Substituent-Directed Oxidation: The Syn Stereochemistry of Addition of High-Valent Oxochromium Reagents to Alkenes

Matthew F. Schlecht*,† and Ho-jin Kim‡

Department of Chemistry, Polytechnic University, 333 Jay Street, Brooklyn, New York 11201

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The transannular oxidative cyclization of cycloalkenols is a useful synthetic method for the intramolecular syn alkoxyhydroxylation of an alkene, a transformation for which there is presently no alternative procedure. Under the influence of certain high-valent chromium reagents, a cycloalkene substrate that also bears a suitably disposed tertiary hydroxyl ligand first binds the oxidant and then undergoes selective oxidative attack of the tethered oxidant on the alkene. The substrate 1-methylcyclooct-4-en-1-ol (**1**) is oxidized in a regiospecific fashion to 1-methyl-9-oxabicyclo[4.2.1]nonan-5-one (**2**) by pyridinium chlorochromate (PCC), while none of the regioisomeric 1-methyl-9-oxabicyclo[3.3.1]nonan-4-one is produced. A regio- and stereospecific oxidative cyclization of 1,5-dimethylcyclooct-4-en-1-ol (**3**) occurs on treatment with PCC, to yield the exo alcohol isomer of 2,6-dimethyl-9-oxabicyclo[4.2.1]nonan-2-ol (**4a**), the result of syn oxidative addition of the hydroxyl-bound oxochromium moiety across the carbon–carbon double bond. The endo alcohol isomer of 2,6-dimethyl-9-oxabicyclo[4.2.1]nonan-2-ol (**4b**) is prepared for comparison by stereospecific addition of tetramethylzirconium to **2**. Standard MCPBA epoxidation of **3** gives rise to a mixture of the cis epoxide, *endo*-1,5-dimethyl-9-oxabicyclo[6.1.0]nonan-5-ol (**5**), and the product of rearrangement of the trans epoxide, *endo*-1,5-dimethyl-9-oxabicyclo[3.3.1]nonan-2-ol (**6**). The cis epoxide **5** on further treatment with PCC is *not* converted to exo alcohol (**4a**), indicating that an epoxide intermediate is not involved in the highly specific transannular oxidative cyclization of **3** with chromate.

The oxidation of alkenes by high-valent chromium reagents traditionally has been found to be capricious, and the factors determining product selectivity are not well defined. One strategy for rendering these reactions synthetically useful is to exploit the high level of selectivity associated with intramolecular reactions.[1] Substituent-directed oxidative cyclization is a powerful method for the selective functionalization of a locally symmetrical cycloalkene under the guidance of an interactive substituent such as hydroxyl. We have found such reactions to proceed with very high regioselectivity in cyclooctenols to yield the corresponding β-keto cyclic ethers.[2b] In a further demonstration of the utility of this method, we have investigated the stereochemistry of addition in a cyclooctenol in which the conversion of the initial oxidatively cyclized adduct to a ketone is blocked. This syn alkoxyhydroxylation of an alkene is not achievable by any other method and would provide a straightforward selective construction of the cis β-hydroxy cyclic ether moiety found in some natural products such as grayanoside D[3] and the triptofordins.[4]

We have found[2] that transannular oxidative cyclizations in simple substrates that contain both a site for oxidative attack (such as an alkene) and an interactive nucleophilic or ligand substituent (such as a hydroxyl) constitute a useful selective synthetic method and provide a discriminating test for different oxidants and oxidation pathways.[5] The oxidation of these substrates may be viewed as proceeding through one of two basic reaction pathways: the type I involving initial activation of the hydroxyl ligand substituent by the oxidant followed by a secondary oxidative attack on the alkene and the type II involving initial oxidative activation of the alkene to form an intermediate, which is attacked in a second step by the nucleophilic hydroxyl substituent.[2]

In the type I process involving a prior binding of the oxidant, the relative geometry of approach of the bound oxidant to the substrate is constrained and the structure of the transition state for oxidative attack will be better defined than in an intermolecular oxidative attack. This restricted approach of the tethered oxidant to the site of attack will foster a much higher degree of product selectivity.[2e] Examples can be drawn from the experimental observation in which an oxoiron heme species undergoes alkylation of the porphyrin ligand by an intermediate generated in the course of alkene oxidation[6] or from the sequence proposed by Baldwin for penicillin biosynthesis that involves attack by a sulfur-bound iron(IV) oxide upon an alkyl (or alkenyl) side-chain substrate.[7] In the type II process, intermediates formed by initial intermolecular attack of the oxidant on the alkene can be efficiently trapped through intramolecular attack by the hydroxyl group. Processes following this pathway include the "elementoetherification" reactions effected, for example, by selenenyl halides[8] and lead(IV)[9] and thallium(III)[10] reagents. The intermediates in question might include epoxides, charge-transfer complexes, olefin radical cations, or the onium ions derived from addition of hypervalent main group oxidants.[2b,c] In both types of mechanism, the special character of intramolecular reactivity due to the influence of an interactive substituent translates into higher product selectivity.[1]

Results

We have shown that substrate **1**, cleanly prepared from the known[11] cyclooct-4-en-1-one by addition of tetra-

† Present address: Du Pont Agricultural Products Department, Stine-Haskell Research Center, 5300/332C, P.O. Box 30, Newark, DE 19804.

‡ Present address: Department of Chemistry, Brown University, Providence, RI 02912.

(1) For a recent review in this area, see: Menger, F. M. *Acc. Chem. Res.* **1985**, *18*, 128.

(2) (a) Schlecht, M. F.; Kim, H.-j.; *Tetrahedron Lett.* **1985**, *26*, 127. (b) Schlecht, M. F.; Kim, H.-j. *Tetrahedron Lett.* **1986**, *27*, 4889. (c) Kim, H.-j.; Schlecht, M. F. *Tetrahedron Lett.* **1987**, *28*, 5229. (d) Kim, H.-j.; Schlecht, M. F. *Tetrahedron Lett.* **1988**, *29*, 1771. (e) Guerrero, A.; Kim, H.-j.; Schlecht, M. F. *Tetrahedron Lett.*, in press.

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(5) For a review on different transition states in addition reactions, see: Freeman, F. *Chem. Rev.* **1975**, *75*, 439.

(6) Ortiz de Montellano, P. R.; Mangold, B. L. K.; Wheeler, C.; Kunze, K. L.; Reich, N. O. *J. Biol. Chem.* **1983**, *258*, 4208 and previous papers in this series.

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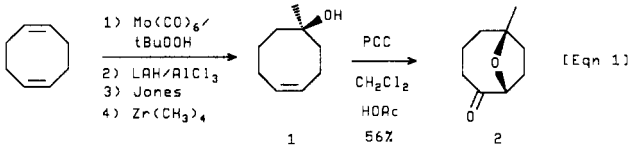
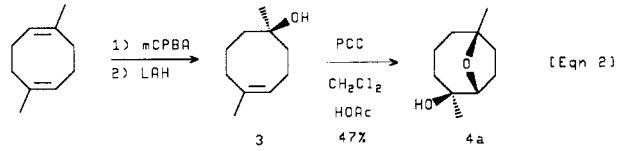
methylzirconium,[12,13] undergoes regiospecific oxidative cyclization with pyridinium chlorochromate (PCC) to yield **2** (eq 1).[2b,14] The importance of the hydroxyl substituent



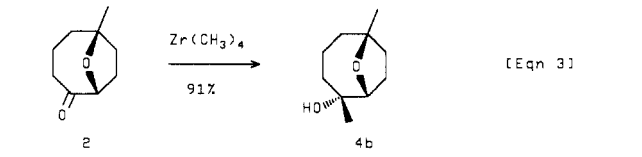
in this selective reaction was tested by carrying out the oxidation on a substrate with a blocked hydroxyl. The methyl ether of **1** is completely inert to PCC, while the reaction of the methyl ether of **1** with Fieser reagent (CrO_3/HOAc/Ac_2O) gives rise to a complex mixture of products. The fact that the alkene function in **1** is unreactive with PCC under our standard conditions (CH_2Cl_2/reflux/2 days) in the absence of an interactive substituent strengthens the utility of this substituent-directed oxidation in selective synthesis.

The stereochemistry of the oxidative addition in the conversion **1** → **2** is not apparent since one of the two carbons of the olefin reverts to sp^2 through further oxidation. A type I mechanism predicts a syn alkoxyhydroxylation, and we expected to realize a stereospecific reaction in substrates that do not permit the subsequent oxidation to the carbonyl.

To this end we prepared the substrate 1,5-dimethylcyclooct-4-en-1-ol (**3**) from 1,5-dimethylcycloocta-1,5-diene.[15] Oxidative cyclization of **3** with PCC proceeds with complete regio- and stereospecificity to give a single β-hydroxy cyclic ether (eq 2). In order to establish a

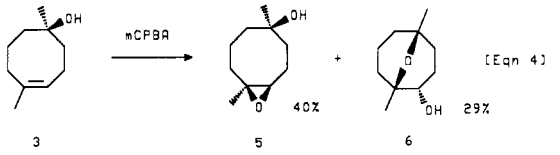


structure proof, we reasoned that the endo stereoisomer **4b** could be prepared for comparison by addition of a methyl nucleophile to the β-keto cyclic ether **2**, since the adduct obtained should result from preferential addition from the sterically least hindered convex face of the oxabicyclo[4.2.1]nonanone. In the event, treatment of **2** with tetramethylzirconium[12,13] (eq 3) gives a single β-hydroxy

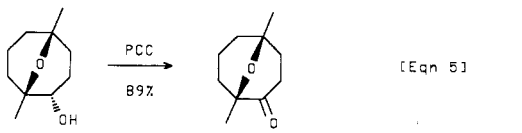


cyclic ether to which the structure **4b** is assigned on the basis of steric approach control. The spectral data for the endo isomer **4b** are clearly different from those of the product of oxidative cyclization with PCC, the presumed exo isomer **4a**.[16] The rationale that predicts a trans arrangement of the oxygens in adduct **4b** thus leads to the cis stereochemical assignment **4a** for the product in eq 2.

We have shown that the transannular oxidative cyclization of **1** in which an epoxide is intentionally generated proceeds with low regioselectivity to give a mixture of two isomeric β-hydroxy cyclic ethers.[2b] In a similar examination of substrate **3**, treatment with MCPBA under mild conditions yields two products (eq 4) whose structures are



assigned from spectral data as the cis hydroxy epoxide **5** and *endo*-1,5-dimethyl-9-oxabicyclo[3.3.1]nonan-2-ol (**6**). In contrast to our chromate-induced oxidative cyclization, the cyclization to **6** through the presumed trans hydroxy epoxide intermediate proceeds with complementary regiospecificity to form the oxabicyclo[3.3.1]nonane skeleton, the expected product of acid-catalyzed opening of such a trisubstituted epoxide. Within the limits of detection by NMR, none of the isomeric oxabicyclo[4.2.1]nonanols **4a,b** were present. Alcohol **6** is oxidized cleanly with PCC to 1,5-dimethyl-9-oxabicyclo[3.3.1]nonan-2-one (**7**, eq 5),



which is the regioisomeric product expected from a nonspecific chromate-induced cyclization of **3**. Examination of the spectral data for **7** confirmed its absence from the product of direct oxidation of **3** with PCC.

The possible conversion of the cis hydroxy epoxide **5** to the exo β-hydroxy cyclic ether **4a** under our standard conditions with PCC was tested. Over a period of 1 day, about one-third of **5** is consumed to yield a mixture of products in which no more than traces of **4a** are evident within the limits of detection by NMR.[17]

Discussion

The uniqueness of this chromate-mediated syn alkoxyhydroxylation as a selective synthetic method prompts a closer examination of the reaction mechanism within the larger context of the reactions of alkenes with transition-metal oxo reagents. Despite a number of experimental[2,6,18-27] and theoretical[28-30] studies on the addition of

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(13) In our hands, methyllithium addition either to cyclooct-4-en-1-one to give **1**, or to **3** to give **4b**, proceeds in approximately 80% yield, with 5–10% of starting ketone recovered. We attribute the lower yield to a competing proton transfer process with the organolithium reagent, which is completely circumvented when the zirconium reagent is used. The addition of methyllithium to **2** to give **4b** is stereospecific within the limits of our detection.

(14) The addition of several equivalents of acetic acid makes the oxidative cyclization more rapid, while the inclusion of sodium acetate makes it slower. There appears to be a significant effect by acidity on the rate of reaction, while the exact nature of this effect is uncertain.

(15) Commercial 1,5-dimethylcycloocta-1,5-diene (Aldrich) contains from 10 to 15% of the isomeric 2,5-dimethylcycloocta-1,5-diene. Cyclooctenol **3** can be separated by careful chromatography from the isomeric product resulting from this impurity, which in any case does not obscure the important NMR absorptions of products **4a,b**.

(16) No **4b** is present in this sample within the limits of detection by ^1H NMR, which is approximately 1%, and the absence of C=O absorption in the IR shows that none of the regioisomeric product **7** is present.

(17) This mixture of products was not purified nor completely characterized; however an absorption corresponding to the methyl singlet at 1.02 ppm in the ^1H NMR of **4a** was clearly absent. New infrared peaks at 1710, 1765 cm^{-1} were evident, indicative of C–C bond cleavage of the epoxide to give a keto γ-lactone. This type of epoxide cleavage has been reported with PCC: Antonioletti, R.; D'Auria, M.; DeMico, A.; Piancatelli, G.; Scettri, A. *Synthesis* **1983**, 890. Other oxidants such as periodate also effect this cleavage: Chatterjee, A.; Majumdar, S. G. *Anal. Chem.* **1956**, *28*, 878. Graber, R. P.; Snoddy, C. S.; Arnold, H. B.; Wendler, N. L. *J. Org. Chem.* **1956**, *21*, 1517. Dean, F. M.; Price, A. W.; Wade, A. P.; Wilkinson, G. S. *J. Chem. Soc. C* **1967**, 1893. Nagarakatti, J. P.; Ashley, K. R. *Tetrahedron Lett.* **1973**, 4599.

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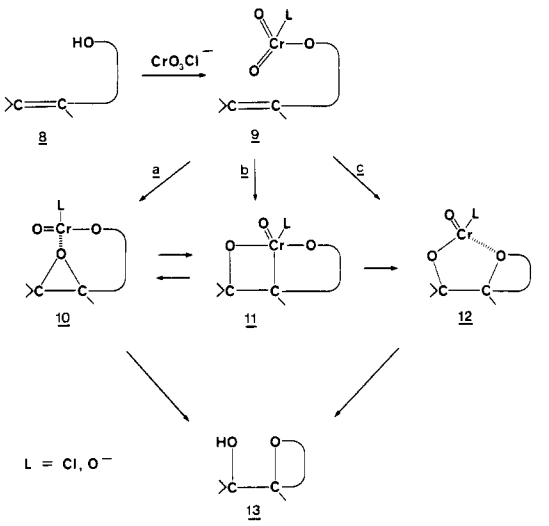
high-valent oxometal species to alkenes, a simple mechanistic description of this process remains elusive. One proposal involves a one- or two-step oxygen transfer from the metal to the alkene to give an epoxide as the primary product, which can be isolated or will react further to give the products ultimately observed.[19-21,30a,c] A second possibility is the Criegee [3 + 2] cycloaddition mechanism, which leads specifically to cis vicinal glycol-type products.[30b,31] A third formulation involves the formation of an intermediate metallaoxetane, which rearranges to give the observed products.[22-27,29] A metallaoxetane can lead to an epoxide by reductive elimination, and it can also lead to cis vicinal glycol-type products by rearrangement. No direct experimental evidence has emerged so far that clearly favors one mechanistic pathway over the others, but calculations indicate that the Criegee mechanism is energetically unfavorable without the stabilization energy that attends the increase in bond order of a "spectator" metal oxo group.[29] There are indications from some studies that epoxides are not precursors of the glycol-related products which are observed.[2b,6,18c]

We believe that our chromium(VI) oxidations typify the type I process. The prior formation of a chromate ester is a reasonable assumption given the evidence for very rapid formation of such esters with primary, secondary, and tertiary alcohols.[32] We attribute the high degree of selectivity observed in this reaction to two influences: the ordered transition state for oxidative cyclization (reinforced by conformational constraints), which dictates the regioselection, and the relative strength of the oxidant, which differentiates between epoxidation and syn dioxygenation. Our preliminary work with 10- and 12-membered ring substrates indicates that the success of the oxidative cyclization is strongly dependent upon the conformational properties of the substrate. Our analysis of the reagent-dependent selectivity is formulated in terms of the relative strength of the oxidants: in this discussion we refer to

Scheme I



stronger chromium oxidants (weaker donor ligands, more ionic medium, lower pH) vs milder oxidants (stronger donor ligands, less polar medium, more neutral pH). There is evidence that these characteristics are reflected in oxidation potential of the reagent, i.e., a thermodynamic property, although these factors may also exercize an effect through kinetic selection.[33]

Earlier work has suggested that stronger high-valent chromium reagents initially transform alkenes into epoxides such as **10**, which subsequently may be converted to other isolable products.[19,20a] From our previous studies,[2b] we also have evidence of intermediate epoxides in reactions with stronger oxidants such as the Fieser reagent (CrO_3/HOAc/Ac_2O) but not with milder reagents such as PCC. This dichotomy is also shown in the reactions of the methyl ether of **1**, where the Fieser reagent gives a complex of products and PCC gives no reaction. Given the syn nature of the stereochemistry for product **4a** and the strong indications of a type I process with prior formation of a chromate ester, three mechanistic pathways can be proposed for this transannular oxidative cyclization (Scheme I). Following the initial step of chromate ester formation (**8** → **9**), attack on the alkene by the tethered oxidant can take place via direct epoxidation (pathway a, **9** → **10** → **13**, or **9** → **10** → **11** → **12** → **13**), via metalloxetane formation (pathway b, **9** → **11** → **12** → **13**, or **9** → **11** → **10** → **13**), or a [3 + 2] cycloaddition/fragmentation Criegee mechanism[31] (pathway c, **9** → **12** → **13**).

Metallaoxetane intermediates such as **11** have been invoked to explain much of the work in this area.[22-27,29] The presence of such species has been demonstrated in the gas phase,[23c,26] although direct evidence for their presence in solution is still tentative.[24a] Pathway c has also been suggested as the mechanism for these oxidative additions[2a,b,22b,23a,31] and proceeds through a Criegee-type syn addition of the ROCr=O moiety across the alkene to give **12**. The transition states for all three oxidative addition pathways a–c would benefit from the stabilization energy

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(22) (a) Sharpless, K. B.; Flood, T. C. *J. Am. Chem. Soc.* **1971**, *93*, 2316. (b) Sharpless, K. B.; Teranishi, N. Y.; Bäckvall, J. E. *Ibid.* **1977**, *99*, 3120.
(23) (a) Walba, D. M.; Stoudt, G. S. *Tetrahedron Lett.* **1982**, *23*, 727. (b) Walba, D. M.; Stoudt, G. S. *J. Org. Chem.* **1983**, *48*, 5404. These authors provided evidence of syn addition in several acyclic substrate examples. These cases are complicated by the presence of other functional groups in the substrate and do not constitute model systems which differentiate between type I and type II processes both in the stereochemistry and the regiochemistry of the addition, as the present examples do. (c) Walba, D. M.; DePuy, C. H.; Grabowski, J. J.; Bierbaum, V. M. *Organometallics* **1984**, *3*, 498.
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(29) Rappé, A. K.; Goddard, W. A., III. *J. Am. Chem. Soc.* **1980**, *102*, 5114. Rappé, A. K.; Goddard, W. A., III. *Ibid.* **1982**, *104*, 448.
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attending the increase in bond order of the chromyl "spectator" oxo group, which has been described by Rappé and Goddard.[29]

The metallaoxetane **11**, while not leading directly to the products observed, provides a convenient mechanistic keystone, since through ligand reorganization it leads to either the epoxide complex **10** or the hydroxy ether complex **12**. The dichotomy between epoxide formation with stronger oxidants and hydroxy ether formation with milder reagents could reflect a correlation between the oxidation potential of the complexed high-valent transition metal and the preference for one rearrangement of **11** over the other. Alternatively, the strength of the oxidant could determine a preference for one of the two direct pathways of addition (a or c).

Stereoelectronic constraints in **11** should also be important, and it is possible that the geometry of approach controls this partitioning. Clearly the reaction benefits from the special acceleration due to intramolecularity.[1] In the oxidations of alkenes with oxometal porphyrin complexes that normally lead to epoxides, the approach is presumed to involve perpendicular axes for the C=C and M=O moieties (where M = transition metal),[24,25] though recent calculations suggest low energy pathways to the epoxide via either perpendicular or parallel modes of approach.[30a,b]

The failure to convert the epoxide **5** into **4** upon treatment with PCC appears to rule out **10** as an intermediate and pathway a as a mechanistic step in the transannular oxidative cyclization of **3** → **4a**. No distinction can be drawn between pathways b and c at present.

Conclusions

The substituent-directed syn oxidative addition of oxochromium reagents to alkenes is a unique and viable synthetic method for which no simple alternatives exist. For example, this methodology provides a straightforward selective construction of the cis β-hydroxy cyclic ether moiety found in some natural products such as grayanoside D[3] and the triptofordins.[4] This reaction also constitutes an interesting mechanistic probe for the attack of metal oxo complexes on alkenes. The intramolecular nature of the oxidative addition step imposes geometric constraints on the transition state from which the high specificity likely arises. In this regard, these results may provide a simple model system for highly selective biochemical oxidations.[6,7,18] Substituent-directed oxidation is a powerful method for the selective functionalization of a locally symmetrical alkene to give adducts that can be further elaborated. For example, preliminary experiments have shown that is possible to convert **2** to the corresponding α,β-unsaturated ketone, which is of interest in the preparation of certain unnatural carbohydrate analogues. We are continuing to investigate the scope of regio- and stereospecific reactions of oxochromium reagents and other oxidants with medium and large ring unsaturated organic substrates.

Experimental Section

General. Chemicals and reagents were obtained from commercial suppliers and used without purification unless otherwise noted. Infrared spectra were determined on either a Perkin-Elmer 1430 or a Shimadzu IR-435 infrared spectrometer. ^{1}H NMR spectra were obtained at 90 MHz on a Varian EM390 NMR spectrometer. ^{13}C NMR spectra were obtained at 22.5 MHz on a JEOL FX-90Q FT NMR spectrometer. Microanalysis was carried out by Desert Analytics, Tucson, AZ. High resolution mass spectra were obtained through the Rockefeller University Mass Spectrometric Research Resource, using electron bombardment or hydroxyl anion negative ionization.[34] Purifications were carried out by the flash column chromatography method, with minor modifications.[35] Reactions at −20 °C were carried out in a carbon tetrachloride/dry ice bath. Cyclooct-4-en-1-one was prepared by modification of the literature procedure,[11] in which cycloocta-1,5-diene was epoxidized with molybdenum hexacarbonyl and *tert*-butyl hydroperoxide in 50% yield after distillation,[36] and the reductive opening of the epoxide was carried out with lithium aluminum hydride/aluminum chloride in 97% yield.[37]

1-Methylcyclooct-4-en-1-ol (1). A solution of tetramethylzirconium[12] was prepared by slowly adding 125 mL (214 mmol) of 1.7 M methyllithium in ether to a flame-dried flask containing 12.397 g (53.3 mmol) of zirconium tetrachloride chilled to −20 °C under argon. The resulting black suspension was stirred for 20 min at −20 °C and was then charged via cannula with a solution of 3.007 g (24.2 mmol) of cyclooct-4-en-1-one in a total of 30 mL of dry THF. The reaction mixture was stirred for 1.5 h at −20 °C and was then allowed to warm to room temperature over 1.5 h. The reaction mixture was poured into 350 mL of 5% HCl (aq), and standard ether/aqueous workup yielded 3.253 g (96%) of 1-methylcyclooct-4-en-1-ol, **1**, as a pale yellow oil: IR (thin film) 3360 (s br), 3010 (m), 2970 (s), 2930 (s), 2880 (s), 1650 (w) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.21 (s, 3 H), 1.4–1.9 (m, 6 H), 2.15–2.4 (m, 4 H), 2.52 (s, 1 H), 5.4–5.9 (m, 2 H); ^{13}C NMR (C_6D_6) δ 23.8, 24.6, 25.5, 30.2, 36.4, 40.9, 73.8 126.4, 132.1; high resolution mass spectrum (−OH neg. ion), calcd for (m − 1) $C_9H_{15}O$ 139.11228, found 139.1095.

1-Methyl-9-oxabicyclo[4.2.1]nonan-5-one (2). To a solution of 1.648 g (11.8 mmol) of 1-methylcyclooct-4-en-1-ol in 130 mL of methylene chloride were added 7.6 g (35.3 mmol) of pyridinium chlorochromate and 15 g of Celite. This was charged further with 2.69 mL (47.0 mmol) of acetic acid, and the resulting mixture was heated to reflux under argon for 1.5 days. The reaction mixture was diluted with 100 mL of ether/petroleum ether (1:1) and was passed through a column of 50 g of alumina, and the column was further eluted with 100 mL of the ether/petroleum ether mixture. The eluate was concentrated, and the crude product was purified by chromatography (40 g of silica, ether/petroleum ether (1:1), to yield 1.015 g (56%) of 1-methyl-9-oxabicyclo[4.2.1]nonan-5-one (**2**) as a pale yellow oil: IR (thin film) 2970 (s), 2920 (s), 2880 (s), 1710 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.33 (s, 3 H), 1.55–3.1 (m, 10 H), 4.21 (dd, 1 H, J = 2, 9 Hz); ^{13}C NMR (C_6D_6) δ 20.6, 29.6, 32.0, 33.2, 41.8 (×2), 84.3, 85.1, 216.4; high resolution mass spectrum (−OH neg. ion), calcd for $C_9H_{13}O_2$ (m − 1) 153.09155, found 153.0885. Anal. Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 70.24; H, 9.27.

1,5-Dimethylcyclooct-4-en-1-ol (3). A solution of 2.31 mL (14.7 mmol) of 1.5-dimethylcycloocta-1,5-diene[15] in 50 mL of methylene chloride containing 2.47 g of sodium bicarbonate in suspension at 0 °C under argon was charged portionwise with 2.53 g (14.7 mmol) of *m*-chloroperoxybenzoic acid (85%). The mixture was stirred for a total of 4.5 h and was filtered through Celite. The solution was concentrated, triturated with pentane, and filtered again, then extracted with brine, dried over magnesium sulfate, and concentrated. The crude product was purified by flash chromatography (60 g of silica; ether/petroleum ether (1:9)) to yield 1.48 g (66%) of 1,5-dimethyl-9-oxabicyclo[6.1.0]non-4-ene, which was immediately carried on to the reduction step. A solution of 1.48 g (9.75 mmol) of 1,5-dimethyl-9-oxabicyclo-[6.1.0]non-4-ene in 20 mL of ether was added dropwise to a suspension of 407 mg (10.7 mmol) of lithium aluminum hydride in 70 mL of ether at 0 °C. After being stirred to room temperature over 45 min, the mixture was heated to reflux for 3 days. The mixture was charged dropwise with 2 mL of saturated aqueous sodium sulfate. The solution was dried by addition of sodium sulfate and was filtered through Celite and concentrated. The crude product was purified by flash chromatography (45 g of silica; ether/petroleum ether (2:8)) to yield 1.31 g (88%) of 1,5-di-

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methylcyclooct-4-en-1-ol (3): IR (thin film) 3370 (m br), 3040 (w), 2960 (s), 2920 (s), 2850 (s), 1470 (m), 1440 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.23 (s, 3 H), 1.5–1.9 (m, 6 H), 1.72 (br s, 3 H), 2.0–2.5 (m, 4 H), 2.08 (s, 1 H), 5.5 (m, 1 H); ^{13}C NMR (C_6D_6) δ 23.0, 24.3, 24.5, 30.4, 31.5, 37.5, 43.7, 73.4, 125.5, 135.7; high resolution mass spectrum ($^-$OH neg. ion), calcd for (m – 1) $C_{10}H_{17}O$ 153.12794, found 153.1266.

***exo*-2,6-Dimethyl-9-oxabicyclo[4.2.1]nonan-2-ol (4a).** A solution of 138 mg (0.895 mmol) of 1,5-dimethylcyclooct-4-en-1-ol in 15 mL of methylene chloride containing 700 mg of Celite was charged with 386 mg (1.79 mmol) of pyridinium chlorochromate and 0.16 mL (2.69 mmol) of acetic acid, and this mixture was heated to reflux under argon for 2 days. The reaction mixture was diluted with 20 mL of a mixture of ether and petroleum ether (1:1), and this was passed through a column containing 10 g of alumina. The column was rinsed with an additional 50 mL of the mixture of ether and petroleum ether, and the eluate was concentrated. The crude product was purified by flash chromatography (5 g of silica; ether/petroleum ether (1:1)) to yield 72 mg (47%) of *exo*-2,6-dimethyl-9-oxabicyclo[4.2.1]nonan-2-ol (**4a**) as a pale yellow oil: IR (thin film) 3550 (w), 3450 (m br), 2960 (s), 2920 (s), 2860 (s), 1470 (w), 1450 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.06 (s, 3 H), 1.34 (s, 3 H), 1.4–2.2 (m, 10 H), 2.92 (br s, 1 H), 4.05 (br dd, 1 H, J = 5.1, 9.7 Hz); ^{13}C NMR (C_6D_6) δ 19.6, 24.5, 26.9, 29.1, 39.4, 41.9, 42.5, 73.8, 81.4, 87.5; high resolution mass spectrum (EI), calcd for $C_{10}H_{18}O_2$ 170.13068, found 170.1308.

***endo*-2,6-Dimethyl-9-oxabicyclo[4.2.1]nonan-2-ol (4b).** A solution of tetramethylzirconium[12] was prepared by slowly adding 6.3 mL (8.84 mmol) of 1.4 M methyllithium in ether to a flame-dried flask containing 515 mg (2.21 mmol) of zirconium tetrachloride at –20 °C under argon. The mixture was stirred for 20 min at –20 °C, at which time a solution of 155 mg (1.01 mmol) of 1-methyl-9-oxabicyclo[4.2.1]nonan-5-one (**2**) in a total of 3 mL of freshly distilled tetrahydrofuran was added. The reaction mixture was stirred for 1.5 h at –20 °C and was poured into 25 mL of 5% aqueous HCl. This mixture was extracted with 30 mL of ether, and the organic portion was extracted with 25 mL each of saturated aqueous sodium bicarbonate and brine. The ether solution was dried over sodium sulfate and concentrated to yield 155 mg (91%) of *endo*-2,6-dimethyl-9-oxabicyclo-[4.2.1]nonan-2-ol (**4b**) as a pale yellow oil: IR (thin film) 3400 (m br), 2960 (s), 2920 (s), 2870 (m), 1475 (w), 1450 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.29 (s, 3 H), 1.35 (s, 3 H), 1.5–2.3 (m, 10 H), 2.4 (br s, 1 H), 4.05 (dd, 1 H, J = 3.8, 9 Hz); ^{13}C NMR (C_6D_6) δ 20.6, 26.8, 29.5, 30.2, 39.9, 40.3, 43.2, 73.8, 82.8, 86.4; high resolution mass spectrum (EI), calcd for $C_{10}H_{18}O_2$ 170.13068, found 170.1324.

***endo*-1,5-Dimethyl-9-oxabicyclo[6.1.0]nonan-5-ol (5) and *endo*-1,5-Dimethyl-9-oxabicyclo[3.3.1]nonan-2-ol (6).** A solution of 204 mg (1.32 mmol) of 1,5-dimethylcyclooct-4-en-1-ol (**3**) in 20 mL of methylene chloride containing 278 mg (3.31 mmol) of sodium bicarbonate at 0 °C was charged portionwise with 274 mg (3.31 mmol) of 85% *m*-chloroperoxybenzoic acid over 30 min and stirring was continued for 6 h at 0–15 °C. The reaction mixture was decanted and was extracted twice with 20 mL of saturated sodium bicarbonate and twice with 20 mL of brine. The organic solution was dried over magnesium sulfate and was concentrated to give 291 mg of crude product, which was purified (9 g of silica; ether/petroleum ether, 1:1) to yield 91 mg (40%) of *endo*-1,5-dimethyl-9-oxabicyclo[6.1.0]nonan-5-ol (**5**) as a pale yellow oil and 65 mg (29%) of *endo*-1,5-dimethyl-9-oxabicyclo-[3.3.1]nonan-2-ol (**6**) as a pale yellow oil. Spectral data for **5**: IR (thin film) 3430 (s br), 2960 (s), 2920 (s), 2870 (s), 1470 (s), 1450 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.28 (s, 6 H), 1.4–2.2 (m, 10 H), 2.33 (s, 1 H), 2.75 (m, 1 H); ^{13}C NMR (C_6D_6) δ 21.1, 21.5, 24.9, 30.6, 35.4, 36.4, 39.1, 59.7, 63.0, 70.9. Spectral data for **6**: IR (thin film) 3400 (s br), 2980 (s), 2940 (s), 1455 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.12 (s, 3 H), 1.21 (s, 3 H), 1.4–2.3 (m, 10 H), 2.52 (s, 1 H), 3.59 (t, 1 H, J = 9 Hz); ^{13}C NMR (C_6D_6) δ 20.1, 28.6, 29.4, 30.0, 31.9, 35.1, 36.7, 69.6, 73.1, 74.5.

1,5-Dimethyl-9-oxabicyclo[3.3.1]nonan-2-one (7). A solution of 36 mg (0.211 mmol) of *endo*-1,5-dimethyl-9-oxabicyclo-[3.3.1]nonan-2-ol (**6**) in 15 mL of methylene chloride containing 180 mg of Celite was charged with 91 mg (0.423 mmol) of PCC and stirred at room temperature for 1 day. The reaction mixture was diluted with 10 mL of a mixture of ether and petroleum ether (1:1), and this was passed through a column of 4 g of alumina. The column was eluted with a further 30 mL of the mixture of ether and petroleum ether, and the eluate was concentrated to yield 32 mg (89%) of 1,5-dimethyl-9-oxabicyclo[3.3.1]nonan-2-one (**7**) as a pale yellow oil: IR (thin film) 2960 (s), 2930 (s), 2860 (s), 1720 (s), 1450 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.21 (s, 3 H), 1.35 (s, 3 H), 1.3–2.3 (m, 8 H), 2.8 (m, 2 H); ^{13}C NMR (C_6D_6) δ 18.5, 24.9, 31.5, 31.7, 33.6, 34.8, 37.1, 70.3, 80.7, 217.0; high resolution mass spectrum ($^-$OH neg. ion), calcd for (m – 1) $C_{10}H_{15}O_2$ 167.10720, found 167.1048.

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Accelerated Photodimerization of Stilbenes in Methanol and Water

Yoshikatsu Ito,* Toru Kajita, Kazuhiko Kunimoto, and Teruo Matsuura

Department of Synthetic Chemistry, Faculty of Engineering, Kyoto University, Kyoto 606, Japan

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Photodimerization of stilbenes **1a–f**, especially that of 4- and 3-acetylstilbenes (**1c** and **1d**, respectively), is more efficient when a hydroxylic solvent (methanol or water) is employed as the reaction medium than when a nonhydroxylic solvent (hexane, benzene, or acetonitrile) is employed. The stilbenes **1a–f** are more strongly fluorescent in methanol than in benzene. It is proposed that this accelerated photodimerization in the hydroxylic solvent originates from formation of a fluorescent solute–solute aggregate.

Strategies for application of hydrophobic interactions to organic syntheses have practical, mechanistic, and biological interests. As a result of the hydrophobic association of organic solutes in water, rates and selectivities of certain bimolecular reactions are profoundly changed by doing the reactions in aqueous medium. For example,

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