phosphite<sup>11</sup>. This is the most widely used route in TTF synthesis. One advantage of this route stems from the ready availability of such thiones(2) or oxones(3) on large scale as precursors, from the salt

of the  $[\text{Zn}(\text{dmit})_2]^{2-}$  (1) dianion (also known as zincate) prepared by the sodium reduction of carbon disulfide in dimethyl formamide<sup>12-13</sup>. See scheme 1.

When we reacted zincate(1) with glucosyl bromide, it yielded the expected thione product (5)<sup>14</sup>. Reaction of (5) with  $\text{Hg}(\text{OAc})_2$  in acetic acid and chloroform gave the oxone(6) in high yield. However, when we attempted to couple thione(5) and oxone(6)



**Scheme 3** Mechanism of trivalent phosphorous coupling to form TTF



**Scheme 4** Reagents and Conditions. i. MeCN, reflux; ii.  $\text{Hg}(\text{OAc})_2$ , AcOH,  $\text{CHCl}_3$ ; iii.  $\text{P}(\text{OEt})_3$ , toluene; iv. NaOMe (4 equiv.), MeCN or MeOH; v. 1,2,3,4-Tetra-O-acetyl-6-deoxy-6-iodo- $\alpha$ -D-glucopyranoside (4 equiv.), DMF, reflux; vi. cat. amt. NaOMe (1/500), MeOH.

using triethyl phosphite, it gave a mixture of many products as shown by its thin layer chromatogram (scheme 2). The absence of any major product and the multitude of spots on TLC made the detection of coupling products difficult.

Considering the coupling mechanism of two thione units as proposed by Yoneda et al.<sup>16</sup> (scheme 3), it is obvious that molecular units containing an electropositive center will be attacked by the trivalent phosphorous. Hence, any other additional carbonyl functionality in the thione or oxone structure will render these molecular units incompatible for this coupling method<sup>17</sup>.

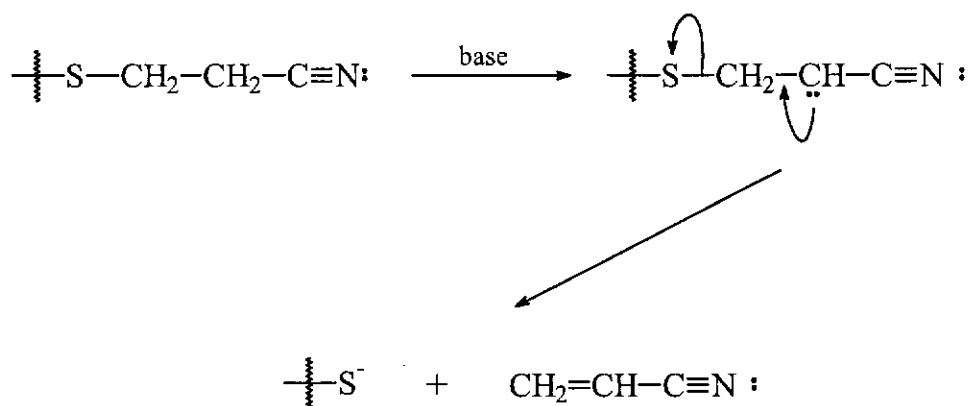
For this reason, the presence of the ester protecting group in the sugar bonded to the thione or oxone structure complicated our coupling reaction attempts. This explains the multitude of products we are getting.

An alternative approach that we did (scheme 4) was to couple suitably protected thione(7) and oxone(8) units. It gave the symmetrical TTF(9) in high yield. Subsequent deprotection using sodium methoxide yielded the desired TTF tetrathiolate anion(10) which further reacted with iodosugar<sup>18</sup> via  $\text{S}_\text{N}2$  mechanism to form the symmetrical sugar functionalized TTF(11). Treatment of(11) with sodium methoxide in methanol afforded the first water soluble symmetrical TTF(12).

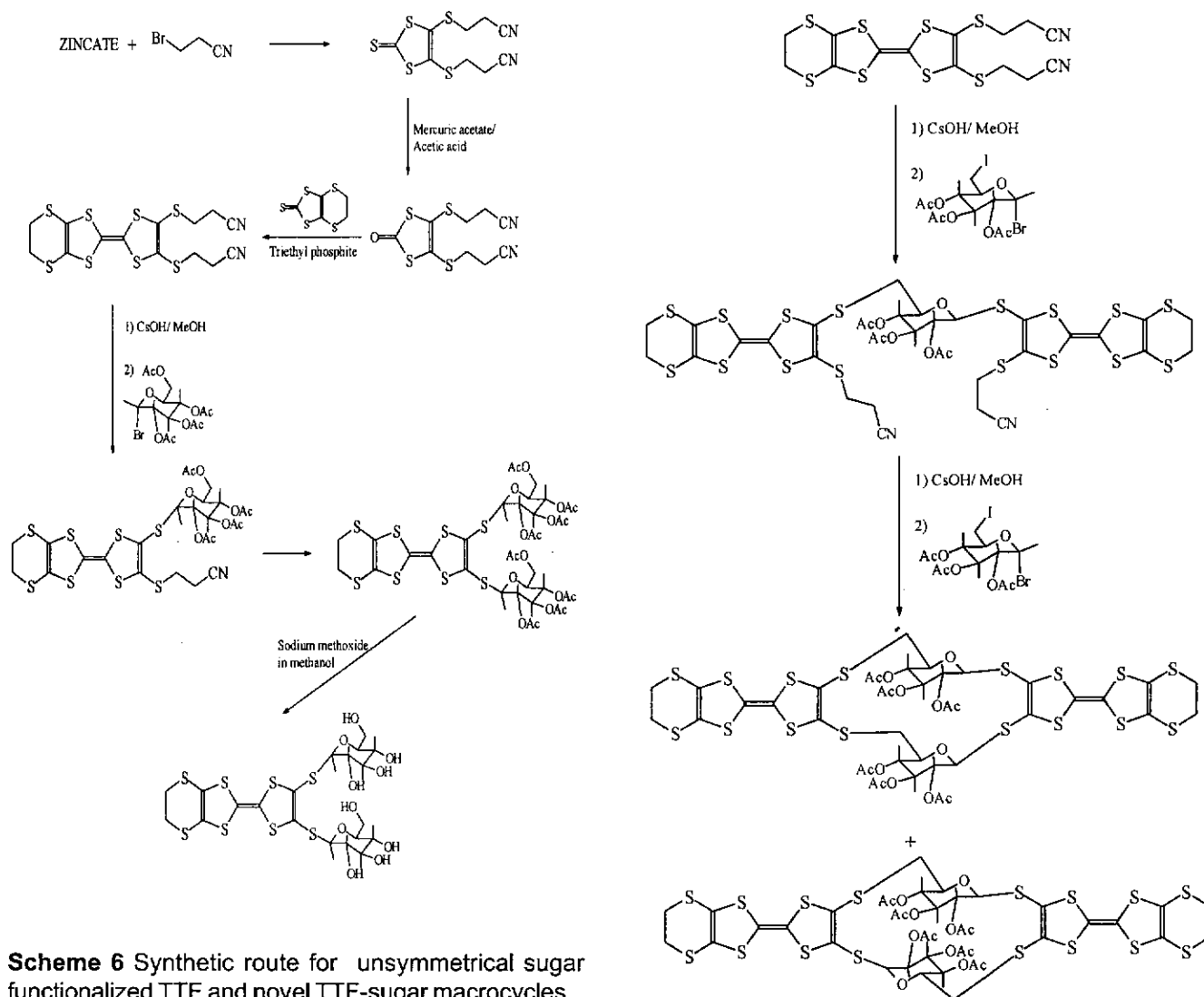
This particular strategy was successful because of the correct choice of protecting group. We used the cyanoethyl-protecting group because of the following reasons:<sup>19-20</sup>

- ✓ It does not interfere with the coupling reactions and generally coupling reaction yields are high.
- ✓ Cyanoethyl protecting group can be removed under conditions in which the redox active TTF unit is unaffected.
- ✓ Deprotection yields are high if not quantitative.

The mechanism of deprotection involves the



**Scheme 5** Mechanism of deprotection of the cyanoethyl protecting group.



**Scheme 6** Synthetic route for unsymmetrical sugar functionalized TTF and novel TTF-sugar macrocycles.

abstraction of alpha hydrogen by a base from the protecting group. The generated carbanion then undergoes elimination which leads to the bond cleavage between carbon and sulfur (scheme 5).

Cross coupling reactions between a thione and an oxone unit is a well-documented route towards the preparation of unsymmetrical TTF derivatives<sup>17</sup>. We also used this route to synthesize some unsymmetrical sugar functionalized TTF and novel TTF-Sugar macrocycles as shown in scheme 6<sup>21</sup>.

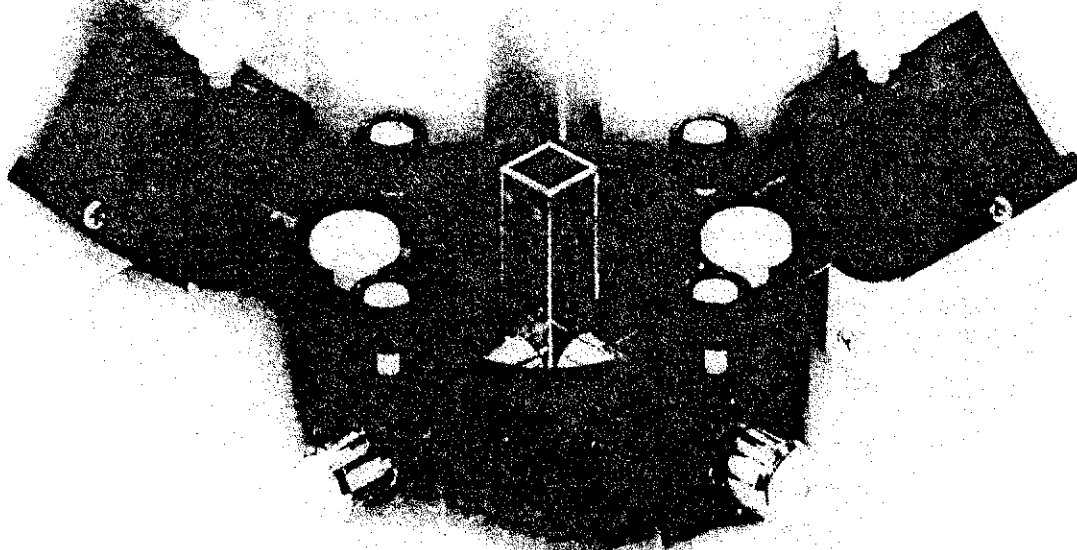
My working group has been quite successful in preparing a number of novel sugar functionalized TTF compounds using the route and strategy I have discussed. We are presently doing some electrochemical characterization and also some biological activity testing of our compounds. We intend to publish the detailed synthesis and characterization and test results in the near future.

Thank you very much for listening.

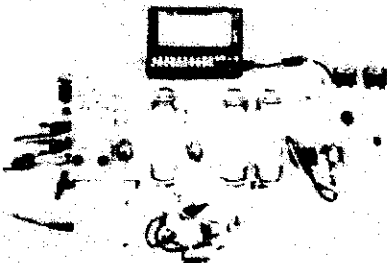
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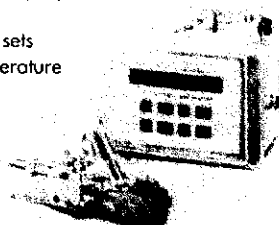


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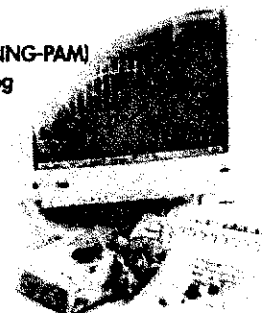
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