CYCLOADDITION REACTIONS OF 2,3-DIDEHYDROTHIOPHENE GENERATED BY FLOW VACUUM THERMOLYSIS OF THIOPHENE-2,3-DICARBOXYLIC ANHYDRIDE

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Abstract - Flow vacuum thermolysis (FVT) of thiophene-2,3-dicarboxylic anhydride (2) in the presence of 2,3-dimethylbutadiene (6) gives, in addition to 5,6-dimethylthianaphthene (9), small quantities of a dihydrodimethylthianaphthene (12) and another dimethylthianaphthene (13) which is probably also formed by dehydrogenation of 12 with chloranil. The partial structures of these minor products are consistent with their being formed by a [2+2]-cycloaddition between 6 and an intermediate aryne, 2,3-didehydrothiophene (1), followed by a rearrangement of the resulting adduct 11 and dehydrogenation. FVT of 2 in the presence of 2,5- (17b) or 3,4-dimethylthiophene (17c) also gave a mixture of the dimethylthianaphthenes (18, 22, 23) which can be rationalized as arising by a [4+2]- and two [2+2]-cycloadditions of the aryne 1 to the thiophenes 17 with subsequent desulfurization. The lack of equilibration of the products 18, 22, and 23 was demonstrated and their origin as a function of the structure and reactivity of the aryne 1 discussed.

Five-membered hetaryne intermediates have proved to be nore elusive¹ than their six-membered analogues.² Recently, however, the intermediacy of 2,3-didehydrothiophene (1) during the flow vacuum thermolysis (FVT) of the anhydride 2 was claimed based on the isolation of thianaphthenes 3 when various dienes 4 were used as trapping



agents.³ The rationale for this reaction was a [4+2]-cycloaddition of the aryne <u>1</u> and the diene <u>4</u> to give the unisolated Diels-Alder adduct <u>5</u> which aromatizes to the thianaphthenes <u>3</u>.

Although [4+2]-cycloaddition reactions with conjugated dienes are so well known that they have been considered diagnostic for arynes,⁴ the alternate [2+2]-cycloadditions have also been observed with certain dienes and a variety of benzyne precursors.⁵⁻⁸ For this reason the reactions of the 2,3-didehydrothiophene (1) with several dienes was reexamined to determine if any evidence for [2+2]-cycloaddition could be obtained.

RESULTS AND DISCUSSION

<u>2,3-Dimethylbutadiene</u> (6). This diene was the first to give both [4+2]- (7) and [2+2]- (8) cycloaddition products with benzyne. With the hetaryne 1, however, the major product was 5,6-



dimethylthianaphthene 9, which presumably arose by dehydrogenation of the [4+2]-adduct 10.³ Traces of two minor products could be collected by preparative vpc, neither of which displayed olefinic protons in the nmr and hence were not the [2+2]-cycloaddition products 11. Although these compounds could not be isolated in pure form, their mass spectral and nmr characteristics were consistent with one being a dihydrodimethylthianaphthene 12 and the other a dimethylthianaphthene 13. The alternative 5,6-dimethyl compound 10 was considered unlikely for the former product since the methyl group resonances would have been expected^{3,9} to be more equivalent than observed. This conclusion was verified by a chloranil dehydrogenation of 12 to a dimethylthianaphthene clearly distinguishable from 9 by its distinct methyl resonances and possibly identical to 13. A comparison with a synthetic sample³ of 4,5-dimethylthianaphthene (13a) was inconclusive



because of the lack of pure material. Regardless of the exact structures of 12 and 13, however, their formation can be rationalized by a [2+2]-cycloaddition of 2,3-didehydrothiophene (1) and 2,3-dimethylbutadiene (6) to the vinylcyclobutenes 11 which then undergo a rearrangement to 12 analogous to the benzene series (14+15).⁸ Aromatization of 12 to the dimethylthianaphthene 13 follows, but apparently not as easily as for $10 \rightarrow 9$ since this latter dihydro compound is not found. Once again this is analogous to observations in the benzene series on the relative ease of dehydrogenation of 15 and 16 to naphthalene.



Dimethylthiophenes. In order to obtain more definitive evidence on the mode of cycloaddition to 2,3-didehydrothiophene (1), the most efficient "diene" trap discovered in the initial study, thiophene (17a), was examined in further detail. The reactions of thiophene (17a) with the hetaryne 1 to give thianaphthene (18a),³ or with benzynes to give naphthalenes, ¹¹ have been assumed to proceed by [4+2]-cycloaddition reactions via 19 followed by extrusion of sulfur. In the absence of a label, however, a pathway involving the recently described [2+2]-cycloaddition-cycloreversion sequence via 20 or 21 with subsequent desulfurization, 12cannot be excluded since the resulting products 22a and 23a would be identical to 18a, thianaphthene. Consequently the FVT of the anhydride 2 in the presence of the "labeled" 2,5- (17b) and 3,4-dimethylthiophenes (17c) was under-The results shown in Table I taken. permit several conclusions.

Table I Product Ratios from the FVT of Anhydride 2 in the Presence of Dimethylthiophenes

Products	from	17b ^a	17c ^b
18b		30	0
18c = 9		0	40
22b = 23c		50	15
22c = 23b		20	45

^aTotal yield = 17%; ^bTotal yield = 20%



First of all, the only thianaphthenes formed are those predicted from [4+2]-cycloaddition (17b+18b and 17c+ 18c) and the two possible modes of [2+2]-cycloaddition (17b+22b + 23b and 17c+22c + 23c). This further substantiates the intermediacy of 2,3-didehydrothiophene 1 in these reactions and also indicates that no wholesale rearrangement of methyl groups on the thianaphthene ring is occuring.¹³

Secondly, the product ratios clearly indicate a preference of [2+2]compared to [4+2]-cycloaddition by a ratio of 70:30 for <u>17b</u> and 60:40 for <u>17c</u>. The slightly greater proportion of [4+2]-product from <u>17c</u> is consistent with reduced steric bulk at the 2- and 5-positions. That the observed ratios are not the result of product equilibration was demonstrated by the constancy of other compositions of mix-

tures of 18b, 22b, and 23b under FVT conditions. It is conceivable, ¹⁴ but unprecedented,¹⁵ that some of the [4+2]products 18 might arise by diversion to the adduct 19 of biradical intermediates such as 24 or 25 from a stepwise [2+2]-cycloaddition pathway. Another, this time precedented, 17 possibility for the formation of 19 would be the isomerization of the initial adducts 26 and 27 of a concerted [2s + 2a]-cycloaddition of 17 and 1. Since there is no evidence supporting or denying these possibilities, however, the only conclusion to be drawn is that the observed product ratios (Table I) represent a minimum of reaction proceeding by a [2+2]-cycloaddition pathway. Finally, it appears that for both 17b and 17c the [2+2]cycloaddition mode which leads to 22 is favored over the one which gives 23 by factors of 2.5:1 and 3:1, respectively. Once again, the stability of the products under the FVT conditions demonstrates the validity of these ratios as measures of reactivity, not product stability.

One rationale for the unique characteristics of these cycloaddition reactions is based on the structure of the intermediate aryne, 2,3-didehydrothiophene (1). The high proportion of $[2+2]- \underline{vs}$. [4+2]-cycloaddition may reflect an increased tendency of 1 to participate in stepwise diradical ¹⁶ or dipolar ¹⁹ [2+2]-cycloaddition reactions because of an increased diradical (1a) or dipolar (1b, 1c) character. This



might come about because of the probably greater separation of the aryne orbitals and/or their interaction with the sulfur atom.¹ Alternatively, the antisymmetric combination (1d) of the aryne orbitals might be of lower energy



than the symmetric one (le), similar to 1,8-didehydronaphthalene 28,²⁰ so that the [2+2]-cycloaddition reaction would now be the lower energy, concerted process.²¹ Both the diradical and symmetry explanations have been proposed to explain the sterospecificity of cycloaddition of 28 to simple alkenes²² and its preference for 1,2over 1,4-addition to conjugated

dienes.²³ Although molecular orbital calculations²⁴ predict that 2,3-didehydrothiophene (1) has a singlet ground state, a low-lying triplet is available which might become more significant if geometry optimization 25 and/or configuration interaction were included. Unfortunately these more sophisticated calculations are not yet available, and an experimental probe of the concertedness of the [2+2]cycloaddition reaction requires the development of alternate methods of generation of the aryne 1 so that the initial adducts and their stereo-14,19 chemistry can be investigated.

If, by analogy to benzyne, a stepwise biradical mechanism of [2+2]cycloaddition is assumed, and if the attack of the aryne 1 on the thiophene 17 parallels the preferential attack of aryl and heteroaryl radicals on the 2-position of thiophenes, then the observed preponderance of 22 over 23 indicates that of the two possible biradical intermediates, 24 and 25, the former is the major one. This preference would be consistent with a polarized aryne lf reacting at its more electrophilic 3-position with the nucleophilic thiophenes 17. A dipolar version²⁹ of the above analysis is equally tenable and would suggest a



major contribution of 1b to the structure of 2,3-didehydrothiophene (1). Stabilization of negative charge adjacent to a thiophene sulfur atom as in 1b or 1f is well-known,³⁰ but the only available molecular orbital calculations²⁴ seem to prefer the alternate formulation 1g. Once again more sophisticated calculations^{25,26} are called for.

The possibility must not be overlooked that the observed ratios of cycloaddition products 18, 22 and 23 may be totally or partially due to the reaction conditions. For example, at the high temperatures of these FVT experiments³ the enthalpic advantage afforded a concerted [4+2] compared to a stepwise [2+2]-cycloaddition may no longer be significant compared to the probably higher entropic constraints imposed on the former by its highly oriented transition state.³¹ Consequently the proportion of [2+2]derived products 22 and 23 may increase with increasing temperature. Unfortunately the range of temperatures in which the FVT of the anhydride 2 could be studied was limited by the stability of the products. Nor are any pertinent temperature studies available for other arynes. Although reaction conditions, therefore, cannot be excluded as being significant, the fact that under these same conditions 2,3-dimethylbutadiene (6) and 1 give a much lower proportion of [2+2]-derived products (12 or 13) than is obtained from benzyne⁵ does seem to indicate that either the nature of the aryne or of the diene is a more important factor.

This last possibility implies that thiophenes prefer to react with arynes or other dienophiles by [2+2]rather than [4+2]-cycloaddition. Although this is true for polar thiophenes and dienophiles, ^{12,32} a recently completed study³³ reveals that for benzyne and a variety of substituted thiophenes the [4+2]cycloaddition is substantially preferred. It therefore appears that the best explanation for the cycloaddition reactions described in this paper is one based primarily on the reactivity and structure of the aryne, 2,3-didehydrothiophene (1).

EXPERIMENTAL SECTION

Infrared spectra (IR) were re-corded on Beckman IR-10 or 33 instruments as thin films between NaCl plates or as 1% dispersions in a KBr disk. The instruments were calibrated with a polystyrene film and the ab-sorbtions are given in cm.⁻¹ Mass spectra (MS) were obtained on a Finnigan 1015 S/L instrument at 70eV and are reported as m/e (relative intensity). All peaks greater than and some less than 10% of the base peak are reported. NMR spectra were obtained on a Varian A-60A instrument in deuteriochloroform and are exprespressed in § relative to internal tetramethylsilane. The apparent first-order coupling constants ("J") are in Hz. Gas chromatographic analyses were performed on an Aerograph Autoprep A-700 instrument with an 18ft x 0.25 in. column of 25% PPE on Chromosorb W at $185-190^{\circ}$. Melting points were obtained on a Thomas-Hoover apparatus and are uncorrected.

Materials. Thiophene-2,3-dicarboxylic anhydride (2) was prepared from the corresponding diacid³⁴ as previously described.³ 2,3-Dimethylbutadiene (6) was obtained from Matheson and 2,5-dimethylthiophene (17b) was synthesized from 2,5-hexanedione and P₂S₅.³⁵ The preparation of 3,4dimethylthiophene (17c) was carried out in 56% yield from n-butyllithium, dimethylsulfate and 3-bromo-4methylthiophene³⁶ according to the procedure of Janda et al.³

FVT Reactions. The apparatus, procedure and general workup procedure have been described in detail elsewhere. FVT of 2,3-Thiophenedicarboxylic Anhy-dride (2) in the Presence of 2,3-Dimethylbutadiene (6). Preparative GC of the worked up reaction mixture from 600 mg (3.9 mmol) of the anhydride 2 separated three peaks with retention from separated three peaks with retention times of 15, 17 and 17.5 m. The second and major peak (80 mg, 13%) was identi-fied as 5,6-dimethylthianaphthene (9) by comparison³ of its mp, IR, NMR, and MS with those of an independently pre-pared sample.³ The first peak (10 mg, 1.5%) had a slight shoulder due to an impurity but appeared to be a dihydroimpurity put appeared to be a dihydro-dimethylthianaphthene (12): NMR 1.90 (s,3H), 1.98 (s,3H), 2.2-2.8 (m,4H), 7.3 (s,2H); MS 166(5), 165(10), 164(68), 149(100), 134(15), 115(20), 97(100), 58(22), 45(39), 43(90), 41(30), 39(95). The last peak (5 mg, 0.8%) also gave evidence of the proceed of also gave evidence of the presence of impurities in the GC, but its spectral properties pointed to a dimethyl-thianaphthene 13: NMR 2.48 (s,3H), 2.58 (s,3H); MS 164(6), 163(11), 2.58 (s,3H); MS 164(6), 163(11), 162(100), 161(58), 147(60), 134(60), 128(21), 115(100), 81(42), 69(50), 65(15), 51(49), 45(35), 39(45). Dehydrogenation of the Dihydrodimethyl-thianaphthene (12). To a 10ml flask fitted with a reflux condenser and pro-tected from moisture with a calcium chloride drving tube was added 10mg of chloride drying tube was added 10mg of chloride drying tube was successful impure dihydrodimethylthianaphthene 12 and 13.5mg (.06mmol) of chloranil in of benzene. The mixture was refluxed for 2 hr and then triturated with 1m1 of 10% sodium hydroxide followed by 10ml of water. This solution was ex-tracted with 2 X 15 ml portions of ligroin. The combined organic fractions were dried over magnesium sulfate and the solvent removed by rotary evapo-ration leaving approximately 4mg of a gummy dimethylthianaphthene, possibly 13: NMR 2.46 (s,3H), 2.53 (s,3H), 6.8-7.4 (m,4H); MS 164(6), 165(13), 164(100). Insufficient quantity and quality of this sample precluded a firm assignment. FVT of 2,3-Thiophenedicarboxylic Anhydride (2) in the Presence of 2,5-GC of the worked up reaction mixture from 60mg (3.9mmol) of the anhydride 2 gave four peaks with retention times of 14 15 17 and 19m The first was of 14, 15, 17, and 19m. The first was identified as 4,7-dimethylthianaphthene identified as 4,7-dimethylthianaphthene (18b), 32mg (5.1%): NMR 2.50 (s,3H), 2.52 (s,3H), 7.03 (s,2H), 7.41 (s,2H); MS 164(6), 163(13), 162(100), 161(70), 149(6), 148(12), 147(100), 128(18), 115(20), 103(10), 120(12), 91(10), 89(10), 86(63), 84(82), 51(44), 49(93), 47(61), and 32(15) (picrate mp 133-34⁰; 1it.³⁸ 133-135.5^oC). The second peak was identified as 6,7-dimethylthianaph-thene (23b), 21mg (3.4%): NMR 2.42 (s,3H), 2.54 (s,3H), 7.28 (s,2H), 7.18 and 7.58 (AB quartet, 2H, J=8.5); MS identical to 18b, with only slight variations in relative intensities (picrate 122-24⁰ lit.³⁸ 122-123.5^oC). The third peak (53mg 8.5%) was identi-fied as 4,5-dimethylthianaphthene fied as 4,5-dimethylthianaphthene

 $(\underline{22b})$, by comparison of its NMR and picrate mp $(\underline{110.5-111.5^{O}})$ with an authentic sample. The fourth peak authentic sample. The fourth peak is an artifact formed during the FVT of 2,5-dimethylthiophene (17b) alone. FVT of 2,3-Thiophenedicarboxylic Anhydride (2) in the Presence of 3,4-Dimethylthiophene (17c). Workup of the FVT reaction from 103mg (0.67mmol) of the anhydride 2 grave 2275 of the anhydride 2 gave 22mg of a product which on GC analysis gave three peaks identified as the dimethylthianaphthenes 22c, 18c and 23c by comparison of retention time with those of the samples prepared as above (22c = 23b; 18c = 9; 23c = 22b) in a ratio of 45:40:15, respectively. Product Stability Studies. Both 40:40:20 and 30:20:50 mixtures of the dimethylthianaphthenes 18b, 23b, and 22b, respectively, were un-changed in composition on passage through the FVT apparatus under the usual conditions (500°C). At 650°, however, the latter mixture changed to a 20:44:36 composition due either to isomerization or selective decomposition to non-GC-detectable products.

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