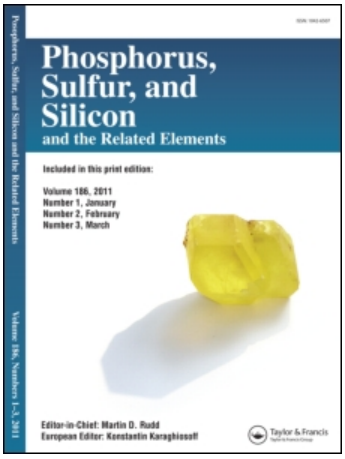

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Selenophene, a Twin-brother of Thiophene?

SALO GRONOWITZ

Organic Chemistry 1, Chemical Center, Lund Unicersity, Box 124, 221 00 Lund, Sweden

Differences in chemistry and NMR-properties between selenophene and thiophene will be discussed. Methods for the preparation of selenophenes, especially the preparation of selenophene through the reaction between acetylene and selenium, will be treated. Atropisomerism in 3,3'-biselenienyls and 3,3'-bithienyls will be discussed. Substituent effects on the ^{77}Se shifts in selenophenes will be analysed. The ring-opening of 3-selenienyllithium derivatives will be compared with that of the corresponding 3-thienyllithium derivatives. Emphasis will be put on tautomerism and reactions of the 2- and 3-hydroxy-systems, reflecting the differences in the aromaticities of thiophene and selenophene. The preparation and reactions of the four classical isomeric selenoloselenophenes, the non-classical selenoloselenophene system, as well as selenolothiophenes will be treated. The preparation of other condensed selenophenes will be touched upon. Other topics, which will be discussed, is the preparation of β-2- and β-3-selenienylalanines. the reactivity of the heteroatom as well as organic metals derived from selenophenes.

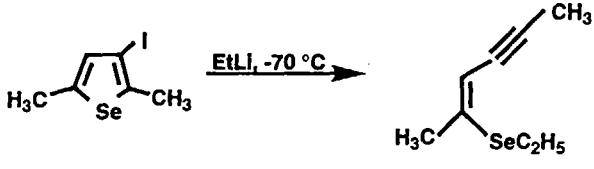
KEY WORDS Selenophenes; selenoloselenphenes; metalation;electrophilic substitution; ring-opening reactions; ^{77}Se-NMR-spectra; tautomerism of hydroxyselenophenes.

INTRODUCTION

This will be quite a personal review of the work on selenophene chemistry carried out in my group since the end of the 60's. I will try to point out characteristic differences between the chemistry of selenophenes and thiophenes. The four more or less aromatic five-membered chalcogen heterocycles offer a very interesting field for comparative studies. Their geometry and spectral properties are wellknown.

Growing up in the school of Arne Fredga in Uppsala, one of the pio-

neers of organic selenium chemistry, I became aware of many aspects of selenium chemistry. I came into the selenophene field in connection with studies on atropisomerism in 3,3'-bithienyls. Already in Uppsala in 1963, we prepared 2,2',5,5'-tetramethyl-4.4'-thiophenedicarboxylic acid, which is easily obtained by iodination of 2,5-dimethylthiophene, followed by halogen-lithium exchange and coupling with cupric chloride to the tetramethyl-3,3'-bithienyl. Renewed iodination and halogen-lithium exchange followed by reaction with carbon dioxide gave the desired product. Using brucine and quinine salts gave both antipodes easily.[1] My idea was to compare the racemization rates of these compounds with those of the analogous benzene and selenophene derivatives. We prepared 2,5-dimethylselenophene by the Knorr-Paal reaction of acetonylacetone with phosphorus pentaselenide. Iodination was smoothly achieved with iodine-iodic acid as in the thiophene series. However, we got a surprise when trying the halogen-lithium exchange at -70 °C. We found that the lithium derivative could not be trapped with carbon dioxide, as a rapid ring-opening occured leading to the ethylsele-

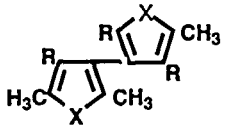


Scheme 1

novinylacetylene (Scheme 1). This opened a new field for our research. I will come back to this in a moment. However, we discovered that the corresponding Grignard reagent from 2,5-dimethyl-3-iodoselenophene was stable giving the carboxylic acid, which after esterification, iodination and Ullman coupling with copper powder gave the desired product. The free acids could not be racemized, but the sodium salts were racemized in dioxane at 140-150 °C. The racemization was slower with the selenophene than the thiophene derivative, which racemized about 90 times faster. The corresponding tetramethyldiphenic acid was not

racemized at all at these temperatures. This was qualitatively in accordance with calculations (Table 1).[2]

Table 1. Transition state functions of racemization of the optically active sodium salts of 4,4'-dicarboxy-2,2'-5,5'-tetramethyl-3,3'-bithienyl (1a) and 4,4'-dicarboxy-2,2'-5,5'-tetramethyl-3,3'-biselenienyl (1b).



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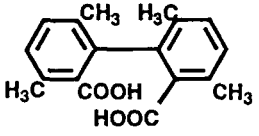


II

a X = S, R = COOH
b X = Se, R = COOH
c X = Se, R = COOH
d X = S, R = CH_2OH
e X = Se, R = CH_2OH

Compound	Temp. C°	k x 10^2 (min^{-1})	$\Delta H^{\neq}$ (kcal/mol)	$\Delta S^{\neq}$ (e.u.)	$\Delta G^{\neq}$ (kcal/mol)
Ia	90	1.12±0.02			
	95	1.73±0.10			
	100	2.58±0.15			
	120	12.5[a]	22.1	-15	27.7
Ib	120	0.141[a]	25	-17	32
	140	0.70±0.02			
	145	1.02±0.02			
	150	1.47±0.05			

[a] Found by extrapolation.

Preparation of selenophene.

Our interest in selenophene chemistry made it necessary to develop a synthetic method for the preparation of selenophene itself. The first reliable preparation of selenophene was reported by Mazza and Solazzo[3]

and by Briscoe and coworkers who heated selenium in a pyrex tube in a current of acetylene at 400 °C.[4,5] This method was also used by Umezawa in his pioneer work on the chemistry of selenophene.[6] However, this method had several disadvantages, as benzene and especially toluene, which has the same boiling-point as selenophene, were formed as by-products and the yield of selenophene in our hands was quite low. Although about 10 % of a higher-boiling fraction was formed. We found that mixing the selenium with alumina solved this problem, since selenophene now became the main product; benzene and toluene amounted only to 2-3 %. A tube oven containing 10 tubes was constructed, which delivered 150-200 g of selenophene per day.[7] In the first 5-6 runs the yields of selenophene were increasing from about 5 % to 50 %. This tendency was also observed by previous workers and was attributed to the formation of a carbonaceous residue, that promotes the reaction even without alumina. We think that the alumina has mainly an area-increasing effect since the alumina pellets became completely covered with the mentioned tarry material, which seems to be a neccessary substance to give good yields. If the reaction temperature is kept below 340 °C the formation of selenophene is very slow and above 550 °C the formation of benzene and toluene becomes a serious drawback. We found that the reaction gave best yields at 450 °C. A detailed investigation of the pyrolysis of acetylene at temperatures ranging from 500 to 1000 °C has been made by Cullis and Franklyn[8], who found that 1-butene-3-yne was the sole initial reaction product, which was subsequently dehydrogenated by carbonasceous reaction products to 1,3-butadiyne. Using this method, kilos of selenophene were prepared in my laboratory between 1975-85. In 1983 an improved version of our method was published by researchers from IBM Research Laboratories in San Jose, which consisted in mixing the selenium with inert material such as sand or glass beads, which assured high yields of selenophene from the beginning.[9] This is of course an advantage especially if small

amounts are needed. In 1987 Voronkov and coworkers described,[10] that a gase-phase synthesis of selenophene can be achieved by reacting acetylene with dimethyl selenide or dimethyl diselenide, which gave selenophene in 78-96 % yield.

We undertook a detailed investigation of the products of the reaction between selenium and acetylene and discovered about 30 other products, such as 2- and 3-alkylselenophenes, 2- and 3-alkylselenoselenophenes, biselenienyls, benzo[b]selenophene and selenolo[3,2-b]-selenophene and the interesting 2-methyl-1,3-diselena-cyclopentene -4, which was formed in appreciable amounts and isolated.[11] It is interesting that we under our conditions only obtained selenolo[3,2-b]selenophene. If the reaction between acetylene and selenium was carried out at below 340 °C as much as 40 % of this compound together with with 20 % of 2-ethylselenoselenophene was obtained. I will come back to the story of the selenoloselenophenes later.

Thus having selenophene available in large amounts, it was possible for us to prepare most selenophene derivatives in similar ways as thiophene derivatives using electrophilic substitution, metalation and halogen-metal exchange reactions. This is still the most important route to various substituted selenophenes. Ring-closure reactions are in the selenophene field not at all of the same importance as in thiophene chemistry. We found, however, that phosphorus pentaselenide freshly prepared from red amorphous selenium was sufficiently reactive towards 1,4-diketones to give 2,5-disubstituted selenophenes in 40-50 % instead of only about 15 % to 20 % as previously described in the literature.[12] Phosphorus sulfide and phosphorus selenides do not react in some cases in the same way. Cava *et al* showed that heating 1,2-dibenzoyl-1, 2-diphenylethane with phosphorus pentasulfide in pyridine directly gave the non-classical thienothiophene, phosphorus pentaselenide on the other hand gave a mixture of *trans* - and *cis* -dihydroselenophtenes. [13] The Hinsberg reaction has been used by us for the preparation of 3,4-

dimethylselenophenecarboxylic acids.[14] Also the reaction of 1,3-dienes with selenium at 450 °C under similar conditions as in the synthesis of selenophene, and in which 1,3-butadiynes are intermediates, has recently been used for the preparation of 3-methyl- and 3,4-dimethyl-selenophene.[15] A novel synthesis of selenophenes has recently been found by Nakayama *et al* and consists in the reduction of α,α'-diketo selenides with a low-valent titanium reagent yielding 3,4-dihydroxyselenolanes, from which the corresponding selenophenes are obtained by acid-catalyzed dehydration.[16] A new synthesis of 5-alkyl-2-selenophenecarboxylates, *via* direct oxidation of 2,4-alkadienoic esters with selenium dioxide, has been described.[17] Recently the successive reactions of β-chlorocinnamonitrile with sodium selenide, produced *in situ* from selenium and sodium borohydride, and α-chloro carbonyl compounds was used for the preparation of 5-substituted 4-amino-2-phenylselenophene-3-carbonitriles.[18]

NMR-spectroscopical investigations

Around 1973, we had facilities for ^{13}C-NMR and were also among the first laboratories having access to ^{77}Se-NMR and later also ^{125}Te-NMR, so we used these various NMR-techniques for a comparative study of the five-membered chalcogen heterocycles in order to obtain a better understanding of their aromaticities. ^{1}H- and ^{13}C chemical shifts of a large number of 2- and 3-substituted furans,[19] thiophenes,[20] selenophenes[21] and of 2-substituted tellurophenes[22] were obtained and compared. Linear correlations between ^{1}H- and ^{13}C- substituent caused shifts of 2- and 3-substiuted selenophenes versus the corresponding thiophenes were found.[21] It is clear that the substituent caused shifts are very similar. In the 2-substituted derivatives, both ^{1}H and ^{13}C shifts are somewhat larger

Table 2. "*Ortho*" - "*para*" ratios of substituent caused ^{13}C-shifts of 2- substituted chalcogen heterocycles

$$\Delta C^{2F}{}_3 = 2.58\ \Delta C^{2F}{}_5$$
$$\Delta C^{2Th}{}_3 = 1.34\ \Delta C^{2Th}{}_5$$
$$\Delta C^{2Se}{}_3 = 1.34\ \Delta C^{2Se}{}_5$$
$$\Delta C^{2Te}{}_3 = 0.91\ \Delta C^{2Te}{}_5$$

for the selenophenes than in the thiophenes. This is also true for the 3-substituted compounds except, 4-hydrogen and 4-carbon shift which is about 5 % smaller in the selenophene series. Good linear correlations between some of the shifts and reactivity parameters according to Swain and Lupton were also observed.[21]

For each of the four five-membered heterocycles from furan to tellurophene a linear correlation between the substituent-caused shifts of the 3 (*ortho*)- and 5 (*para*)-hydrogens or 3-and 5-carbons is observed.[19] However, the *ortho-para* ratio of the ^{13}C shifts (Table 2) decrease systematically in the series furan (2.58) > thiophene (1.34) > selenophene (1.34) > tellurophene (0.91). The more efficient transmission of substituent effects to the 5-position of the higher chalcogen heterocycle has has been ascribed to the high polarizability of these heteroatoms allowing the transmittance of both mesomeric and inductive effects. In 2-substituted derivatives, as I just mentioned the 3- and 5-positions are *ortho* and *para* like respectively, while the 4-position is *meta* like. For 3-substituted derivatives the situation is more complicated. The 2-position is considered to be *hyper-ortho*, while the 4-position is *hypo-ortho* and the 5-position is *meta* like. The question now arises how does the heteroatom feel the substituent? Of course for 2-substituted derivatives it seems to be *ortho* like, but for a 3-substituted derivative the interaction could be either *meta* like or *para* like.

A study of the substituent effects on the ^{77}Se spectra of 2- and 3-substituted selenophene gave us the answer (Table 3).[23] If we look at the

Table 3. ^{77}Se NMR chemical shifts (ppm) and coupling constants (Hz) of some 2- and 3- monosubstituted selenophenes in deuterioacetone solution at 19.135 MHz using selenophene as an external standard.

2-substituted

Substituent	Δ^{77}Se	^3JSe-H$_3$	^3JSe-H$_4$	^2JSe-H$_5$	JSe-H$_x$
H	0	9.5	9.5	47.5	
OCH_3	-91.3	4.2	7.5	48.9	
SCH_3	41.7	7.0	7.0	45.7	1.0
F	-95.4	2.9	6.3	48.5	54
Cl	41.2	4.5	7.2	46.9	
Br	66.0	4.9	8.3	46.4	
I	112.6	6.7	9.1	45.2	
CH_3	3.8	7.8	8.8	46.8	
CH_2OH	-8.6	7.5	8.5	46.7	7.5
CHO	-6.4	4.9	7.4	46.0	8.0
$COCH_3$	11.7	3.7	6.9	44.8	
COOH	26.2	5.2	7.4	45.2	
$CON(CH_3)_2$	42.3				
$COOCH_3$	24.4				
$OCOCH_3$	-32.5	4.1	5.5	45.7	
CN	104.3	4.0	7.8	47.8	
NO_2	5.6	1.6	5.8	45.8	

3-substituted

Substituent	Δ^{77}Se	^2JSe-H$_2$	^3JSe-H$_4$	^2JSe-H$_5$	JSe-H$_x$
H	0	47.5	9.5	47.5	
OCH_3	-80.7	44.4	9.4	44.4	
SCH_3	19.5	45.6	9.3	46.1	
Cl	13.6	43.4	8.0	44.9	
Br	38.1	44.0	7.8	45.1	
I	72.4	45.4	8.0	46.2	
CH_3	-15.2	46.1	10.1	48.1	
CHO	55.3	42.4	10.0	46.6	1.0
$COCH_3$	44.8	44.1	10.6	46.1	
COOH	43.5	44.6	10.2	46.3	
CN	58.4	41.8	8.0	46.0	
NO_2	45.8	39.1	9.0	43.8	

2-substituted derivatives first, linear correlations were observed between the substituent caused ^{77}Se shifts of 2-substituted selenophenes and similarly *ortho*-positioned ^{13}C-shifts, when carbonyl-containing derivatives and 2-nitroselenophene were excluded. The anomalously small downfield shifts and in some case upfield shifts compared with selenophene in the carbonyl derivatives were explained by through space binding interaction between Se-*d*-orbitals and the the carbonyl oxygen lone-pair of the *cis* -conformation of the 2-carbonyl derivatives. As can be seen in table 3 the substituent caused shifts ^{77}Se shifts in the 3-substituted series are almost of the same magnitude as those for the 2-substituted derivatives. For the carbonyl containing derivatives they are even appreciably larger which depends upon the contribution of both the -I and -M effect to downfield shifts in this case and of course upon the absence of the d-orbital binding effect. This is hardly what is expected for a *meta*-position. The ^{77}Se can be linearly correlated both

Table 4. Correlations between substituent caused ^{13}C chemical shifts and those of the heteroatom of some monosubstituted selenophenes.

ΔC^2_3	=	$0.16\ \Delta Se^2$	- 5.2	r = 0.98 (1)
ΔC^3_2	=	$0.19\ \Delta Se^2$	- 13.2	r = 0.94 (2)
ΔC^2_5	=	$0.10\ \Delta Se^2$	- 2.0	r = 0.97 (3)
ΔC^3_2	=	$0.24\ \Delta Se^3$	- 9.45	r = 0.91 (4)
ΔC^2_5	=	$0.16\ \Delta Se^3$	+ 0.08	r = 0.98 (5)
ΔC^3_5	=	$0.04\ \Delta Se^3$	+ 0.76	r = 0.95 (6)
ΔC^3_5	=	$0.24\ \Delta C^2_5$	+1.00	r = 0.95 (7)
ΔC^2_2	=	$-0.40\ \Delta Se^2$	+ 11.6	r = 0.92 (8)

the 2-carbon shift (*ortho* eq 4) and the 5-carbon shift (*meta* equation 6) of the 3-substituted derivatives and also with the 5-carbon shifts (*para* eq. 5) of the 2-substituted derivatives. The best evidence that the substituent caused shifts of the 3-substituted derivatives heteroatom and

the substituent are *para* and not *meta* related is the following: In 2-substituted selenophenes the ortho-para ratio of the substituent caused shifts has been found to be 1.34. The same value is obtained for the slope in a plot of ΔSe^2 against ΔSe^3 again excluding the shifts of the carbonyl and nitro compounds. The substituent caused ^{77}Se shift of 3-substituted selenophenes are about six times larger than the ^{13}C shifts of similar positioned carbons indicating, a shift of about 940 ppm per unit charge.[23] We also found excellent linear correlations between the ^{77}Se shifts and ^{125}Te shifts of simlarly substituted derivatives.[24]

Electrophilic substitution of selenophenes

Upon this topics I will only touch shortly. Pioneering quantitative work was done by professor Gianlorenzo Marino of Perugia and his coworkers in the end of the 1960's. It has been long known that selenophene underwent the same electrophilic substitution reactions as thiophene, reacting somewhat faster. Depending upon reaction, selenophene reacts between 50 and two times faster than thiophene.[25] For Vielsmeyer formylation the rates for all four chalcogen heterocycles have been measured, with a minimum reactivity for thiophene (Table 5).[26] In my group we have not carried out any quantitative studies of reactivity, but have for preparative purposes extensively used electrophilic substitution reactions.

Table 5. Relative rates for Vilsmeyer formylation at 30 °C.

Furan	107	
Thiophene		1
Selenophene		3.64
Tellurophene	36.8	

However, recently, I have together with the group from the Zelinsky Institute, which previously made many contributions to various aspects of selenophene chemistry studied the selectivity in the bromination of

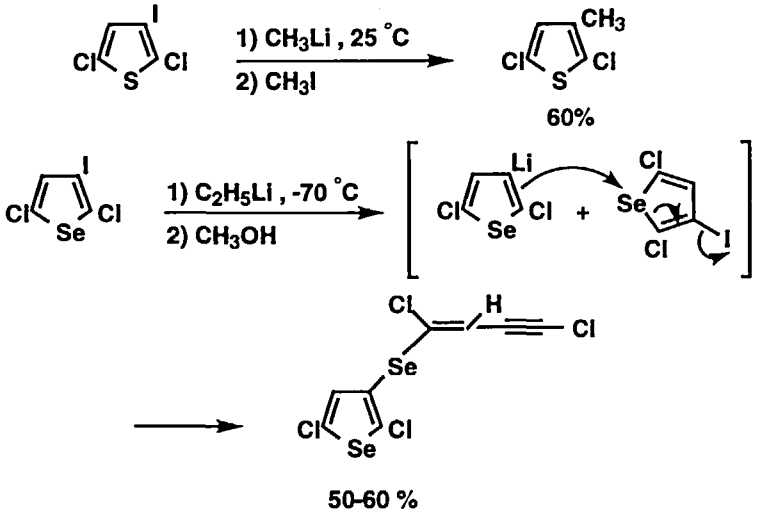
selenophene-2-carbonyl derivatives in methylene chloride in the presence of aluminium trichloride and the reactivity and selectivity was compared with that of the corresponding thiophene derivatives.[27] In the absence of aluminium trichloride, bromination of 2-selenophene-carboxaldehyde occurs exclusively in the 5-position. With an equimolar amount of aluminium trichloride this bromination practically does not occur at all. An excess of at least 1.8 mol per mol aldehyde suppresses completely the dissociation of the aluminium trichloride complex and now a mixture of 95 % of the 4-bromo-2-formyl- and 5 % of 5-bromo-2-formylselenophene is obtained. Similar results were obtained for 2-acetylselenophene which gave the 4-and 5-substituted derivatives in the proportion of 90 to 10. However, the reaction is not as selective in the selenophene series as in the thiophene series were more than 99 % of the 4-isomer is formed. This can be ascribed to the higher α-positional selectivity in selenophene than thiophene. Competitive experiments showed that the selenophenecarboxaldehyde complex reacted a few times faster.

Metalation, halogen-metal exchange and ring-opening

As I mentioned in the beginning, our attempts to prepare biselenienyls lead to the discovery of a new ring-opening, which occured in the selenophene series already at -70 °C.[28] In order to prepare 3-substituted selenophenes in reasonable yields, it is necessary in most cases to carry out the halogen-lithium exchange at -100 °C. An important consequence was, that this lead to the discovery that 3-thienyllithium derivatives undergo similar ring-opening at room temperature and this was used for the preparation of alkylthiovinyl- and alkylselenovinyl derivatives of vinylacetylenes and various natural products derived from them for review (cf ref.[29]).

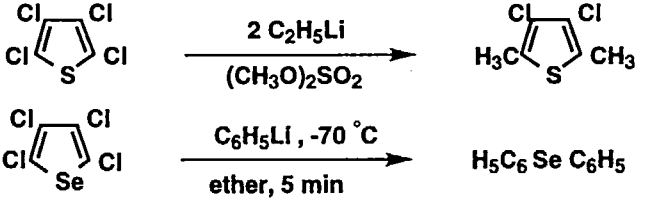
From selenophenes certain compounds hardly available in any other way could be prepared. Thus the treatment of 3-bromo-2-methyl-5-

methylthioselenophene gave a mixed methylthio ethylselenoketene acetal with defined stereochemistry, while the isomeric 3-bromo-2-methylthio-5-methylselenophene gave 2-ethylselenovinylacetylene with an methylthio substituted on the acetylenic bond.[30]



Scheme 2

However, there is an important difference in the reactivity of certain 3-halosubstituted selenophenes compared to the corresponding thiophenes. The selenium is much more electrophilic than the thiophenic sulfur. Thus while 2,5-dichloro-3-iodothiophene even at room temperature gives halogen-metal exchange followed by reaction with methyl iodide

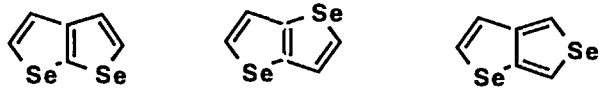


Scheme 3

to give 3-methyl-2,5-dichlorothiophene, the 2,5-dichloro-3-selenienyllithium formed by halogen-metal exchange even at -70 °C, immediately attacks the selenium of the starting iodide to give the ring-opened product.[31] Another example is that tetrachlorothiophene with two equivalents of ethyllithium gives chloro-lithium exchange of the α-chlorines and upon reaction with dimethyl sulphate 3,4-dichloro- 2,5-dimethylthiophene is obtained, while tetrachloroselenophene upon treatment with ethyllithium at -70 °C in ether gives 54 % of diphenyl selenide due to attack on the ring-selenium.[32] Finally also the solvent is of importance. Thus 2,3,5-tribromoselenophene similar to 2,3,5-tribromothiophene gives halogen-metal exhange with alkyllithia in ether at -70 °C, yielding 2,4-dibromoselenophene upon hydrolysis. In tetrahydrofuran at -110 °C the primarily formed 3,5-dibromo-2-selenienyllithium immediately attacks the selenium atom of 2,3,5-tribromoselenophene with ring-opening, giving 3,5-dibromo-2-selenienyl 1-bromo-1-buten-3-yn-1-yl selenide.[33]

Selenoloselenophenes also called selenophtenes

Now I am coming back to the reaction between acetylene and selenium. As mentioned in the beginning a higher boiling fraction is obtained, which already Umezawa studied in the end of the thirties. He claimed the isolation of three isomeric selenophtenes (Scheme 4), the major one with a m.p. of 123-124.5 °C, he erronously assigned the structure of se-



1 2 3

Scheme 4

lenolo[3,4-*b*]selenophene.[34] Using ^{1}H, ^{13}C and ^{77}Se-NMR, we proved

that this compound was the [3,2-*b*]-isomer.[35] We also prepared an authentic sample of selenolo[3,2-*b*]selenophene, starting from 3-bromo- 2-selenophene carboxaldehyde.[36] Of course the best method is its synthesis from selenium and acetylene at temperatures below 340 °C giving up to 40 % yield. Umezawa also obtained a second isomer with a melting-point of 51-51.5 °C, which he thought was the selenolo[3,2-*b*]-selenophene. Starting from 3-selenophenecarboxaldehyde, we carried out an authentic synthesis of selenolo[2,3-*b*]selenophene, which had a m.p of 56-57 °C.[36] This makes it highly probable that Umezawa also had obtained this isomer, which we, however, could not reproduce. Finally, Umezawa obtained a liquid isomer, b.p. 90- 93°/14 mm Hg, which he believed to be the [2,3-*b*]-isomer and which we could not obtain from the reaction of acetylene with selenium. We prepared the third classical selenophtene, selenolo[3,4-*b*]selenophene, in two different ways.[37] The best route route shown used 4-methylseleno-3-selenophene-carboxaldehyde as the key intermediate. The yield was 44 % from the aldehyde and 10 % from selenophene. Also this selenophtene was crystalline and had a m.p of 46-47 °C. We also, like Umezawa, prepared picrates and tetrabromo derivatives of the three compounds. In summary, it is clear that he had isolated isomers **1** and **2** from the reaction of selenium with acetylene, although he made completely wrong structure assignments. However, his so called liquid selenophtene must be something else.

In contrast to the [3,4-b]-fused thiophtene, the [3,4-b]-fused selenophtene was stable and could be kept for a long time in the refrigerator. This gave me the hope that the non-classical [*c,c*]-fused selenophtene would be more stable than the corresponding thiophtene.

As a Ph.D topic Andreas Konar prepared the non-classical selenoph-

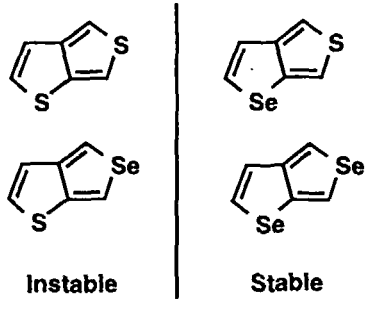
[3,4-*b*] [3,4-*c*]

Scheme 5

tenes. He tried many of the metods used by Cava for reaching such systems. As I mentioned, the direct reaction of the tetraphenyl derivative from tetrabenzoyl methane and phosphorus selenide failed. However, we found evidence for the existence of 1,3-dimethyl-, 1,3-dicarbethoxy- and 1,3-diphenyl derivatives of the selenolo[3,4-c]selenophene. The best synthetic routes were the acid-catalyzed dehydration of the corresponding selenoxide and the base-catalyzed reductive debromination of the selenium dibromides, which were already used by Cava for the non-classical thiophtenes.[38] The non-classical selenophtenes were stable for hours in hexane solution and gave strongly violet solutions. They could be trapped with dienophiles like *N*-phenyl maleimide and dimethyl acetylenedicarboxylate, but gave dicyanomethyl ylides with tetracyanoethylene.

Konar also carried out extensive work on preparing non-classical selenolothiophenes. Most routes were not successful. Only Cavas original method for the preparation of thieno[3,4-c]thiophenes was also successful in this case, namely decomposition of sulfoxides or selenoxides by acid and selenium dibromides with base either starting from thiophene and building on the selenophene ring or starting from selenophenes and building on the thiophene ring.[39]

We also prepared the mixed selenolothiophenes and studied their chemistry and spectroscopical properties. The synthetic methods were similar as for the selenoloselenophenes. We have now four classical isomers. There are two *b,*c-fused isomers, which showed different stabilities.

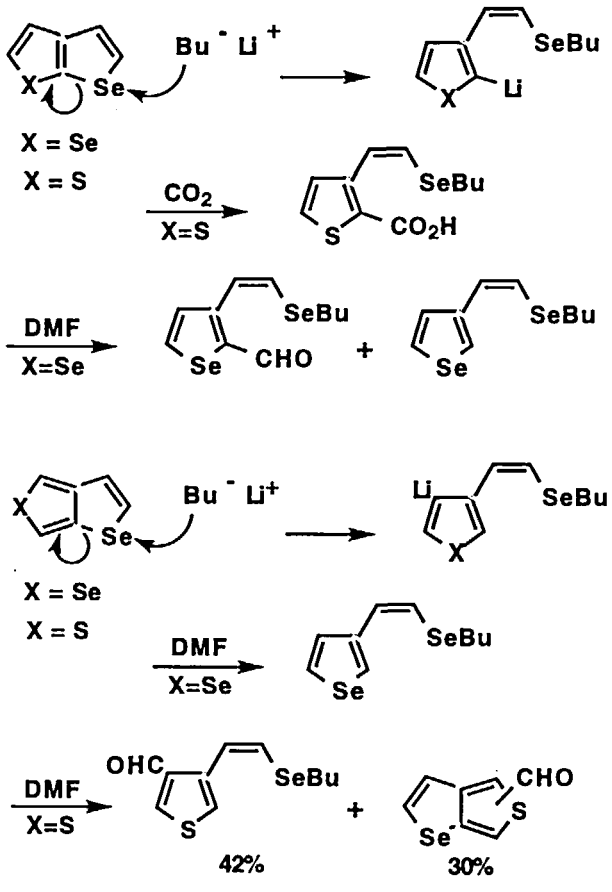


Scheme 6

Compounds with *c*-fused thiophene rings were unstable, while those with *c*-fused selenophene rings were stable. The instability of selenolo[3,4-b]thiophene was illustrated by the fact that the hydrolysis of the 2-carbethoxy derivative could not be achieved, while as mentioned before the selenolo[3,4-*b*]selenophene easily was obtained *via* this route. The other isomer, selenolo[2,3-c]thiophene, was easily prepared from 3-methylthio-4-selenophenecarboxaldehyde. The reason for this instability is most probably the tendency to aromatize the thiophene ring through cycloaddition over the dienic part in the same way as in benzo[*c*]-thiophene, while this driving force is not as important for selenophene.

Metalation reactions

Metalation of the selenoloselenophenes and their thiophene analogues were studied both by us and Goldfarbs group at the Zelinsky Institute and also by us together with Victor Litvinov from that group. It was found that the [3,2-*b*]-systems behaved normally. Lithiation occured in the 2-position of selenolo[3,2-*b*]selenophene and after reaction with carbon dioxide the 2-carboxylic acid was isolated in 69 % yield. The selenolo[3,2-*b*]thiophene showed no selectivity and with one equivalent followed by reaction with carbon dioxide a mixture of the two α-substituted acids were obtained in the proportion of 48:52, with two equivalents the dicarboxylic acid was obtained.[40,41] The [2,3-*b*]-fused systems and the [3,4-*b*]-fused systems behaved quite differently.[40,41,42,43] At -20 °C butyllithium attacked at the selenium atom of selenolo[2,3-*b*]-thiophene yielding 3-ß-(butylselenoethenyl)-2-thienyllithium, which upon reaction with carbon dioxide gave the acid. The selenolo[3,4-*b*]-selenophene reacted similarly and gave upon reaction with DMF the corresponding selenophenecarboxaldehyde and also the unsubstituted ß-(butylselenoethenyl)selenophene probably formed by hydrolysis of the intermediate lithium derivative (scheme 7).



Scheme 7

The [*b,c*]-fused system, selenolo[3,2-*c*]thiophene is not attacked as fast by butyllithium and a mixture of the 4- and 6-formylated products, about 30 %, are formed together 42 % of the β-(4-butylselenoethenyl)-3-thiophenecarboxaldehyde. It is interesting to note that selenolo[3,4-*b*]selenophene gave beside unreacted starting material (38%), 3-(β-butylselenoethenyl) selenophene in 58 % yield upon reaction with DMF. The reason why the intermediate lithium does not react with DMF is not obvious, steric hindrance has been suggested.

Electrophilic substitution reactions

We carried out quantitative studies on acylation, formylation and chlorination of selenolo[3,2-*b*]selenophene and selenolo[3,2-*b*]thiophene. Only α-positions were substituted and thus no partial reactivities of the β-positions could be calculated. The overall reactivity order was found to be selenolo[3,2-*b*]selenophene > selenolo[3,2-*b*]thiophene > thieno-[3,2-*b*]thiophene.[44] From the literature the overall relative reactivities of the compounds could also be determined relative to thiophene and in the case of acetylation and formylation also relative to selenophene. The selenolothiophene shows no selectivity between the α-positions. Thus for formylation, a 35:65 ratio of the 2- and 5-formyl derivatives were obtained. Bromination of the [3,2-*b*] isomer with NBS in acetic acid gave 20 % of the dibromo derivative. However, only the 5-bromo selenolo[3,2-*b*]selenophene was obtained in 70 % yield. Selenolo[2,3-*b*]-thiophene, which was studied by Gol'dfarb and coworkers did not show such a high selectivity. It was found that bromination with one equivalent of NBS resulted in a mixture of 20 % of the dibromo derivative and 65 % of both 2- and 5-monobromo derivatives in a ratio of 13:87. We have also studied the formylation of the [2,3-*c*]isomers.[43,45] No selectivity was observed. The total yields were about 70 % .

We also extensively studied the ^{1}H, ^{13}C and ^{77}Se-NMR-spectra of the various selenoloselenophenes and their thiophene analogues[46,47]. I want only to mention the results obtained on their ^{77}Se spectra and especially the determination of the ^{77}Se-^{77}Se coupling constants of the selenoloselenophenes and of alkylselenosubstituted selenophenes from the selenium satellites of the proton-noise decoupled ^{77}Se NMR-spectra.[48] The variations in J_{Se-Se} was discussed in relation to the conformation of the alkylseleno substituents and the aromaticity of the selenophtene systems.

Other heterocyclic-fused selenophenes

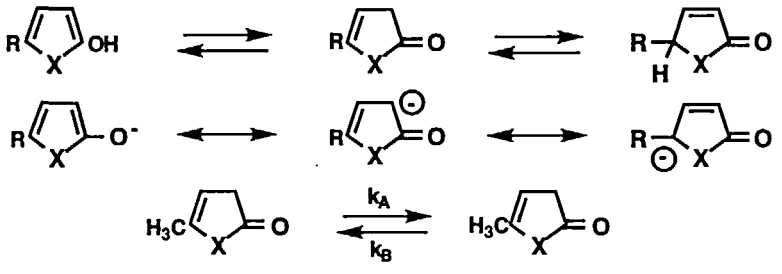
We have also prepared and studied some other heterocyclic fused selenophenes and compared with the similarly fused furans and thiophenes. Most of this work was carried out by Christer Westerlund in his Ph.D thesis. The 3-bromo-2-formyl derivatives of furan, thiophene and selenophene easily underwent nucleophilic aromatic substitution with sodium azide in DMSO at 60 °C to give the 3-azido-2-formyl derivatives in 45-60 % yield. The azido aldehydes could be oxidized with silver oxide to the carboxylic acid, *via* the oxime transformed to the nitrile and with hydrogen sulfide reduced to the 3-amino-2-formyl derivatives.[49] The previously unknown amino aldehydes were quite stable and constituted excellent starting materials for the synthesis of the fused heterocyclic systems. Thus applying the Friedländer reaction to the 3-amino-2-formyl derivatives lead to a convenient synthesis of furo-, thieno- and selenolo[3,2-*b*]pyridines and their 5- and 5,6-disubstituted derivatives. Direct condensation with acetaldehyde failed. However, condensation with freshly distilled pyruvic acid in alkaline water/etanol gave 43-48 % of the 5-carboxy derivatives, which were decarboxylated in almost quantitative yields by heating over their melting-point. With acetone 71-7 % of the 5-methyl derivatives were obtained.[50] Rate-constants for deuteriodeprotonation in D_2SO_4 at the 2- and -3-positions of the furo [3,2-*b*]-, thieno[3,2-*b*]- and selenolo[3,2-*b*]pyridines, as well as the pyrollo-analogue and some other related systems have been determined.[51] Aldol condensation of the 3-azido-2-formyl derivatives with acetone or nitroacetone followed by ring-closure lead to the [3,2-b]-fused pyrolle systems. Heating of the 3-azido-2-formyl derivatives at 120-125 °C in xylene gave the furo-, thieno- and selenolo[3,2-c]isoxazoles with a best yield of 40 % for the selenolo derivative.[52] Unsubstituted thieno- and selenolo[3,2-c]pyrazoles were prepared by the

reaction of the 3-amino-2-formyl derivatives with hydrazine hydrate or by diazotization and subsequent reduction of the 3-amino-2-formyl derivatives. The yields were quite low.[53] Detailed NMR-spectroscopical studies were undertaken and also the reactivity of these new heterocylic systems was investigated.

Tautomerism of hydroxy derivatives

We found interesting differences in the tautomeric properties of the 2-hydroxy systems of furan, thiophene and selenophene. In principle, they can exist in three different tautomeric forms, having a common tridentate

The hydroxysystems and their anions.



Scheme 8

anion (scheme 8). Depending upon the presence of other substituents different forms dominate at equlibrium. In simple 5-alkyl derivatives, no hydroxy form can be observed, and at equilibrium a mixture of the 3- and 4-ones are obtained.[54,55] With electron-withdrawing and chelating substituents in the 3-position, the hydroxy forms become the most stable. Upon acidification of a solution of their salts the less stable 4-one is formed and can be isolated and the base-catalyzed tautomerization could be studied. A comparison of the oxygen and sulfur systems showed that in benzene solution with triethylamine as base the furan derivatives, the butenolides, are found to tautomerize at rates three to four powers of ten

slower than the corresponding thiolenes. We can also notice that there is more of the non-conjugated form at equilibrium in the furan than the thiophene case. In the selenophene case the tautomerization is faster than

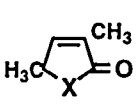
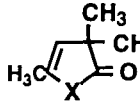
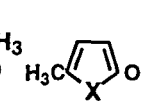
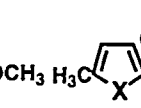
Table 6. Equilibrium constants and specific rate constants in benzene solution.

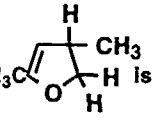
	Triethylamin	Pyridine	Temp. °C	K	k_1	k_2
5-Methyl-butenolide	0.5		45	3.2	2.0×10^{-4}	6.3×10^{-4}
5-Methyl-thiolene-2-one	0.005		36	5.1	11.6×10^{-2}	2.3×10^{-2}
5-Methyl-thiolene-2-one		0.24	40	4.1	2.56×10^{-4}	0.62×10^{-4}
5-Methyl-selenolene-2-one		0.24	40	14.4	6.5×10^{-4}	0.45×10^{-4}

in the thiophene case and especially compared to the furans, so in this case triethylamine could not be used as base, instead pyridine was used. We can notice that the equilibrium position now is far to the conjugated form (K 14 instead of 4) and the rate is about three times faster.

We also studied the alkylation of the anions with soft and hard electrophiles using the ion-pair technique and it is interesting to note how the results reflect the aromaticity of the five-membered heterocycles.[55,56] Thus in the thiophene series the soft metyl iodide yields 86 % of the 3-carbon methylated product and 12 % of the O-methylated products, besides smaller amounts of C,C-dimetylated and C,O-dimethylated products in a total yield of 53 %. In the selenophene series only 38 % of the 3-carbon methylated product was obtained as this is further methylated to the C,C-dimethylated product in 50 % yield and only very little of the O-methylated products were obtained. In the furan case no O-methylated products were observed. Instead both pos-

Table 7. Distribution of products in methylation of the 5-methyl-2-hydroxy systems of furan, thiophene and selenophene with methyl iodide and dimethyl sulphate using ion-pair extraction.

Reagent					Total Yield
CH_3I, X = S	86	2	12	-	53
X = Se	38	50	4	3	37
X = O	24+(30)*	46	-	-	26
DMS, X = S	4	2	90	4	89
X = Se	6	3	76	15	44
X = O	100	0			7

* 30% of  is also formed

sible 3-methylated forms were obtained, the 3-butenolide (24 %) and the 4-butenolide (30 %) in addition to 46 % of the C,C-dimethylated product. The total yield was quite low. When the hard electrophile dimethyl sulphate was used 90 % of the O-methylated product was obtained in the thiophene case together with small amounts of the other methylated products and in a good total yield of 89 %, small amounts of C-methylated products were obtained but the main product in 76 % yield was the O-methylated product. An interesting difference is the formation of 15 % of O,C-dimethylated product. The furan system behaved very differently, only the 3-C-methylated product was obtained but in very low yield, only 7 %. Most of the butenolide was hydrolyzed.

The 3-hydroxy systems might exist in only two forms the hydroxy form and the ketoform.[57] They tautomerize very rapidly and the different forms cannot be isolated. However, using UV-technique, it was found that in methanol there is 10 000 times more of the ketoform than the

hydroxyform in the furan series, about 200 times more in the selenophene series and about equal amounts in the thiophene case.[58] The same order is also observed in cyclohexane. However, the differences are not as marked. This order is a clear reflection of the aromaticities of the three systems. The same trend is noticeable for the methylation of the ambident anion with methyl iodide and dimethyl sulphate.[58] Especially the latter gives good yields and the proportion of O- to C- alkylation is 90:10 for thiophene 93:7 in the selenophene case, although the total yield is much lower, and 54:46 in the furan series. The proportions with the soft methyl iodide were 35: 65 for thiophene, 15:85 for selenophene and 2:98 for furan.

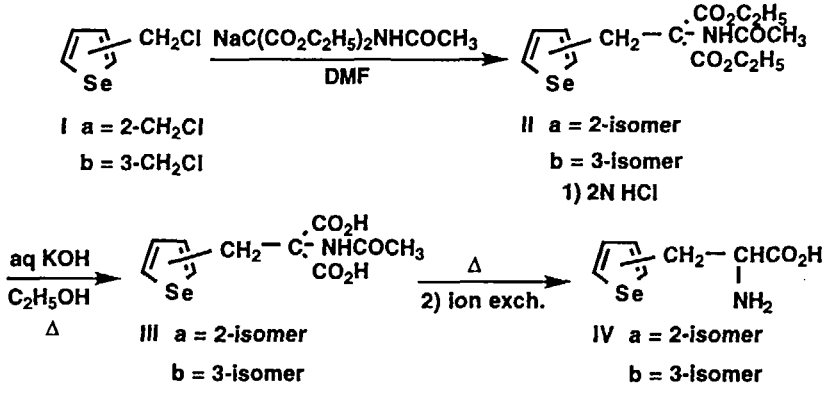
Reactivity at the heteroatom.

Very little comparison of the reactivity between the heteroatoms of thiophene and selenophenes has been carried out. We made many attempts to prepare the corresponding selenophene-1,1-dioxide but without success. However, recently professor Nakayama, from Saitama University, managed to prepare the dioxide from tetraphenylselenophene and as expected they were quite unstable and decomposed rapidly. They do not have the same synthetic potential at all as the thiophene-1,1-dioxides.[59] Together with professor Bien from Technion in Haifa, we prepared the bismethoxycarbonyl methylides through the rhodium(II) acetate catalyzed addition of dimethyl diazomalonate to selenophenes.[60] Reasonable yields were obtained only with 2,5-dichloro- and 2,5-dibromoselenophene. They were found to be less stable than the corresponding thiophene derivatives.

Various investigations on selenophene derivatives

Certain amino acids labelled with radioactive isotopes have been shown

to localize in the pancreas.Of these ^{75}Se-selenomethionine was used at least in the 80's as pancreatic imaging agent for external visualization by γ- ray scintigraphy, but as it has some drawbacks, we planned to use the β-2- and β-3- selenienylalanines, which being analogous to phenylalanine could be expected to have superiour pancreas to liver ratio. So in collaboration with Dr Davis at Harvard Medical school and Dr Sadeh from the Soreq Nuclear Research Center in Israel, we tried several methods for their synthesis and found the classical route (scheme 8) being the best one.[61]



Scheme 8

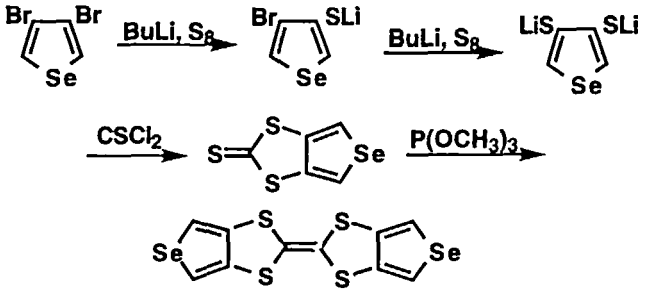
Davis also worked out a method were the selenophene ring is formed in the last step by ring-closure of a diacetylene derivative. We later worked out an asymmetric synthesis of the selenienyl alanines first by asymmetric hydrogenation of the corresponding 2-acetamidoacrylic acids using [Rh/(+)DIOP as chiral catalyst, which gave the optical active acetamido acids in high enantiomeric excess[62]. Unfortunately some racemization occured during the hydrolysis of these acids. However using instead Schöllkopfs method, starting from S-(+)2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine and 2- and 3- chloromethylselenophene gave optically pure amino acids.

Organic metals

The great interest in organic metals, especially polythiophenes, has also spilled over into the selenophene field. Already in 1981[63] we prepared together with Dr Kovacic group at the University of Wisconsin Milwaukee, polyselenophenes by nickel-promoted coupling of the Grignard reagent from 2,5-dibromoselenophene, which afforded poly (2,5-selenienylene) containing 6-12 selenophene units. The conductivity of doped material was investigated but to our disappointment it was not as high as for the polythiophene.[64] Together with professor Zimmer, we also prepared mixed oligomeric heterocycles containing thiophene and selenophene rings through $NiCl_2$(dppp) catalyzed cross-coupling reactions between 2-bromoselenophene, 2-bromo-3-methylselenophene or 2,5-dibromoselenophene and the Grignard reagent derived from the appropiate bromothiophene and studied their UV-spectra and oxidation potentials.[65-67] These studies were extended to compounds also containing furan rings. Also Pd(0)-catalyzed reactions have been used in connection with the preparation of a wide range of terheterocycles. Thus we prepared 2,5-di-(2-selenienyl)thiazole through coupling of 2,5-dibromothiazole with 2-tributylstannylselenophene.[68] In connection with our interest in antiviral compounds, we also prepared various selenienylpyrimidines through the Pd(0)-catalyzed Suzuki coupling from the selenopheneboronic acids and halopyrimidines or from the protected pyrimidineboronic acids and the bromoselenophenes.[69]

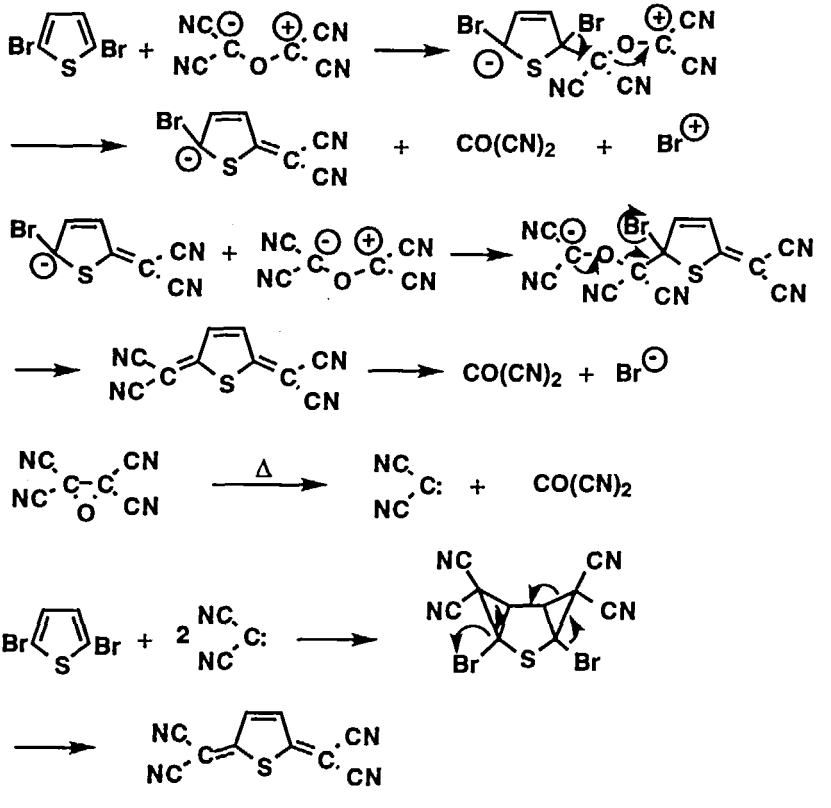
Charge-transfer complexes

We have also been interested in preparing anlogues of tetrathiafulvalenes, which are electron donors in electrical conducting charge transfer complexes. Together with professor Roger Ketcham from San Francisco, we prepared a tetrathiafulvalene doubly fused to the 3,4-position of sele-



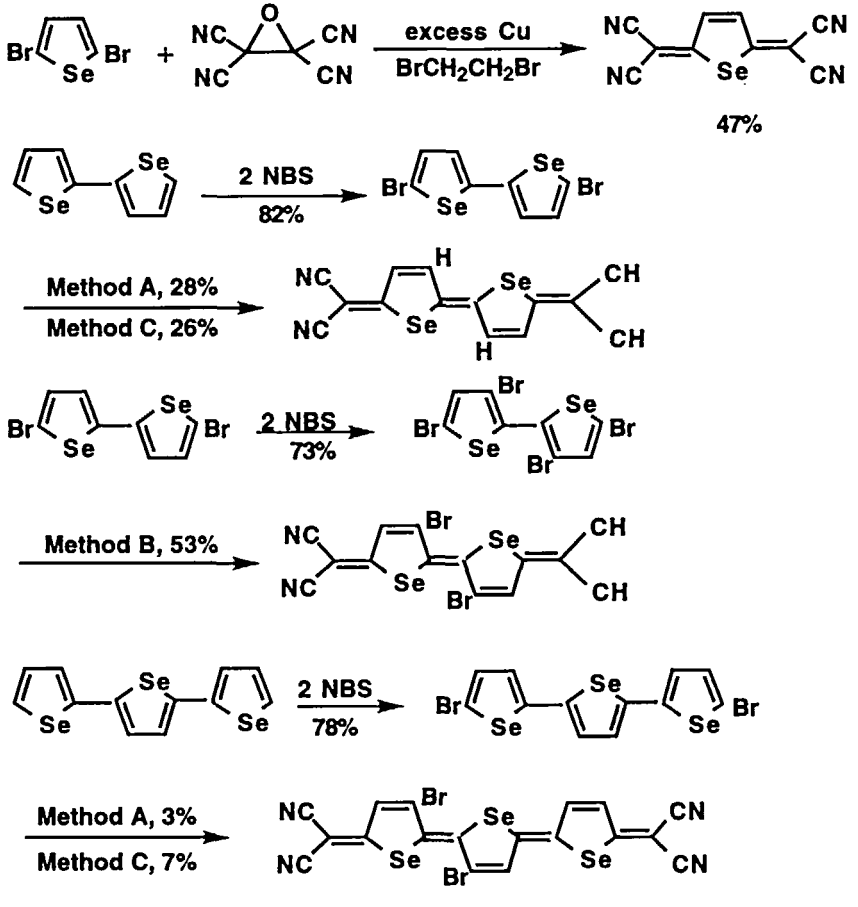
Scheme 9

nophene starting from the 3,4-dibromoselenophene and going through the dithiol.[70] Our interest in this field started with a completely unexpec-



Scheme 10

ted discovery, that 2,5-dibromoselenophene and 2,5-dibromothiophene reacted with tetacyanoethylene oxide to give 2,5-bis (dicyanomethylene)-5,5'-dihydro-2,2'-bi-selenophene, an analogue of TCNQ.[71] The mechanism of this reaction has not been elucidated and we suggested two alternatives which are in accordance with the product formed.



Method A : TCNEO (4 equiv.), Cu(10 equiv.) in 1,2-dibromoethane, reflux, 2h

Method B : TCNEO (10 equiv.) in 1,3-dibromopropane, reflux, 2h.

Method C : 1) $CH_2(CN)_2$ (4equiv.), NaH (8 equiv.), cat. $(Ph_3P)_4Pd$, in 1,2-methoxyethane, reflux, 60-80 min ; 2) Bromine water.

Scheme 11

In collaboration with professor Fred Wudl at that time at Bell Laboratories, electrochemistry and electron spin resonance spectroscopy of the selenophene and thiophene-TCNQ was studied. They were found to be rather poor electron acceptors.[72] However, in 1988 Japanese researcher continued in this field they improved the synthesis of selenophene-TCNQ by scavenging the bromine formed with copper powder and synthesized extensively conjugated homologues of selenophene-TCNQ.[73] The 3,3'-dibromo compound possessed a considerably better accepting character than selenophene-TCNQ or the other extended homologues and formed highly conductive polymers.

Acknowledgments

Finally I have to thank the Swedish Natural Science Research Council for the economic support and my coworkers, whose names appeared on the slides, for their dedicated collaboration.

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