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Intramolecular Catalysis of Biomimetic Michael Additions to Cyclopentenones[1]

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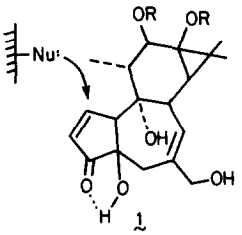
A study of the Michael addition of *n*-propyl mercaptan to a series of cyclopentenones shows that intramolecular hydrogen bonding enhances the rate. The possible significance of this observation is discussed.

The importance of biological alkylating agents is well known, and numerous studies of electrophilic conjugated systems in antitumor and cytotoxicity have appeared (*1*). The mechanism of drug action clearly involves the cooperative assistance of all the structural features present in a molecule and the active site. Of particular interest is the role of intramolecular catalysis, a special feature of multifunctional molecules which may have a profound effect on structure/activity relationships. During the course of a recent examination (*2*) of the structural features of the tumor promoter phorbol **1**, we considered that alkylation of a biological nucleophile by the reactive cyclopentenone moeity was a likely mode of action.



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Since the 4-hydroxyl group was known to be necessary for biological activity (*3*), enhancement of the reactivity of the cyclopentenone system by H-bonding with the neighboring hydroxyl group seemed like a possibility.

Intramolecular catalysis can enhance the reactivity of a multifunctional molecule. Barton and Houminer studied (*4*) the effect of a neighboring hydroxyl group on the opening of epoxides by azide ion. It was found that **2** reacts rapidly whereas the 7α-methoxyepoxide **3** is inert. It was believed that this results from intramolecular neighboring group participation which allows charge delocalization in the

[1] Contribution No. 3170 from the Department of Chemistry, Indiana University. Taken in part from a thesis of H-T. Chen (manuscript 1976).

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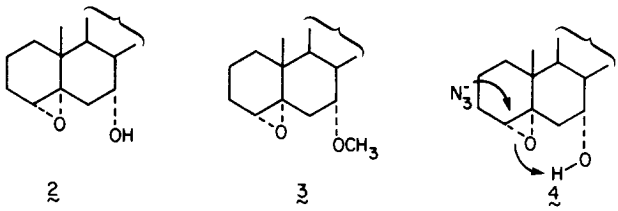
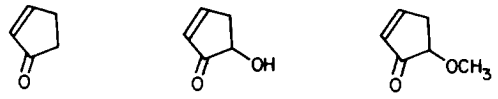
transition state (**4**). Such assistance of epoxide opening has also been suggested as a key factor in triptolide and tripdiolide antitumor activity (*5*) and in alkylation of DNA by arene oxides (*6*).[2]



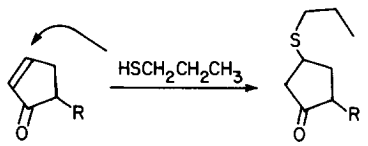
2 **3** **4**

Because there have been no studies of such intramolecular catalysis on the Michael addition reaction, the chemical reactivities of cyclopentenones **5–7**



5 **6** **7**

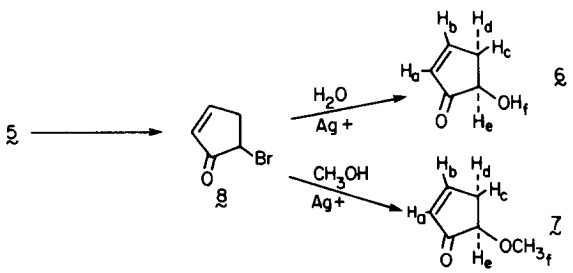
toward a model sulfur nucleophile have been studied (Eq. [1]).



[1]

SYNTHESIS AND REACTIONS OF CYCLOPENTENONES

The method of Goliasch (*8*) was used to prepare **6** and **7**. *N*-Bromosuccinimide treatment of **5** gave bromide **8**. When **8** was refluxed in water containing Ag_2O, 5-hydroxy-2-cyclopenten-1-one **6** was formed in ~50% yield.



[2] The proposal by Hubert (*6*) has subsequently been discredited. The *anti*-isomer for which H-bonding is thought not to be involved is considerably more mutagenic than the *syn*-isomer in mammalian cells. The *anti*-isomer has also been identified as the major isomer bond to DNA in rodent, bovine, and human cells (*7*). Calculations have recently supported the idea (*14*), although chemically, the *syn*-isomer is more reactive (*15*).

TABLE 1

MICHAEL ADDITION OF CYCLOPENTENONE AND ITS DERIVATIVES WITH 1-PROPANETHIOL IN DIOXANE

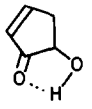
Compound	Reaction conditions			$t_{1/2}$ (hr)
	X:	SH:	H_2O	
5	1:	5:	1	120
6	1:	5:	1	84
7	1:	5:	1	120
5	1:	5:	2	168
6	1:	5:	2	108
5	1:	5:	5	180
6	1:	5:	5	240

Compound **6** shows carbonyl absorption at 1725 cm^{-1} and –OH stretch at ~3300 cm^{-1}. The nmr spectrum of **6** is quite characteristic, showing a methine proton next to oxygen 5.00 δ as well as other cyclopentenone features (*9, 10*). When bromide **8** is reacted with methanolic Ag_2O, 5-methoxy-2-cyclopenten-1-one **7** is formed in 36% yield. The ir spectrum of **7** has no –OH but C=O at 1704 cm^{-1}. The nmr spectrum shows a three-proton singlet at 3.41 δ and one proton next to oxygen at 4.56 δ.

Compounds **5–7** react slowly with *n*-propylmercaptan in $CDCl_3$ at room temperature. The reactions may be conveniently followed by nmr, monitoring the disappearance of vinyl protons and the appearance of a single-proton multiplet near 3.4 δ(–CH–S). Surprisingly, under these conditions the reaction of **5** is actually *faster* than that of **6** ($t_{1/2}$ = 33 and 46 hr, respectively). However, if the reactions are carried out in dioxane solution containing 1 mol of water, compound **6** reacts significantly faster than either **5** or **7**. If the water concentration is increased substantially, however (Table 1), the rate of reaction of **6** falls.

RESULTS AND DISCUSSION

As expected, the neighboring OH group in **6** does catalyze the Michael addition under suitable conditions (Table 1), presumably by intramolecular hydrogen bonding (**9** and **10**).



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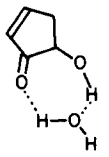

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Studies (*11*) show that a five-atom hydrogen-bonded structure such as **9** is not as favorable as a seven-atom structure such as **10**. This appears to be the case here, since a small amount of water is necessary to observe the intramolecular catalysis. A large excess of water however disrupts the delicate catalytic bridge in **10** by competition with solvent. Because of the role of solvent in the catalysis, the exact "water inventory" at a particular active site may thus be a crucial factor in determining drug activity. This could explain the failure of attempts to correlate the rate of cysteine addition with the cytotoxicity of various antitumor agents (*12*). Cyclopentenone **5** itself is reported to possess significant antitumor activity (*13*).[3]

EXPERIMENTAL

General. ^{1}H nmr spectra were recorded on a Varian HR-220 spectrometer and chemical shifts are reported in parts per million downfield from internal tetramethylsilane. Mass spectra (70 eV) were obtained on Varian MAT CH-7 and AEI MS-9 spectrometers. Infrared spectra were obtained on neat samples using a Perkin–Elmer 137 Infracord. Analytical gas chromatography was performed with a Varian Aerograph Model 940 with FID detector on 1.5% OV-101 on a Chromasorb G column (5 ft × $\frac{1}{8}$ in.) with helium carrier gas. Column chromatography work was done with MCB silica gel, 100–200 mesh.

2-Cyclopentenone (**5**). Compound **5** was purchased from Aldrich Chemical Company, Inc. Infrared (neat) 1701 cm^{-1}. Nuclear magnetic resonance ($CDCl_3$): δ = 2.32 (2H, m), 2.66 (2H, m), 6.14 (1H, m), 7.68 (1H, m).

5-Hydroxycyclopent-2-en-1-one (*6*). Compound **6** was prepared by the method of Goliasch (*9*). Infrared (neat) 3380, 1725, 1105 cm^{-1}. Nuclear magnetic resonance ($CDCl_3$) δ 2.25 ($1H_c$, dd, J_{dc} = 19, J_{cb} = 3), 2.29 ($1H_f$, broad), 2.75 ($1H_d$, dd, J_{dc} = 19, J_{de} = 7), 5.00 ($1H_e$, m), 6.15 ($1H_a$, dd, J_{ab} = 6, J_{ax} ~1), 7.51 ($1H_b$, dd, J_{ab} = 6, J_{bc} = 3). Mass spectrometry: *m/e* (relative intensity) 98 (59), 96 (20), 71 (51), 70 (55), 65 (28), 56 (20), 55 (44), 54 (20), 53 (29), 44 (40), 43 (87), 42 (100), 39 (20).

Anal. Calcd for $C_5H_6O_2$: MW = 98.0368. Found: MW = 98.0365.

5-Methoxycyclopent-2-en-1-one (*7*). 5-Bromocyclopent-2-en-1-one (2.1 g) (*9*) in 5 ml methanol was refluxed with 3 g Ag_2O at 70°C for 18 hr. After the reaction mixture was cooled the Ag_2O and AgBr were removed by filtration and washed with methanol. The methanol was removed and the residue chromatographed on silica gel to give **7** in 36% yield. Infrared (neat) 1704, 1587 cm^{-1}. Nuclear magnetic resonance ($CDCl_3$) δ 2.25 ($1H_c$, dd, J_{cd} = 19, J_{bc} = 2), 2.64 ($1H_d$, dd, J_{cd} = 19, J_{de} = 6), 3.41 ($3H_f$, s), 4.56 ($1H_e$, m), 6.20 ($1H_a$, dd, J_{ab} = 6, J_{ax} ~1), 7.61 ($1H_b$, dd, J_{ab} = 6, J_{bc} = 2). Mass spectrometry: *m/e* (relative intensity) 112 (68), 84 (67), 82 (52), 81 (52), 69 (38), 58 (37), 54 (32), 53 (100), 43 (50), 41 (50).

Anal. Calcd for $C_6H_8O_2$: MW = 112.0525. Found: MW = 112.0525.

Kinetics. Michael addition reactivities of cyclopent-2-en-1-one (**5**), 5-hydroxy-

[3] To our knowledge, compound **6** has not been evaluated biologically, however, it is reported (*8*) to be a strong skin irritant.

cyclopent-2-en-1-one (6), and 5-methoxycyclopent-2-en-1-one (7) toward 1-propanethiol in dioxane, at various water ratios, were studied in sealed nmr tubes using dioxane as internal standard. The following serves as an example: 19.6 mg (0.2 mmol) of 6 and 76 mg (1 mmol) of 1-propanethiol were dissolved in 0.4 ml dioxane (dried over $LiAlH_4$) containing a calculated amount of H_2O (0.2 mmol) added by syringe. The reaction was followed by integration of the vinyl protons of 6 at 6.15 δ and 7.51 δ with respect to the dioxane singlet at 3.7 δ.

ACKNOWLEDGMENTS

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REFERENCES

1. E. FUJITA AND Y. NAGAO, *Bioorg. Chem.* **6**, 287 (1977).
2. S. R. WILSON AND J. C. HUFFMAN, *Experientia* **32**, 1489 (1976).
3. E. HECKER AND R. SCHMIDT, *Fortschr. Chem. Org. Naturst.* **31**, 378 (1974).
4. D. H. R. BARTON AND Y. HOUMINER, *J. Chem. Soc. Chem. Commun.*, 839 (1973).
5. S. M. KUPCHAN AND R. M. SCHUBERT, *Science* **185**, 791 (1974).
6. P. B. HULBERT, *Nature (London)* **256**, 146 (1975).
7. A. M. JEFFREY, I. B. WEINSTEIN, K. W. JENNETTE, K. GRZESKOWIAK, K. NAKANISHI, R. G. HARVEY, H. AUTRUP, AND C. HARRIS, *Nature (London)* **269**, 348 (1977).
8. K. HAFNER AND K. GOLIASCH, *Chem. Ber.* **94**, 2909 (1961).
9. C. H. DEPUY, C. E. LYONS, AND L. B. RODEWALD, *J. Chem. Eng. Data* **11**, 102 (1966).
10. M. P. L. CATON, G. DARNBROUGH, AND T. PARKER, *Syn. Commun.* **8**, 155 (1978).
11. R. D. GANDOUR, *Tetrahedron Lett.*, 295 (1974).
12. S. M. KUPCHAN, M. A. EAKIN, AND A. M. THOMAS, *J. Med. Chem.* **14**, 1147 (1971).
13. K-H. LEE, I. H. HALL, E-C. MAR, D. O. STARNES, S. A. ELGEBALY, T. G. WADDELL, R. I. HADGRAFT, C. G. RUFFNER, AND I. WEIDNER, *Science* **196**, 533 (1977).
14. C. Y. YEH, P. P. FU, F. A. BENALD, AND R. G. HARVEY, *Bioorg. Chem.* **7**, 497 (1978).
15. H. YAGI, O. HERNANDEZ, AND D. M. JERINA, *J. Amer. Chem. Soc.* **97**, 6881 (1975).