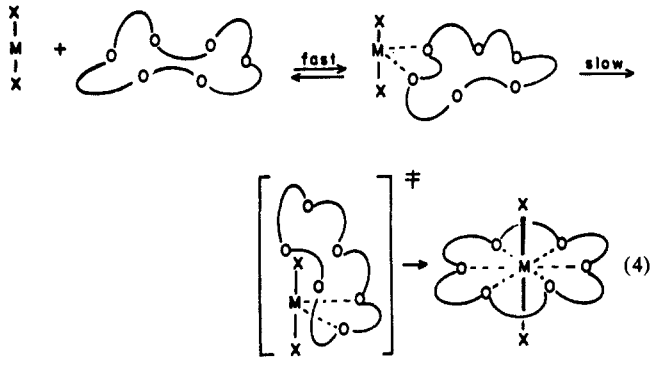
Table I.

reaction	rate constant (23 °C)	solvent	approx half-life[b]
$Hg(CN)_2 + 2 \xrightarrow{k_2} 2\cdot Hg(CN)_2$	3.1×10^{-2} M^{-1} s^{-1}	A/B[a]	1 h
$Hg(CN)_2 + 2 \xrightarrow{k_2} 2\cdot Hg(CN)_2$	1.7×10^{-2} M^{-1} s^{-1}	A/C[c]	2 h
$Hg(CN)_2 + 4 \xrightarrow{k_2} 4\cdot Hg(CN)_2$	2.75×10^{-4} M^{-1} s^{-1}	A/C	4–5 days
$3\cdot Hg(CF_3)_2 \xrightarrow{k_1} 3 + Hg(CF_3)_2$	5.5×10^{-4} s^{-1}	A/B	15 min
$Hg(CF_3)_2 + 7 \xrightarrow{k_2} 7\cdot Hg(CF_3)_2$	4.0×10^{-4} M^{-1} s^{-1}	$CDCl_3$	3 days
$Hg(CF_3)_2 + 7 \xleftarrow{k_1} 7\cdot Hg(CF_3)_2$	2.6×10^{-7} s^{-1}	$CDCl_3$	1 month
$Hg(CF_3)_2 + 8 \xrightarrow{k_2} 8\cdot Hg(CF_3)_2$	2×10^{-5} M^{-1} s^{-1}	$CDCl_3$	2 months
$Hg(CF_3)_2 + 8 \xleftarrow{k_1} 8\cdot Hg(CF_3)_2$	1×10^{-7} s^{-1}	$CDCl_3$	3 months[d]

[a] Acetone-d_6/benzene-d_6 (1:1, v/v); solubility problems precluded the use of a single solvent system for all reactions. [b] Calculated for 0.01 M reactants in the solvent indicated. [c] Acetone-$d_6$0$CDCl_3$ (1:0.8, v/v). [d] Extrapolated from the initial rate (10%) reaction.

preassociation conformational changes in the macrocycle (the Chock mechanism[8]). For the cases at hand, solvation forces between the organomercurials and solvents are expected to be weak and short-lived, and the structural dynamics of the crown ethers become important. The facts best fit a combined mechanism (eq 4).



(4)

A rapidly formed initial complex exists in which the metal center binds to a few of the ethereal oxygens of the macrocycle. The rearrangement of this complex to the rotaxane-type structure[9] of the final complex is slow. The macrocycle must assume an improbable, high-energy conformation in order to permit the covalently bound ligands of the Hg to penetrate the ring. The severe restrictions on the internal rotations caused by this motion are consistent with the large negative activation entropy observed ($\Delta S^{\ddagger} = -25$ eu). For a spherical ion, on the other hand, sequential replacement of solvent is not expected to require such drastic conformational changes in the macrocycle. Indeed, we found that allosteric effects involving these macrocycles and alkali metals[10] were much smaller than those involving $Hg(CF_3)_2$. Finally, we note that the rearrangement of eq 4 is reminiscent of the slow conformational transitions responsible for hysteretic behavior in enzymology.[11]

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Registry No. 1, 33100-27-5; **2**, 17455-13-9; **3**, 33089-36-0; **4**, 14187-32-7; **5**, 71638-20-5; **7**, 41051-91-6; **8**, 76453-08-2; $Hg(CN)_2$, 592-04-1; $Hg(CF_3)_2$, 371-76-6.

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Synthesis of Covalently Linked DNA/RNA Cross Sections

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The classical Watson–Crick double-helical model of DNA/RNA possesses well-defined hydrogen bonds that hold the two strands in complementarity (Figure 1a).[1] A covalently linked cross section (Figure 1b) with molecular architecture[2] similar to the hydrogen-bonded base pair would be a good mimic of the Watson–Crick cross section and hence a potential candidate for incorporation into various biological systems. In this paper we report the first syntheses of covalently linked DNA/RNA duplex cross sections starting from readily available *O*-acetylated deoxyribonucleosides and ribonucleosides.

The synthetic strategy is outlined in Scheme I. The reaction of 2′,3′,5′-tri-*O*-acetyladenosine (**1a**)[3] with chloroketene diethyl acetal (**2**)[4] in ethyl acetate in the presence of a catalytic amount of *p*-toluenesulfonic acid gave N^6-(1-ethoxy-2-chloroethylidene)-2′,3′,5′-tri-*O*-acetyladenosine (**3a**)[5] in quantitative yield. The subsequent condensation of **3a** with 2′,3′,5′-tri-*O*-acetylcytidine (**5a**)[6] was carried out in benzene/acetonitrile in the presence of a catalytic amount of *p*-toluenesulfonic acid under reflux to afford the bis(ribonucleoside) **7a** in 27% yield. Some of the loss in this reaction was accounted for by reversion of **3a** to **1a** and cyclization of **3a** to 8-ethoxy-3-(2′,3′,5′-tri-*O*-acetylribofuranosyl)imidazo-[2,1-*i*]purine (**4a**).[5] The decision as to the direction of ring closure of the putative transient intermediate **6a** was made on the basis of ^1H NMR guidelines.[5] It was evident from the shift to lower field of the original 2-proton on the purine nucleus in **7a** that ring closure had occurred on the adenosine side of **6a** to yield **7a**, as indicated. The structure of 8-N^4-(2′,3′,5′-tri-*O*-acetylcytidino)-3-(2′,3′,5′-tri-*O*-acetyl-β-D-ribofuranosyl)imidazo[2,1-*i*]purine (**7a**) was further confirmed by its ^{13}C NMR spectrum (75.2 MHz) and by high-resolution FAB mass spectral analysis. The bis(deoxyribonucleoside) **7b**, 8-N^4-(3′,5′-di-*O*-acetyl-2′-deoxycytidino)-3-(3′,5′-di-*O*-acetyl-2′-deoxy-β-D-ribofuranosyl)-imidazo[2,1-*i*]purine, was made in a similar manner from 3′,5′-di-*O*-acetyl-2′-deoxyadenosine (**1b**), **2**, and 3′,5′-di-*O*-acetyl-2′-deoxycytidine (**5b**). The mixed dinucleoside **7c**, 8-N^4-(2′,3′,5′-tri-*O*-acetylcytidino)-3-(3′,5′-di-*O*-acetyl-2′-deoxy-β-D-ribofuranosyl)imidazo[2,1-*i*]purine, was made from 3′,5′-di-*O*-acetyl-2′-deoxyadenosine (**1b**), **2**, and 2′,3′,5′-tri-*O*-acetylcytidine. In order to accomplish the oxidative ring closure of **7a–c**, iodobenzene diacetate[7] was first selected since it had been demonstrated to be effective for the construction of the related 1,3,4,6-tetraazapentalene ring system.[8] When the oxidative cyclization of **7a** was attempted in the high-dielectric, low-nucleophilic solvent

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(2) The dimensions indicated have not yet been determined but have been calculated from a composite structure consisting of two separate entities in the formula, the 1,N^6-ethenoadenosine side and the 3,N^4-ethenocytidine side. The dimensions of these entities have been determined by single-crystal X-ray structure analysis. See: Leonard, N. J. *CRC Crit. Rev. Biochem.* 1984, *15*, 125 and references therein. [Note: interchange pages 157 and 158.]
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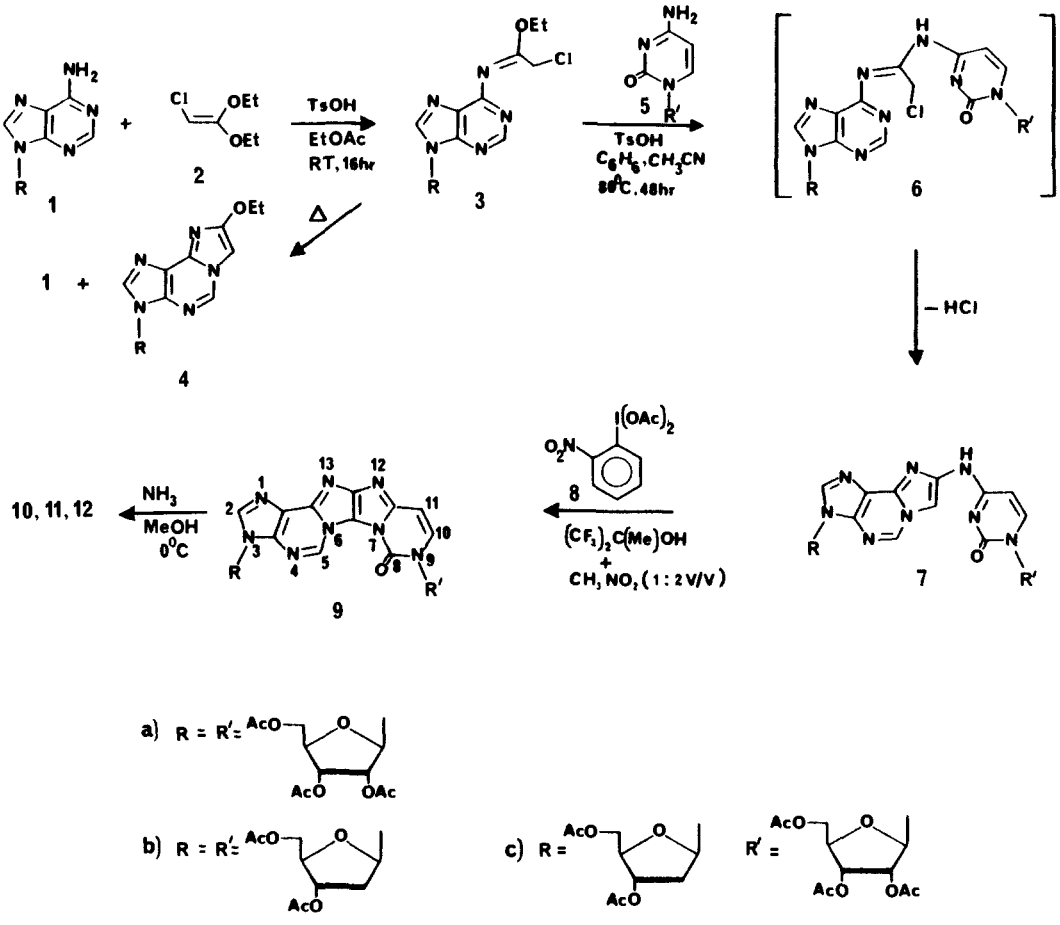
Scheme I



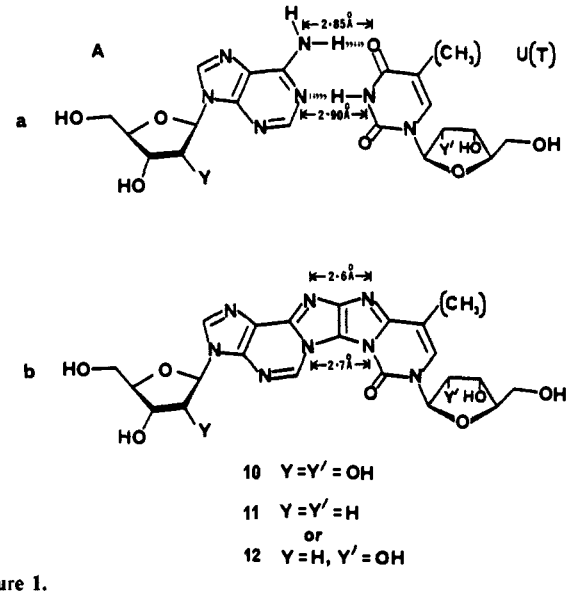


Figure 1.

2,2,2-trifluoroethanol,[9] the only product isolated was an adduct of 2,2,2-trifluoroethanol with the reactive intermediate generated from **7a**. Consequently, nitromethane was employed as a cosolvent to moderate the reactivity of the trifluoroethanol (2:1 v/v). The desired product **9a** was obtained by oxidation of **7a** with iodobenzene diacetate, albeit in low yield (10%). The initial identification of **9a** was based on FAB mass spectrometry and upon its fluorescence properties. The yield of **9a** was improved significantly by using a more hindered solvent, i.e., 1,1,1,3,3,3-hexafluoro-2-propanol or 1,1,1,3,3,3-hexafluoro-2-methyl-2-propanol, with nitromethane (1:2 v/v) and with 2-nitroiodobenzene diacetate (**8**)[10] as the oxidizing agent. The oxidative cyclization did not proceed in either solvent alone. With the improved methodology, compounds **9a–c** were obtained in yields of 36%, 40%, and 26%, respectively.

Structures **9a–c** were established by ^1H and ^{13}C NMR spectroscopy, $^1H/^{13}C$ short range[11] and long range[12,13] correlations, and FAB mass spectrometry. The triacetylribosyl and/or diacetyldeoxyribosyl proton chemical shifts were readily discerned as were the four protons attached to unsaturated carbon atoms. The 5-proton in the bay region displayed a marked downfield shift of ~1.0 ppm when it was compared with the corresponding proton in each precursor (**7a–c**), due to the anisotropy of the now-neighboring carbonyl group. The chemical shift difference between the 10- and 11-protons was diminished appreciably (~0.56 ppm) upon oxidative cyclization, which is indicative of the second etheno annelation occurring on the cytidine moiety.[5] The ^{13}C NMR spectra of **9a–c** exhibited seven quaternary carbon resonances and four unsaturated C(H) resonances for the aglycon portion. The unambiguous assignments of the ^{13}C NMR signals were based on the analysis of the proton-coupled ^{13}C NMR spectra and long-range $^1H/^{13}C$ heteronuclear correlations.[14] The short-range $^1H/^{13}C$ correlations directed the assignments of the saturated and unsaturated C(H) resonances. Thus, 2D-heteronuclear correlation experiments established the carbon–carbon connectivity in the aglycon and the sugar moieties.

Complete deacetylation of **9a–c** was achieved in methanolic ammonia at 0 °C during 3 hours. The low-resolution FAB mass

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(14) We thank Gary L. Clauson for his help in obtaining the $^1H/^{13}C$ long-range heteronuclear correlation spectra.

spectra showed $(M + 1)^+$ peaks at m/z 531, 499, and 515 for **10**, **11**, and **12**, respectively, with no appreciable, higher m/z values in any of the spectra. The molecular formulas were confirmed by high-resolution FAB mass spectra.

Thus, we have accomplished the total synthesis of three representative compounds which have a high degree of complexity (five N-heteroaromatic rings containing a total of eight nitrogens; ribosyl or deoxyribosyl groups on the appropriate nitrogens for cross-sectional analogy; and, pro forma, eight, six, or seven asymmetric carbons). The synthesis requires only three steps from ribo- or deoxyribonucleosides plus initial O-protection and final O-deprotection. The compounds represent respectively a covalently linked RNA cross section, 1,9-di-(β-D-ribofuranosyl)-3*H*-pyrimido[1″,6″:1′,2′]imidazo[4′,5′:4,5]imidazo[2,1-*i*]purin-8(9*H*)-one (**10**); a covalently linked DNA cross section, 1,9-bis-(2′-deoxy-β-D-ribofuranosyl)-3*H*-pyrimido[1″,6″:1′,2′]imidazo[4′,5′:4,5]-imidazo[2,1-*i*]purin-8(9*H*)-one (**11**);[15] and a covalently linked DNA/RNA hybrid cross section, 1-(2′-deoxy-β-D-ribofuranosyl)-9-(β-D-ribofuranosyl)-3*H*-pyrimido[1″,6″:1′,2′]-imidazo[4′,5′:4,5]imidazo[2,1-*i*]purin-8(9*H*)-one (**12**). These highly fluorescent molecules are worthy of further chemical and biological investigations.

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(15) The pyrimidine methyl group is lacking in this initial model in the bis(deoxyribosyl) series.

Oxidation of 3,5,5-Trimethyl-2-oxomorpholin-3-yl (TM-3) with Molecular Oxygen. Generation of a Persistent Aminyl Radical[1]

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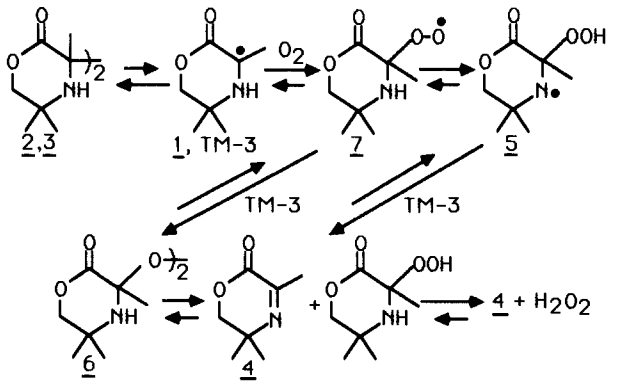
The captodative free radical 3,5,5-trimethyl-2-oxomorpholin-3-yl (**1**, TM-3) from bond homolysis of *meso*- and *dl*-bi(3,5,5-trimethyl-2-oxomorpholin-3-yl) (**2** and **3**) is oxidized to 5,6-dihydro-3,5,5-trimethyl-1,4-oxazin-2-one (**4**) by molecular oxygen.[2] Because the oxomorpholinyls have pharmaceutical potential as mild one-electron reducing agents for in vivo manipulation of quinone antitumor drugs,[3] we initiated a study of the mechanism of their oxidation by molecular oxygen including determination of the reduced oxygen species produced. Earlier studies of other redox reactions of TM-3 suggested that reduction occurred by single electron transfer.[4]

Here we report that oxidation of TM-3 with molecular oxygen gives a quantitative yield of **4** and hydrogen peroxide at least in part via covalent bond formation and with the generation of a persistent aminyl radical. Quantitative or near quantitative (95 ± 5%) formation of **4** was observed for oxidation in chloroform, acetonitrile, ethanol containing 0.32 M magnesium perchlorate, and methanol solvents as indicated by UV and ^{1}H NMR spectroscopy. Quantitative formation of hydrogen peroxide, 1 equiv per radical dimer, was observed in the latter three media; the best yield in chloroform, where hydrogen peroxide was not stable, was 58%. Hydrogen peroxide analyses were performed initially by HPLC/peroxychemiluminescence spectroscopy[5] and subsequently by spectrophotometric analysis of the product of reaction with titanium tetrachloride.[6] Oxidation of TM-3 dimer **2** or **3** followed first-order kinetics, monitoring formation of **4** spectrophotometrically at its maximum, 320 nm. The rate constant was the rate constant for bond homolysis of **2** or **3**;[7] at 25.0 ± 0.1 °C, k = (3.1 ± 0.2) × 10^{-6} (**2** in chloroform), (1.82 ± 0.004) × 10^{-5} (**2** in acetonitrile), (2.22 ± 0.01) × 10^{-3} (**2** in ethanol containing 0.32 M magnesium perchlorate), (2.38 ± 0.02) × 10^{-3} (**2** in methanol), and (4.49 ± 0.03) × 10^{-3} s^{-1} (**3** in methanol). TM-3 also reacted with hydrogen peroxide with formation of oxazinone **4**, but the rate was more than 2 order of magnitude lower.

Scheme I



The initial observation which indicated that oxidation of TM-3 by molecular oxygen might involve covalent bond formation was the observation of a paramagnetic species giving a three-line 1:1:1 EPR signal with g = 2.0060 and a_N = 14 G and g = 2.0057 and a_N = 15 G in air-saturated chloroform and ethanol containing 0.32 M magnesium perchlorate solutions of radical dimers **2** or **3**, respectively; the 24-line signal characteristic of TM-3 was absent. With solutions of **2** at high concentration (e.g., 0.1 M), the three-line signal increased in intensity with time and then abruptly disappeared after a period approximately equal to the time necessary for reduction of at least 95% of the dissolved oxygen, calculated from the rate constant for bond homolysis and the solubility of oxygen which is in the range of 1.5 × 10^{-3} M.[8] At this point the 24-line TM-3 EPR signal appeared. Shaking with air restored the three-line signal and destroyed the 24-line signal. The cycle could be repeated several times. The three-line EPR signal suggested the formation of either an aminyl or nitroxide bonded to unprotonated carbons. A nitroxide structure was eliminated because the EPR signal still appeared as a 1:1:1 pattern with 80% enriched $^{17}O_2$ as the oxidant. The hydrogen peroxide formed contained ^{17}O, detected by using the hydrogen peroxide to oxidize 4-oxo-2,2,6,6-tetramethylpiperidine to its [^{17}O]nitroxide and subsequent EPR analysis.[9,10]

A mechanism for the oxidation of TM-3 with the intermediacy of aminyl **5** is shown in Scheme I. Two pathways to oxazinone **4** and hydrogen peroxide are proposed because the rise in the concentration of **5** is not synchronous with the formation of **4** and hydrogen peroxide. The nonsynchronous behavior was observed when the oxidation was conducted with an excess of oxygen in ethanol containing 0.32 M magnesium perchlorate. In fact, under these conditions **5** could be easily observed even at low initial

(1) Research support was received from the National Institutes of Health (CA-24665), the National Science Foundation (CHE-8419718), and the Petroleum Research Fund, administered by the American Chemical Society. We thank James Poulson and John Birks for assistance with the HPLC/peroxychemiluminescence spectroscopy.

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