(2.0 g, 9.64 mmol) dissolved in chloroform (5 mL) and DMF (5 mL). The reaction was heated under reflux for 1 h and then allowed to cool and poured into ice–water (500 mL). Saturated $NaHCO_3$ was cautiously added over 1.5 h to effect neutralization, and the resulting mixture extracted with methylene chloride (2 × 400 mL). The organic extracts were washed with water (2 × 400 mL), dried ($MgSO_4$), filtered, and evaporated to yield a yellow oil. Chromatography over silica gel (100 g), eluting with 1:1 methylene chloride–Skellysolve B afforded the trichloroisoxazole as a clear syrup, which slowly crystallized (2.28 g, 90%). Recrystallization from ether–Skellysolve B gave white prisms: mp 49–50 °C; IR (Nujol) ν 1595, 1570, 1445, 1400, 1206, 1100, 952, 883, 777, 752, 740, 694 cm^{-1}; NMR ($CDCl_3$) δ 6.62 (s, 1 H, $CHCl_2$), 7.35–7.90 (m, 5 H, Ar); MS, *m/e* (relative intensity) 265 (2), 263 (7), 261 (7), 228 (35), 226 (56), 162 (11), 140 (15), 138 (48), 128 (20), 77 (100), 76 (11). Anal. Calcd for $C_{10}H_6Cl_3NO$: C, 45.74; H, 2.29; N, 5.34; Cl, 40.54. Found: C, 45.41; H, 2.45; N, 5.41; Cl, 40.57.

5-Chloro-3-phenylisoxazole-4-carboxylic Acid (17). A solution (10 mL, 10 mmol) of 1 M sodium hydroxide was added to a stirred solution of silver nitrate (0.85 g, 5 mmol) in water (10 mL). After the mixture was stirred for 10 min, the chloroaldehyde **15** (0.50 g, 2.41 mmol) was added and stirring continued for 5 h. The reaction was filtered and the filtrate treated with concentrated HCl (ca. 1 mL). The resultant yellow precipitate was filtered and washed with a little water and dried. Recrystallization from chloroform–hexane gave the chloro acid as very pale yellow crystals (0.394 g, 73%): mp 180 °C dec (lit.[6] mp 176–179 °C); IR (Nujol) ν 2660, 2560, 1680, 1572, 1548, 1300, 1155, 1140, 760 cm^{-1}; MS, *m/e* (relative intensity) 225 (14), 223 (42), 188 (67), 144 (75), 116 (33), 77 (100), 63 (15). Anal. Calcd for $C_{10}H_6ClNO_3$: C, 53.72; H, 2.70; N, 6.26; Cl, 15.85. Found: C, 53.47; H, 2.77; N, 5.73; Cl, 15.98.

5-Methoxy-3-phenylisoxazole-4-carboxaldehyde (18). The chloroaldehyde **15** (1.0 g, 4.82 mmol) was stirred in methanol (25 mL), and 120 drops (ca. 1.5 mL) of a 25% solution of sodium methoxide in methanol was added. After 1 h the solvent was removed and the residue partitioned between ether (100 mL) and water (50 mL). The ether was dried ($MgSO_4$), filtered, and evaporated to afford the methoxy compound (0.92 g, 94%), mp 89–91 °C. Recrystallization from hexane gave white flakes (0.67 g, 68%): mp 92 °C; IR (Nujol) ν 1694, 1681, 1586, 1573 (s), 792, 773, 739, 693 cm^{-1}; NMR ($CDCl_3$) δ 4.32 (s, 3 H, OCH_3), 7.35–7.60 (m, 3 H, Ar), 7.65–7.90 (m, 2 H, Ar), 9.74 (s, 1 H, CHO); MS, *m/e* (relative intensity) 203 (34), 144 (92), 130 (50), 129 (33), 116 (28), 104 (32), 77 (100). Anal. Calcd for $C_{11}H_9NO_3$: C, 65.02; H, 4.46; N, 6.89. Found: C, 65.10; H, 4.60; N, 6.92.

The Trichloro Isoxazole 16 and Methoxide. The trichloro isoxazole **16** (200 mg, 0.76 mmol) was stirred in methanol (10 mL) and 70 drops (ca. 0.9 mL) of a 25% methanolic sodium methoxide solution added. After 2 h the solvent was removed and the residue partitioned between water (20 mL) and chloroform (20 mL). The chloroform was dried (Na_2SO_4), filtered, and evaporated to afford the crude acetal 5-methoxy-4-(dimethoxymethyl)-3-phenylisoxazole as a pale yellow viscous oil (200 mg, 99%): NMR ($CDCl_3$) δ 3.34 (s, 6 H, 2 × OCH_3), 4.16 (s, 3 H, OCH_3), 5.18 (s, 1 H, CH), 7.30–7.55 (m, 3 H, Ar), 7.65–7.90 (m, 2 H, Ar). The oil was stirred with 1 N HCl (10 mL) for 1 h and then extracted with chloroform (20 mL). After drying ($MgSO_4$), filtering, and evaporating, there was obtained the crude aldehyde as a white solid (150 mg, 97%). Recrystallization from hexane gave pure 5-methoxy-3-phenylisoxazole-4-carboxaldehyde (**18**) as white plates (114 mg, 74%), mp 92 °C.

Acknowledgment. I thank Arlen J. Taylor for some of the laboratory experiments and Connie Chidester, Charlotte G. Waber, and William Watt for collection and refinement of the X-ray data and determination of the structure of **7**. In addition, I thank Professors Charles W. Rees and Scott Denmark for stimulating mechanistic discussions.

Registry No. **1**, 1076-59-1; **6**, 5272-46-8; **7**, 100230-70-4; **8**, 100230-71-5; **15**, 100230-72-6; **16**, 65926-99-0; **17**, 3357-00-4; **18**, 65927-06-2.

Photochemistry of Methyl Viologen Dicarboxylate and Polycarboxylate Ion Pairs

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Methyl viologen (1,1′-dimethyl-4,4′-bipyridinium ion, MV^{2+}) has received considerable attention in recent years as an efficient relay in the photocatalyzed reduction of water to hydrogen.[1] The tendency of MV^{2+} to ion pair or to form complexes with a variety of "donor" ions or molecules is now recognized as a general feature to be taken into account in the design of photoredox systems.[2-7] For example, the ion pairing or complexation characteristics of MV^{2+} in combination with the familiar donors, EDTA and triethanolamine (TEOA), have been recently described.[8,9] The pH dependence of the enhanced 350–450-nm absorption for complexes of EDTA (K_{eq} = 5.3 and 68 M^{-1} at pH 4.6 and 11.2, respectively) and TEOA (K_{eq} = 0.3 M^{-1}, pH 10.2) clearly demonstrates that the state of protonation of complexing species is important and that both nitrogen lone pair donor moieties and carboxylate charged groups play a role in binding.

As part of a broader study of complexes of methyl viologen,[10] we have investigated the binding of MV^{2+} to a series of simple dicarboxylic acids in water. One focus for the work involves the comparison of binding to acids of different chain length, where the relationship of sites of electrostatic attraction to carboxylate groups would vary with acid structure. Another comparison was made of the behavior of this diacid series with that of two polymers, polyacrylic (PAA) and polymethacrylic (PMAA) acids. For the polyelectrolytes, MV^{2+} would be expected to be attracted to the field of charge on the polymer, which in turn would be altered according to pH and polymer conformation. The binding of a photoredox reagent to polymers is important, since polymers are commonly used to stabilize colloidal metals which act as catalysts for formation of hydrogen from water and related photoredox reactions.[11]

In this paper, we report the spectra and binding properties of MV^{2+} in the presence of relatively high concentrations of the various acids. The results of steady and flash photolysis of MV^{2+} carboxylate ion pairs are reported also, including the observed net decarboxylation of acids and formation of reduced viologen, $MV^{+}\cdot$. Also of interest, is an apparent effect of excitation wavelength on the quantum yield of net electron transfer (higher yields of escaped radicals on irradiation at higher frequencies), a result related to earlier observations made for charge-

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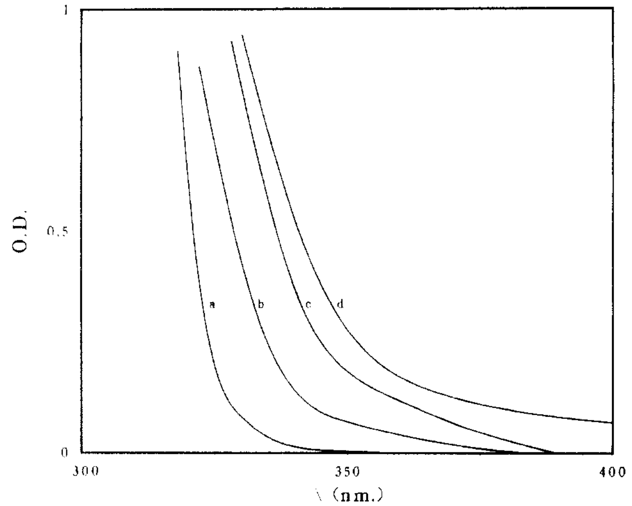

Figure 1. Absorption spectra for MV^{2+} solutions (pH 9.0, μ = 5.0): (a) 0.050 M MV^{2+}; (b) 0.050 M MV^{2+}, 0.833 M glutarate; (c) 0.050 M MV^{2+}, 1.0% PMAA; (d) 0.050 M MV^{2+}, 1.0% PAA.

transfer complexes[12-14] and other viologen/amine complexes.[10]

Experimental Section

The diacids, malonic, succinic, and glutaric, were purified by multiple recrystallization or sublimation. The polymer, PAA (Aldrich, M_r 250 000) was used as received; PMAA was prepared by radical polymerization[15] and its molecular weight determined to be approximately 15 000 daltons by viscosimetry. 1,1′-Dimethyl-4,4′-bipyridinium dichloride was obtained commercially and was recrystallized from methanol and dried in vacuo. Samples were prepared with distilled water with adjustment of ionic strength to μ = 5 with analytical grade anhydrous sodium sulfate. Association constants for ion pairing of MV^{2+} and the dicarboxylates were obtained from absorption data at 340 nm with the method of Nash[16] (plots of 1/[dicarboxylate] vs. $1/(1 - A_{\mathrm{complex}}/A_{\mathrm{MV^{2+}}})$, typically, $[MV^{2+}]$ = 0.05 M, [dicarboxylate] = 0.50 M → 1.00 M.)

Steady photolysis of viologen carboxylate solutions was carried out with a monochromator/light pipe apparatus which has been described previously.[12] Quantum yields were calculated from the slopes of plots of OD (605 nm, $MV^{+\cdot}$) following brief periods of photochemical scavenging of trace residual oxygen for Ar-purged solutions. Flash photolysis was conducted with a Quantel 581-10 Nd-YAG laser with appropriate optics for the tripled frequency (355 nm, ca. 130 mJ/8 ns pulse). The laser and detection system have been described.[17] The conversion of malonic acid to acetic acid was monitored by GLC analysis (for appearance of acetic acid) with a Varian 1400 instrument equipped with a 3-m column of 5% FFAP on Chromosorb-G HP at 120 °C.

Results and Discussion

Aqueous solutions of methyl viologen with added malonic, succinic, or glutaric acids revealed no spectral changes in the 320–450-nm region for solutions at low pH (<3.5.) However, solutions of MV^{2+} with diacids in the 0.5–1.0 M range at pH 4–9 (at constant ionic strength, μ = 5) displayed enhanced absorption in the near-UV region as shown in Figure 1. The profile of altered absorption showed a general increase with pH (optical density monitored at 340 nm), at a fixed concentration of diacid (e.g., 1.0 M), with absorption values reaching a plateau at pH >6.0 (values above the second p*K* of the diacids which appears at 5.4–5.7). (The maximum in absorption for associated species actually appears at pH 4–5 for malonic and succinic acids (but not for glutaric acid), suggesting a structure-dependent specific complexation of MV^{2+} with the monoanion form in two cases.)

Table I. Association Constants for Methyl Viologen Carboxylate[a]

carboxylate	K_{eq}/M^{-1}	$(\sigma)^b$	$\epsilon/M^{-1}\ cm^{-1}$
malonate	0.027	(0.05)	200
succinate	0.051	(0.05)	169
glutarate	0.26	(0.12)	40

[a] Aqueous solutions, pH 9.0 (μ = 5.0); $[MV^{2+}]$ = 0.05 M. Malonate, succinate, and glutarate = $^-O_2C(CH_2)_nCO_2^-$ (*n* = 1, 2, and 3, respectively. [b] Standard deviation of parameter (see text).

With a modified Benesi–Hildebrand technique, the formation constants for complexes or ion pairs of the diacids were computed as shown in Table I, along with extinction coefficients for transitions for the aggregated species. (The weakness of the interactions between the simple acids and MV^{2+} necessitated the use of an analysis developed by Nash[16] which takes into account the interfering absorption of any uncomplexed acceptor. A large degree of uncertainty results for the measurement of K_{eq} (note standard deviations, Table I). The data suggest a stronger association with the longer chain (glutaric acid, more opportunities for site binding), but the degree of uncertainty precludes a more quantitative comparison.) For comparison, complexation of MV^{2+} with a simple monocarboxylic acid, propanoic acid, was tested. A very weak enhancement appeared at 340 nm, and a limit for the association constant was estimated ($K_{eq} < 0.01$). For the analysis of association equilibria, a 1:1 complex or ion-pair stoichiometry was assumed for the unpolymerized acids.

Relatively modest concentrations (0.01–0.02 wt %) of added polyacids, PAA and PMAA, resulted in new absorption bands for aqueous MV^{2+} solutions at pH >5.0, where the polymers are ionized (pH 5.0–7.0).[19] The higher degree of complexation for the polyacids vs. the diacids is suggested by the spectral data in Figure 1; enhanced absorption is readily apparent for solutions 10 mM in concentration of monomer units of the polyacids.

Steady photolysis of MV^{2+} carboxylate solutions, generally at 334 nm (monochromator system) resulted in the formation of the reduced species, $MV^{+\cdot}$, which persisted indefinitely in Ar-purged aqueous solutions. Quantum yields for viologen photoreduction were obtained (Table I) from the slopes of plots of OD (vs. time) monitored at an absorption maximum for $MV^{+\cdot}$ [605 nm (ϵ = 13 700)].[20]. The effect of excitation wavelength on quantum efficiency was inspected for one of the polymers, PAA, where absorption due to the aggregate extended to longer wavelengths.

Measurement of relative yields of electron transfer for the viologen carboxylate systems was carried out along with a search for photochemical transients using laser flash photolysis techniques. Pulsed irradiation (Nd-YAG laser) resulted in the appearance of the $MV^{+\cdot}$ species within 80 ns (100-MHz digitization) consistent with the rapid formation of the reduced species noted recently for methyl

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Table II. Quantum Yields of $MV^{+\cdot}$ Formation on Steady and Flash Photolysis of Methyl Viologen Carboxylates

carboxylate	conc/M	λ_{exc}/nm	Φ^a	$\Phi_{rel}{}^b$
succinate	0.60	334	0.017	
		355		1.0
glutarate	0.83	334	0.019	
		355		1.3
polyacrylate (PAA)	0.14[c]	334	0.074	
		366	0.018	
		405	<0.001	
	0.014[c]	355		2.5
polymethacrylate (PMAA)	0.116[c]	334	0.051	
	0.023[c]	355		2.1

[a] Steady irradiation (HG lamp, monochromator[12]), Ar-purged aqueous solution (pH 9.0, $\mu = 5$); $[MV^{2+}] = 0.05$ M. Polyacrylate = $CH_2CH(CO_2^-)_n$, polymethacrylate = $CH_2C(CH_3)CO_2{}^-{}_n$. [b] Pulsed Nd-YAG laser photolysis (conditions as in *a* for dicarboxylates; for PAA and PMAA, $[MV^{2+}] = 0.01$ M, along with lower acid concentrations, employed for laser photolysis to match OD of dicarboxylates at 355 nm). Relative yield based on ΔOD at 605 nm, 1.0 μs following laser pulse. [c] Calculated monomer concentration.

viologen thiocyanate;[3] the radical did not decay within 100 ms (vide supra). Transient absorption by other species was not observed outside the absorption regions for the viologen radical (λ_{max} = 395, 605 nm.)[20] Relative yields for net electron transfer for the dicarboxylates and the polycarboxylates with matched absorbances at the excitation wavelength (355 nm) are reported in Table II.

Steady or laser flash photolysis of viologen malonate (pH 9.0) did not result in formation of $MV^{+}\cdot$ in significant yield ($\Phi < 0.001$). However, an examination of products revealed that net photochemistry did take place for this system. Carbon dioxide, an expected product of carboxylic acid photooxidation (in the presence of methyl viologen[21-23]), was analyzed by acidification of the solutions followed by GC analysis.[24] Along with this product, which was obtained from succinate and glutarate photolysates, malonate solutions revealed the presence of acetic acid on acidification (GLC analysis). The approximate quantum yield for acetate formation for viologen malonate solutions was 0.02.

The principal findings of this study are that (1) methyl viologen may be complexed or ion paired with simple carboxylic acids in their ionized forms, although the association constants and the resulting enhanced absorption in the visible and near-UV region are modest, (2) the strength of complexation with MV^{2+} follows the trend monoacid < diacids < polyacids, (3) excitation of viologen carboxylate ion pairs at longer wavelengths (the "charge-transfer" band) results in net electron transfer (reduction of MV^{2+} to $MV^{+}\cdot$ and presumed oxidation of the acids) without the intervention of free radical transients in the common ns–ms regime, (4) the yield of reduced viologen ($MV^{+}\cdot$) is somewhat enhanced for polyacids vs. diacids, and (5) photodecomposition of malonate proceeds without net reduction of MV^{2+}.

To the extent that the diacids provide a model for carboxylate binding of MV^{2+} to a species such as EDTA, we observe that the latter donor is more effective in association within the relevant pH range (5.0–10.0) due to a combination of favorable interactions of the viologen cation with a larger assembly of carboxylate moieties and (at high pH's) the additional interaction with nitrogen lone pairs. The stronger interaction with the polyacids is consistent with the model of polyelectrolytes in which the polymer provides a cylindrical array of anionic groups[25] with which the viologen cation associates. This field of charge is concentrated in regions of the polymer–water interface according to polymer conformation and state of ionization; the absence of site-binding for the polyacids[25] stands in contrast to the diacids which provide only highly localized charge fields. The enhancement of net electron transfer (viologen reduction) for the polyanions is possibly due to a retarded rate of back electron transfer resulting from a longer distance of separation for the photogenerated radical pair (vide infra).

Scheme I

$$\begin{array}{lcl}
MV^{2+} + RCO_2^- & \rightleftarrows & [MV^{2+},RCO_2^-] \\
[MV^{2+},RCO_2^-] & \xrightarrow{h\nu} & [MV^{+\cdot},RCO_2\cdot] \\
[MV^{+\cdot},RCO_2\cdot] & \rightarrow & [MV^{2+},RCO_2^-] \\
[MV^{+\cdot},RCO_2\cdot] & \rightarrow & [MV^{+\cdot},R\cdot] + CO_2 \\
[MV^{+\cdot},R\cdot] & \rightarrow & MV^{+\cdot} + \text{products}
\end{array}$$

Scheme II

$$\begin{array}{lcl}
[MV^{2+},{}^-O_2CCH_2CO_2^-] & \xrightarrow{h\nu} & [MV^{+\cdot},{}^-O_2CCH_2CO_2\cdot] \\
[MV^{+\cdot},{}^-O_2CCH_iCO_2\cdot] & \rightarrow & [MV^{+\cdot},{}^-O_2CCH_2\cdot] + CO_2 \\
[MV^{+\cdot},{}^-O_2CCH_2\cdot] & \rightarrow & MV^{2+} + {}^-O_2CCH_2^- \\
{}^-O_2CCH_2^- + H_2O & \rightarrow & CH_3CO_2^- + OH^-
\end{array}$$

A mechanism for photoinduced electron transfer for viologen carboxylate ion pairs is shown in Scheme I (where R = $^-O_2C(CH_2)_n$ for diacid structures). The decarboxylation path is consistent with that proposed for the photooxidation of benzilate by MV^{2+}.[22,23] The scheme employs back electron transfer within a caged radical pair, to account for the generally low efficiency of viologen reduction (no recombination of transient free radicals observed). Caged radicals, R·, resulting from decarboxylation are not sufficiently oxidizing for efficient back electron transfer, ensuring that some reduced viologen species will be freed. The exceptional case of malonate follows the general path but is diverted following decarboxylation since back electron transfer involving the known $^-O_2CCH_2\cdot$ radical[26] yields the relatively stable acetate enolate, $CH_2CO_2{}^{2-}$ which is protonated (Scheme II).

The wavelength dependence of viologen reduction noted for MV^{2+}/PAA was suggested in the early work of Ledwith[22] on viologen carboxylate ion pairs. The result is best viewed as part of a general observation relevant to the dynamics of geminate radical pairs generated by charge-transfer excitation (here, a formal electron transfer between two ions). A variety of organic complexes have now shown this characteristic of higher yields of radical pair dissociation on excitation at higher frequencies within the CT band.[10,12-14] We refer to our earlier discussions of this phenomenon in terms of population of upper vibrational levels of the excited CT state which are dissociative with respect to radical pair separation (a deposition of the excess energy of Franck–Condon states in translational motion of the radicals).

Investigation of the effects of ion pairing of sensitizers[27,28] and relays[10] which are important in the development of photoredox systems continue in our laboratory.

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Registry No. PAA, 9003-01-4; PMAA, 25087-26-7; methyl viologen, 1910-42-5; malonic acid, 141-82-2; succinic acid, 110-15-6; glutaric acid, 110-94-1.

Diels-Alder Reactions of Aza Dienes: A Facile Approach to the Synthesis of Pyridine- and Pyridazine-Substituted Pyrimidine Nucleosides

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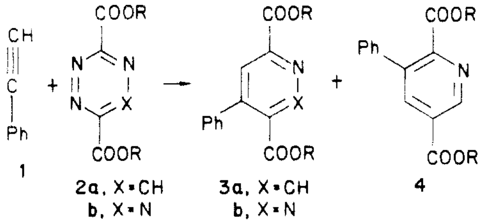
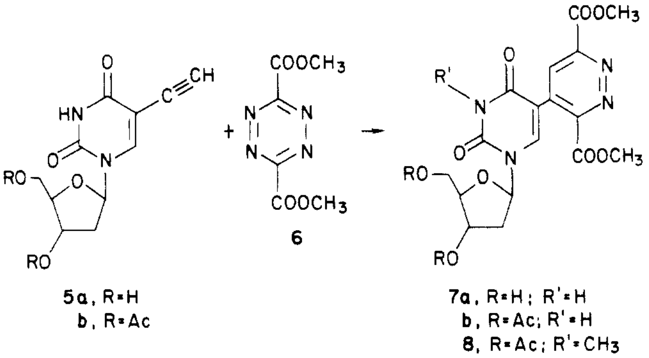
Recently, we initiated studies on the mechanism of the redox chemistry of the enzyme thymidylate synthetase. For this purpose we have needed derivatives of the substrate that would act as probes for studying two-electron transfer via a nicotinamide derivative and one-electron transfer via a metal chelated to a pyridazine dicarboxylate derivative. Therefore, methods have been explored for the synthesis of 5-pyridine- and 5-pyridazine-2′-deoxyuridines. Previous studies on the synthesis of 5-arylpyrimidine nucleosides have shown that both photochemical[1] and palladium(0)-catalyzed coupling reactions[1a,2] are possible routes to a variety of substituted phenyl derivatives. However, preliminary studies on the synthesis of heteroaromatic derivatives of pyrimidine nucleosides were not promising using these methods.

Diels-Alder reactions of both triazines and tetrazines have been found to be versatile routes for the preparation of a variety of heterocyclic systems.[3] The general reaction of alkyne 1 with electron-deficient 1,2,4-triazines (**2a**) or 1,2,4,5-tetrazines (**2b**) via a [4 + 2] cycloaddition reaction results, after nitrogen elimination, in the formation of the corresponding pyridine **3a** or pyridazine **3b**. In the former, addition proceeds exclusively across carbons 3 and 6 of the tetrazine. However, phenylacetylene addition to the triazine **2a** was not regioselective, yielding both the 4-phenyl and the 3-phenyl derivatives **3a** and **4**.[4]



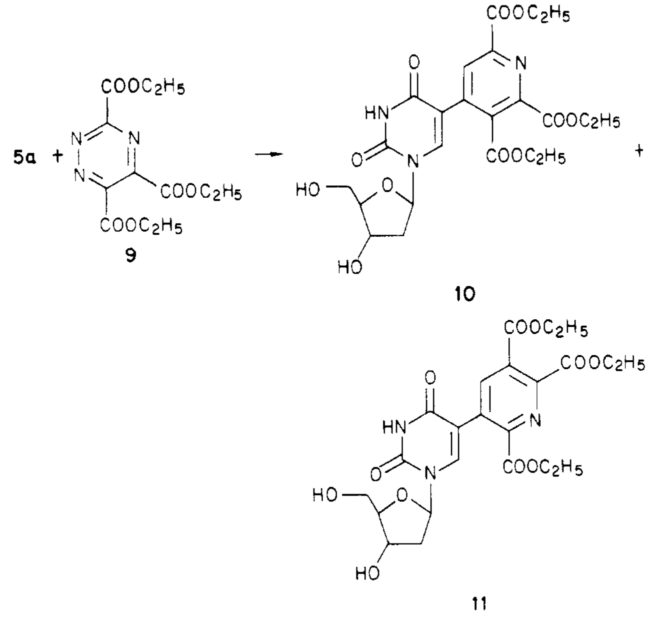
We have investigated methods for synthesizing the target compounds using the inverse electron-demand Diels-Alder reaction between alkyne-substituted deoxynucleoside and heterocyclic aza dienes. The former serves as the electron-rich dienophile, and the carboxylate-substituted tetrazine or triazine serves as the electron-deficient diene. This cycloaddition reaction offers a new method for introducing a nitrogen heterocycle onto a nucleoside that has not been previously explored and has not been reported by other routes.

The reaction of 5-ethynyl-2′-deoxyuridine[5] (**5a**) or the di-*O*-acetyl derivative **5b** and dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate[6] (**6**) at 60 °C in dioxane leads to the 5-substituted pyrimidine deoxynucleosides **7a** or **7b** in 70% yield. The course of the reaction can be visually monitored because the initial red color of the reaction changes to yellow as the tetrazine derivative is consumed.



It has been reported that dicarboxylate-substituted pyridazines participate in Diels-Alder reactions at 100 °C with electron-rich dienophiles.[7] For this reason further elaboration of compound **7b** via a second Diels-Alder reaction with 1,1-dimethoxyethylene to synthesize a 5-substituted phenyl nucleoside was attempted. However, even at 165 °C the cycloaddition reaction did not occur. The only product that was isolated from the reaction was the 3-*N*-methyl nucleoside **8**. Since nucleosides, as a rule, are not stable to Lewis acids these catalysts were not studied in this reaction.

The reaction of **5a** with triethyl 1,2,4-triazine-3,5,6-carboxylate[8] (**9**) provided a 30% yield of the 5-pyridine-substituted deoxynucleosides **10** and **11**. It has been re-



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