part but not all of the rate enhancement. The rate of hydrolysis of the monoanion of *S*-(4-nitrophenyl) phosphorothiolate is retarded by organic solvents, whereas the rate for the dianion is increased. The latter observation is consistent with solvent stabilization of a transition state with dispersed charge and not with perturbation of the pK_a. This is because the rate for the dianion is faster than that for the monoanion in the case of *S*-(4-nitrophenyl) phosphorothiolate;[22] therefore, a perturbation of pK_a would lead to a decreased rate rather than the observed increase.

Hydrolysis of Me$_4$MTP. The rate enhancement induced by bridging S in Me$_4$MTP, relative to bridging O in Me$_4$PP$_i$, is profoundly smaller than the enhancements in the phosphoanhydride and phosphoryl ester anions (Table IV). The hydrolytic reactivity of Me$_4$MTP is only 48-fold greater than that of Me$_4$PP$_i$. Moreover, the activation parameters for the hydrolysis of the tetramethyl esters are very different from those for MTP and PP$_i$, respectively. The entropies of activation for both Me$_4$MTP and Me$_4$PP$_i$ are large and negative, and the enthalpies of activation are much smaller than those for MTP and PP$_i$. The values of $\Delta S^\ddagger$ for Me$_4$MTP and Et$_4$PP$_i$ are consistent with bimolecular processes, and the values of $\Delta H^\ddagger$ are consistent with there being much less bond cleavage to the leaving groups in the transition state than in the reactions of MTP and PP$_i$. The nucleophile in the hydrolysis of Me$_4$MTP appears to be water and not hydroxide because the rate is insensitive to pH between pH 6 and pH 7.

The difference of 48-fold between Me$_4$MTP and Me$_4$PP$_i$ is 4-fold less than that between bis(5,5-dimethyl-2-oxo-1,3,2-dioxaphosphorinanyl) sulfide and its isomer, in which the sulfur atom is nonbridging (Table IV). These latter compounds are MTP and μ-oxo-thiopyrophosphate esterified with 2 equiv of 2,2-dimethyl-1,3-propanediol. One would expect that the ester of μ-oxo-thiopyrophosphate would be hydrolyzed at a rate similar to that of the same ester of pyrophosphate, on the basis of the similar reactivities of tetraethyl pyrophosphate and tetraethyl μ-oxo-thiopyrophosphate, in which the sulfur does not bridge.[25]

The tetraalkyl esters of MTP and PP$_i$ appear to react with water by an associative mechanism, in which there is substantial bonding between the reacting P and both the leaving group and attacking water in the transition state (Scheme II). An associative transition state is one in which the sum of bond orders between P and the attacking and leaving groups is the same as or greater than in the ground state.[41] Bonding between phosphorus and the leaving group is much stronger than in a dissociative transition state. This mechanism is consistent with the activation parameters, and it explains why Me$_4$MTP reacts only 48-fold faster than Me$_4$PP$_i$ despite the weakness of the P–S bond. In contrast to the reaction of MTP compared with PP$_i$, the P–S bond weakness is only slightly expressed in the rate because cleavage of the bond to the leaving group is not well advanced in the transition state for the hydrolysis of the tetramethyl esters.

The activation entropy is much less negative for Me$_4$MTP than for Et$_4$PP$_i$, although still negative enough to be typical of associative character for the transition state.[42] Moreover, the enthalpy of activation for Et$_4$PP$_i$ is smaller than that for Me$_4$MTP. These differences suggest that the transition state for the reaction of Et$_4$PP$_i$ may be more associative than that for Me$_4$MTP.

Acknowledgment. This research was supported by a predoctoral fellowship to C.J.H. from the National Science Foundation and by Grant No. GM 30480 to P.A.F. from the National Institute of General Medical Sciences, USPHS. We gratefully acknowledge the assistance of Eric S. Lightcap, who measured the rate constants in dioxane/water mixtures reported in this paper.

Registry No. MTP, 136862-87-8; Me$_4$-MTP, 71861-22-8.

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Surface-Mediated Cycloaddition: 1,4-Addition of Atomically Adsorbed Oxygen to 1,3-Butadiene on Ag(110)

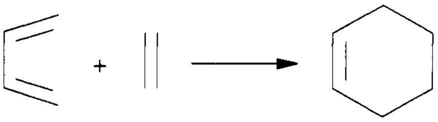
Jeffrey T. Roberts, Armand J. Capote, and Robert J. Madix*

Contribution from the Department of Chemical Engineering, Stanford University, Stanford, California 94305.
Received November 5, 1990

Abstract: The reaction of 1,3-butadiene with atomically adsorbed oxygen on Ag(110) has been studied with use of temperature-programmed reaction mass spectrometry. Oxygen adds to C$_1$ and C$_4$ of 1,3-butadiene via a reaction that is formally a chelotropic 1,4-cycloaddition. 2,5-Dihydrofuran and furan, the cycloaddition products, evolve into the gas phase at 465 K. Other reaction products are water, carbon dioxide, 2(5*H*)-furanone, maleic anhydride, 4-vinylcyclohexene, and styrene. The reaction of oxygen and 1,3-butadiene on Ag(110) resembles a number of other reactions in which simultaneous bond making and breaking occur on the pathway leading from reactants to products. Among these reactions are the epoxidation of norbornene and styrene on silver, the Diels–Alder dimerization of 1,3-butadiene on clean Ag(110), and the trimerization of acetylene to benzene on Pd(111) and Cu(110). We propose (i) that these reactions are all formally related, (ii) that they may also be mechanistically related, and (iii) that they be classified as surface-mediated cycloaddition processes.

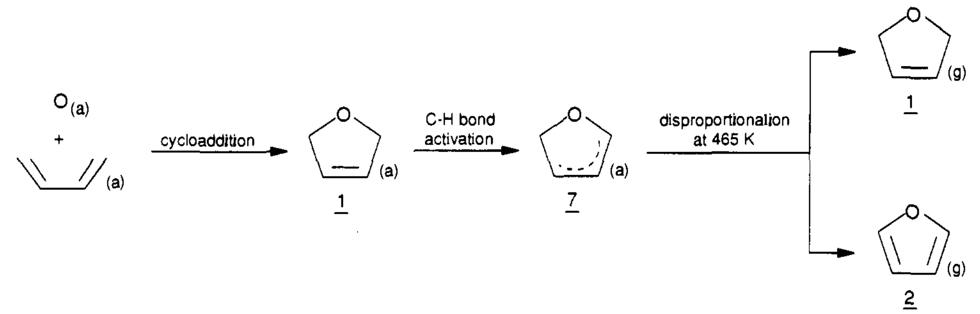
The word cycloaddition refers to an extremely broad family of chemical reactions in which a cyclic molecule is formed via a reaction that involves the concurrent making and breaking of bonds in the reacting molecule(s). Cycloaddition reactions can be concerted (that is, bond making and breaking occur simultaneously) or nonconcerted (bond making and breaking occur in a stepwise fashion). Perhaps the best known cycloaddition process is the Diels–Alder reaction, exemplified by the addition of ethylene to 1,3-butadiene to form cyclohexene (Scheme I). Cycloaddition is an extremely powerful synthetic tool because (i) bonds are made and broken at the same time, (ii) an extremely broad range of molecular types undergo cycloaddition, and (iii) cycloaddition processes can often be executed with an impressive degree of

Scheme I



0002-7863/91/1513-9848$02.50/0 © 1991 American Chemical Society

Scheme II



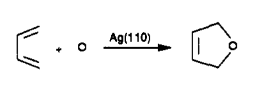
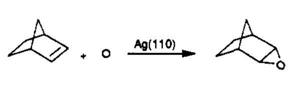
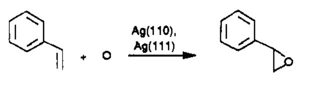
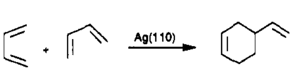
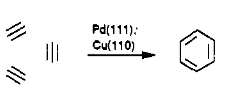
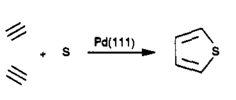
stereochemical control in the product.[1] Cycloaddition processes have therefore been the subject of innumerable studies, in both the gas[1,2] and solution phases.[1]

Despite the intense interest that cycloaddition has generated in gas- and solution-phase reactions, there has been remarkably little consideration of whether cycloaddition can occur on surfaces. This is not to say that cycloaddition reactions have not been observed on single-crystal surfaces; they do occur, but they are not generally understood to be *formally related*. In this paper we report the addition of atomically adsorbed oxygen (O(a)) to 1,3-butadiene on Ag(110), a reaction that is formally a chelotropic 1,4-cycloaddition. (The word chelotropic used in the context of cycloaddition indicates that addition occurs at a single atom in one of the reacting molecules.[3] O(a) is therefore a chelotrope). Oxygen addition occurs at the terminal carbon atoms (C_1 and C_4) in 1,3-butadiene to form the five-membered oxygen-containing ring 2,5-dihydrofuran (**1**). Though not specifically discussed as such previously, a wide variety of other cycloaddition reactions have been reported, from the epoxidation of norbornene and styrene on silver[4,5] to the cyclotrimerization of acetylene to benzene on copper[6] and palladium,[7] as summarized in Table I. It is the purpose of this paper to propose that all of the reactions shown in Table I be considered *surface-mediated cycloaddition* processes. These reactions are all formally related; they may be mechanistically related as well.

Figure 1 shows that gaseous 2,5-dihydrofuran (**1**) and furan (**2**)[8] are both formed at 465 K when coadsorbed 1,3-butadiene and atomic oxygen are heated from 100 to 750 K on Ag(110).[9] The overall reaction is not totally selective for cycloaddition products. Carbon dioxide evolves into the gas phase in a sharp peak at 400 K, and in a broad peak at 490 K with a shoulder at 550 K. Water evolution reaches a maximum rate at 280 K, a temperature indicative of surface hydroxyl disproportionation:[10]

$$2OH(a) \rightarrow H_2O(g) + O(a)$$

Table I. Cycloaddition Reactions Known To Occur on Single-Crystal Surfaces

reaction	reference
	*this work*
	4
	5
	13
	6, 7
	15

Water evolution also occurs at 480 K, approximately concomitant with carbon dioxide, furan, and 2,5-dihydrofuran.[11] Unreacted 1,3-butadiene desorbs between 100 and 300 K. The initial, sharp desorption feature at 115 K does not saturate with increasing 1,3-butadiene exposure and is assigned to the sublimation of a 1,3-butadiene multilayer. The broad tail on the multilayer feature, extending out to 300 K, is assigned to the desorption of reversibly chemisorbed 1,3-butadiene from the Ag(110) surface. Several products not shown in Figure 1 also evolved into the gas phase during temperature-programmed reaction mass spectrometry. Maleic anhydride (**3**) and 2(5*H*)-furanone (**4**), both resulting from the oxidation of 2,5-dihydrofuran by O(a), evolve near 500 K.[12] 4-Vinylcyclohexene (**5**) is formed at ≈365 K via the Diels–Alder dimerization of 1,3-butadiene, a cycloaddition reaction which also proceeds on clean Ag(110),[13] and styrene is formed at ≈365 K

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(1) *Advances in Cycloaddition*; Curran, D. P., Ed.; Jai Press: Greenwich, CT, 1990; Vol. 2.

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(8) All products were identified on the basis of their cracking in the mass spectrometer.

(9) Experiments were performed in a stainless steel ultra-high-vacuum chamber described elsewhere.[13] Heating rates during the temperature-programmed reaction were ≈6 deg K/s. Oxygen (Matheson, extra dry, 99.6+%) and 1,3-butadiene (Aldrich, 99+%) were used as received.

(10) Stuve, E. M.; Madix, R. J.; Sexton, B. A. *Surf. Sci.* **1981**, *111*, 11.

(11) The broad, asymmetric water feature at ≈150 K is an experimental artifact, caused by the 1,3-butadiene-induced displacement of water from the glass mass spectrometer shield.

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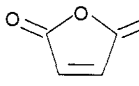
(13) Capote, A. J.; Madix, R. J. To be published.

via oxydehydrogenation of the ring in vinylcyclohexene.



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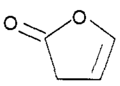

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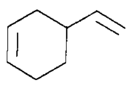

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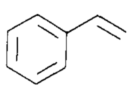

6

The reaction of coadsorbed O(a) and 1,3-butadiene on Ag(110) may clearly be considered a surface-mediated cycloaddition. However, the details of the pathway which leads to 2,5-dihydrofuran and furan evolution are at this point unclear. When 2,5-dihydrofuran is adsorbed on O(a)-precovered Ag(110), 2,5-dihydrofuran desorption occurs at 250 K. Because O(a) and 1,3-butadiene react to form 2,5-dihydrofuran well above its characteristic desorption temperature, we infer that the rate-limiting step for 2,5-dihydrofuran evolution is the reaction of a surface-stabilized intermediate to form 2,5-dihydrofuran at 465 K followed by immediate desorption. Furthermore, 1,3-butadiene desorption is complete by 300 K (Figure 1), strongly suggesting that O(a) addition to 1,3-butadiene occurs below 300 K. Finally, the temperature maximum and line shape of the furan evolution curve are nearly identical with those of the 2,5-dihydrofuran curve, indicating that the kinetics for furan and 2,5-dihydrofuran evolution are equivalent. Taken together, these facts support a mechanism such as that shown in Scheme II. The initial reaction step is cycloaddition of 1,3-butadiene and O(a) to form adsorbed 2,5-dihydrofuran. Cycloaddition of O(a) and 1,3-butadiene must occur below 300 K, the temperature at which 1,3-butadiene desorption is complete. 2,5-Dihydrofuran reacts with O(a) before it can desorb, forming a 2,5-dihydrofuran-derived allyl intermediate (**7**). Activation of acidic allylic C–H bonds by O(a) on Ag(110) is a reaction with ample precedent; **7** is formed via the oxidation dehydrogenation of an allylic C–H bond in 2,5-dihydrofuran by O(a). **7** is stable until ≈465 K, when it reacts via a disproportionation reaction to simultaneously form gaseous 2,5-dihydrofuran and furan. A similar disproportionation is known to occur for $CH_2CN(a)$ on Ag(110) at 475 K:[14a]

$$2CH_2CN(a) \rightarrow CH_3CN(g) + HCN(g) + C(a)$$

Admittedly, $CH_2CN(a)$ is structurally quite different from **7**, but the observation that it reacts at 475 K demonstrates that Ag(110) is active for disproportionation processes involving C–H bond scission near 465 K. A second example of disproportionation involving C–H bond activation near 465 K on Ag(110) is the disproportionation of formate ($HCO_2(a)$) to gaseous carbon dioxide and formic acid at 410 K:[14b]

$$2HCO_2(a) \rightarrow CO_2(g) + HCO_2H(g)$$

The formal relationship between the reactions depicted in Table I is immediately apparent. Less clear, however, is the mechanistic relationship between these disparate reactions, although there is evidence for such a relationship between these reactions. The addition of O(a) to 1,3-butadiene on Ag(110) bears close functional resemblance to the epoxidation of norbornene on Ag(110)[4] and styrene on Ag(111)[5a] and Ag(110),[5b] and it seems likely that the oxygen addition steps in these reactions are mechanistically connected. A strikingly similar oxygen addition reaction is seen on another metal, Pd(111). On this surface, both acetylene and 1,3-butadiene undergo cycloaddition with O(a) to form furan.[15] The oxygen addition reactions also appear to be related to the tricyclization of atomic sulfur with two acetylene molecules to thiophene on Pd(111);[16] the key step in every one of these reactions is addition of a heteroatom to a hydrocarbon skeleton. Thiophene formation in turn resembles the trimerization of acetylene to benzene, a reaction that proceeds on Pd(111)[7] and Cu(110),[6] among other surfaces. Acetylene trimerization on Pd(111) has been extensively studied,[7] and the reaction mechanism is probably better understood than any other surface-mediated cycloaddition. The reaction is almost certainly a two-step process, and the key step leading to benzene formation is the 1,4-cycloaddition of coadsorbed acetylene and a C_4H_4 intermediate.[7h,17] Acetylene trimerization over a Pd catalyst proceeds similarly.[7i] This reaction bears a strong mechanistic resemblance to the 1,4-cycloaddition of O(a) and 1,3-butadiene on Ag(110).

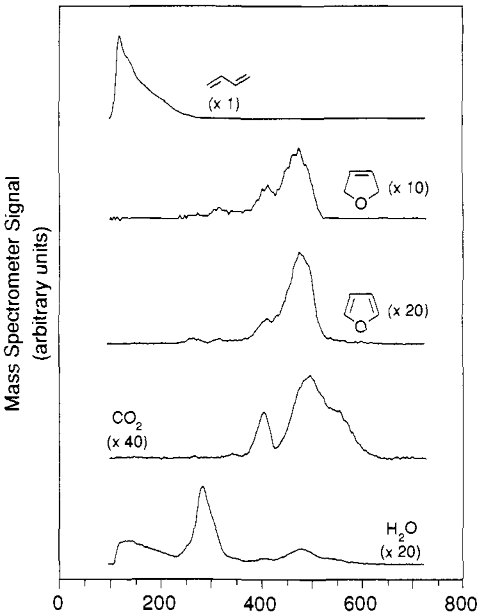

Figure 1.

Surface-mediated cycloaddition has by now been frequently enough observed that it may be considered to be a general class of surface reaction. As yet, the reaction has been observed only on late transition metal surfaces (Ag,[4,5,13] Pd,[7,14-16] Cu[6]), but there seems to be no reason why cycloaddition could not occur on any metal surface. We note that ethylene sulfide and trimethylene sulfide react on Mo(110) to form the desulfurized products ethylene and cyclopropane, respectively.[18,19] These reactions are the *reverse* of a chelotropic cycloaddition process, and may therefore be considered surface-mediated cycloreversion. It is not clear yet exactly what role the surface plays in promoting cycloaddition, although in some cases the reaction barrier is clearly lower than that in the gas phase. The barrier to the Diels–Alder dimerization of 1,3-butadiene in the gas phase is 27 kcal/mol, for instance,[20] while the dimerization barrier on Ag(110) is <19 kcal/mol.[13,21] The lower barrier for surface-mediated cycloaddition may have several origins. Chemisorption may result in alignment of the frontier orbitals in a configuration that leads to optimum orbital overlap and therefore facile reaction via a concerted process. Alternatively, there may be low-energy, non-

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[14] (a) Capote, A. J.; Hamza, A. V.; Canning, N. D. S.; Madix, R. J. *Surf. Sci.* **1986**, *175*, 445. (b) Barteau, M. A.; Bowker, M.; Madix, R. J. *Surf. Sci.* **1980**, *94*, 303.

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[21] (a) The activation energy is estimated assuming a first-order reaction with a preexponential factor of 10^{13}.[20b] The value of 19 kcal/mol is an upper limit, based on the temperature of desorption-limited 4-vinylcyclohexene evolution from 1,3-butadiene dimerization. (b) Redhead, P. A. *Vacuum* **1962**, *12*, 203.

concerted reaction pathways on a surface that simply do not exist in the gas phase. These and other possibilities are currently under investigation in our laboratory.

Acknowledgment. We gratefully acknowledge the support of the National Science Foundation (NSFCBT 8701342) and the donors of the Petroleum Research Fund, administered by the American Chemical Society.

Registry No. 1, 1708-29-8; **2**, 110-00-9; **3**, 108-31-6; **4**, 20825-71-2; **5**, 100-40-3; **6**, 100-42-5; $H_2C{=}CHCH{=}CH_2$, 7782-44-7; Ag, 7440-22-4.

Communications to the Editor

Synthesis and DNA-Cleaving Abilities of Functional Neocarzinostatin Chromophore Analogues. Base Discrimination by a Simple Alcohol

Masahiro Hirama,* Takuya Gomibuchi, and
Kenshu Fujiwara

Department of Chemistry, Faculty of Science
Tohoku University, Sendai 980, Japan

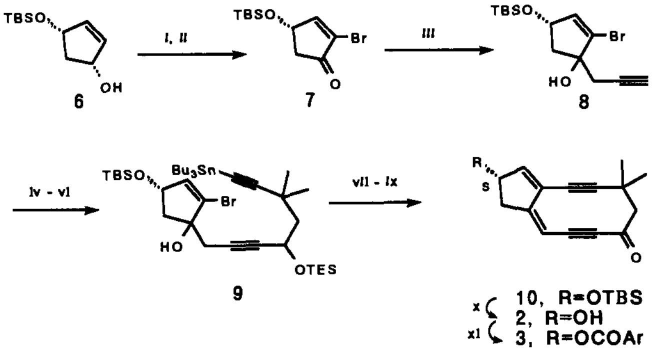
Yukio Sugiura* and Motonari Uesugi

Institute for Chemical Research, Kyoto University
Uji, Kyoto 611, Japan

Received July 10, 1991

The precise roles of aglycon, carbohydrate, and intercalative aromatic moieties of DNA-binding antibiotics in site-specific DNA cleavage is a topic of intense current interest.[1,2] Neocarzinostatin (NCS) is a macromolecular antitumor agent that consists of biologically active chromophore **1**[3] and an apoprotein acting as a stabilizer and a carrier for **1**.[4] The labile dienediyne molecule **1** equipped with both a substituted naphthoic acid and an amino sugar moiety exhibits DNA-cleaving activities through carbon radical generation.[5] The base (T > A ≫ C > G)[6] and sequence (GN_1T)[7] specificities in the cleavage of oligonucleotides by **1** have been attributed to the specific intercalation of the naphthoic acid moiety. Whereas we recently demonstrated that 10-membered-ring analogues **4** and **5**[8] undergo the thiol-triggered[5d] or radical-triggered[9] aromatization in a manner related to **1**,[10-12] both molecules were not capable of affording appreciable cytotoxic activities, probably due to the lack of hydrophilic and/or DNA-binding groups. We designed the second generation of NCS models, alcohol **2** and naphthoate **3**, to improve these points and have found **2** to possess striking guanine-selective DNA-cleaving ability.

Scheme I[a]



[a] (a) $(COCl)_2$, DMSO, Et_3N, −60 °C; (ii) Br_2, CH_2Cl_2, 0 °C; (iii) propargylmagnesium bromide, ether, −88 °C; (iv) BuLi, THF–HMPA, −78 °C, and then 3,3-dimethylpent-4-yn-1-al; (v) TESCl, pyr; (vi) BuLi, THF, −78 °C, and then Bu_3SnCl; (vii) $(Ph_3P)_4Pd$, THF, 60 °C, 89 h; (viii) K_2CO_3, MeOH; (ix) $(COCl)_2$, DMSO, Et_3N, −60 °C; (x) THF–H_2O–AcOH (1:1:1); (xi) $Me_2HN^+(CH_2)_3N{=}C{=}NEt,Cl^-$, $ArCO_2H$, CH_2Cl_2.

Key intermediate **7** was synthesized from readily available optically pure 3(*S*)-[(*tert*-butyldimethylsilyl)oxy]-5(*R*)-hydroxycyclopent-1-ene (**6**)[13] by the standard procedure (85%, Scheme I). Conversion of **7** to **2** and **3** essentially followed the synthetic scheme employed in the synthesis of **4**.[8a] Addition of propargylmagnesium bromide to **7** (91% yield) and condensation with 3,3-dimethylpent-4-yn-1-al by using BuLi at low temperature

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