Halogenated Ketenes. XVI. Steric Control in Unsymmetrical Ketene–Olefin Cycloadditions[1]

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Abstract: The *endo*:*exo*-methyl isomer ratios for the cycloaddition of methylchloroketene with cyclohexene, 1,3-cyclohexadiene, cyclooctene, and dihydropyran were found to vary from only 4.5 to 5.1. The isomer ratios for the cycloaddition of methylbromoketene with 1,3-cyclohexadiene, dihydropyran, and ethyl vinyl ether were 0.53–0.60 *endo*:*exo*-methyl. A quantitative relationship utilizing Taft's substituent constants (E_s) for the ketene substituents is described which reveals that the strong preference for endo or cis selectivity is due to the size of the larger substituent on the ketene molecule.

The stereochemistry of the cycloaddition of unequally substituted ketenes to cyclopentadiene has recently received a considerable amount of attention.[1-8] The isomer with the larger ketene substituent in the endo position has been found to be very strongly sterically preferred. This isomer has even been formed to the exclusion of the exo isomer when a large difference in size exists between the two ketene substituents. Moreover, the orthogonal ketene–olefin transition state model proposed by Woodward and Hoffmann predicts this stereochemistry.[9]

We now wish to report on the stereochemistry of the cycloaddition of some unequally substituted ketenes with some olefins other than cyclopentadiene. The results reveal that the unusual stereoselectivity in [2 + 2] cycloadditions of this type is due to the steric requirements associated with the ketene substituents.

Methylchloro- and methylbromoketenes were selected because of the ease in distinguishing the isomers by nmr. The methyl resonance appears as a singlet and the chemical shift of the *endo*-methyl is considerably more upfield than the *exo*-methyl resonance.[6,8] Consequently, the nmr spectrum not only distinguishes the isomers, but also yields the distribution of the isomers.

Methylchloro- and methylbromoketenes were prepared by the dehydrohalogenation of 2-halopropanoyl halides. Due to the labile nature of the ketenes, the cycloadditions were run *in situ* by effecting the dehydrohalogenation with triethylamine in hexane in the presence of the olefin. The isomer distributions were determined during and after the dehydrohalogenation by nmr and vpc.

Results and Discussion

The isomer ratios thus determined, together with some previous results, are summarized in Table I. The variations in the yields of the cycloadducts are undoubtedly due to the differences in reactivities of the various olefins. It is well known that activated or nucleophilic olefins are more reactive in ketene cycloadditions than simple olefins.[10]

It is quite interesting that both methylchloro- and methylbromoketenes underwent cycloaddition with the variety of olefins listed with such a small variation in the *endo*:*exo*-methyl ratio of isomers. Since these olefins are of widely varying reactivities, the electronic effects in the two transition states leading to the two

Table I. Stereochemistry of Methylchloro- and Methylbromoketene Cycloadditions in Hexane

Compd	Ketene	Olefin	*endo*:*exo*-Methyl ratio	Temp, °C	% yield
	MCK[a]	Cyclopentadiene	4.3	0–5	75
	MCK[a]	Cyclopentene	4.2	0–5	35
I	MCK	Cyclohexene	4.5	25	26
II	MCK	1,3-Cyclohexadiene	4.9	25	50
III	MCK	Cyclooctene	5.1	25	15
IV	MCK	Dihydropyran	5.0	25	40
	MBK[a]	Cyclopentadiene	0.71	0–5	63
V	MBK	1,3-Cyclohexadiene	0.53	25	40
VI	MBK	Dihydropyran	0.60	25	50
VII	MBK	Ethyl vinyl ether	0.59	25	39

[a] Reference 6.

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isomers are either negligible or cancel and the isomer ratios are sterically controlled by the ketene substituents.

This led us to examine a quantitative relationship utilizing Taft's substituent constants (E_s) for the ketene substituents.[11] We took the *endo*:*exo*-alkyl isomer ratios for a series of alkylbromoketene–cyclopentadiene adducts[8,12] (Table II) and found a linear relationship

Table II. Alkylbromoketene–Cyclopentadiene Adduct Isomer[a] Distributions in Hexane at 25°

Ketene	ΔE_s	Endo:exo isomer ratio
Methylbromo-	0	0.71
Ethylbromo-	−0.07	1.6
Isopropylbromo-	−0.47	6.7
tert-Butylbromo-	−1.54	~100

[a] Reference 8.

between the logarithms of the isomer ratios and the Taft substituent constants for the alkyl substituents on the ketene; log endo:exo = $1.5\Delta E_s$. This relationship enables quantitative or at least semiquantitative predictions to be made regarding the stereochemistry of unsymmetrical ketene cycloadditions. If one of the substituents on the unsymmetrical ketene is methyl or bromo, the ΔE_s value is simply the E_s of the other substituent on the ketene since E_s for both bromo and methyl groups is zero. This is illustrated with the methylethylketene–cyclopentadiene system. The E_s value for the ethyl substituent is −0.07; hence the predicted isomer ratio is 1.3 *endo*:*exo*-ethyl. The experimental value was 1.5.[2]

We have reported along with others on the stereochemistry of unsymmetrical ketenes and cyclopentadiene. The above described relationship predicts the results obtained as illustrated in Table III.

Table III. Predicted and Experimental Isomer Ratios of Some Unsymmetrical Ketene–Cyclopentadiene Adducts

Ketene	ΔE_s	Endo:exo isomer ratios[a] Predicted	Found[b]	Ref
Methylethyl-	0.07	1.3	1.5	*c*
Methylchloro-	0.18	1.9	4.3	*d*
Methyliodo-	0.20	2.0	2.0	
Phenylbromo-	0.90	22	>20	*e*
Phenylmethyl-	0.90	22	>20	*e*
Bromo-	1.24	72	>20	*f*
Methyl-	1.24	72	>20	*f*

[a] The endo isomer is the isomer with the largest substituent on the ketene in the endo position. [b] All of the isomer distributions were obtained from preparations in hexane at 25° except the methylethylketene adduct which was prepared in chloroform at 20°. Isomer distributions were determined by vpc and nmr methods and the limits of detection are at least >5%. [c] Reference 2. [d] Reference 6. [e] Reference 7. [f] Reference 5.

It is pertinent to note that the constant, 1.5, in the above equation was obtained by employing a series of alkylbromoketene–cyclopentadiene adducts. Consequently, the predictions for bromo- and methyl-substituted ketenes are relatively good. However, this constant should be reevaluated for other series of ketenes.

In conclusion, these ketene–olefin cycloadditions owe the strong preference for endo or cis selectivity to the size of the larger substituent on the ketene molecule.

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(12) This series was selected because the Taft substituent constants for the bromo and methyl substituents are zero.

Experimental Section

Proton nmr spectra were recorded on a Varian A-60 nmr spectrometer employing tetramethylsilane as an internal standard. Vapor phase chromatography (vpc) was accomplished on an F & M Scientific Model 700 chromatograph employing a 10 ft × 1/4 in. column packed with 2% silicone fluid FS-1265, QF-1 on Chromosorb G. All of the acid halides were prepared from commercially available acids by standard procedures. Hexane was dried over Linde 4A molecular sieve. The olefins, cyclohexene, 1,3-cyclohexadiene, cyclooctene, dihydropyran, and ethyl vinyl ether were commercially available and were dried over molecular sieve and further purified by fractional distillation immediately prior to each cycloaddition.

General Procedure for *in Situ* Ketene–Olefin Cycloadditions. To a solution of 0.2 mol of triethylamine and 0.5 mol of olefin in 200 ml of hexane was added 0.2 mol of acid halide in 25 ml of hexane. The addition was made dropwise over a period of 1 hr with good stirring. After the addition was complete, the stirring was continued for 2 hr. The amine salt was removed by filtration and washed with three 50-ml portions of hexane. The filtrate was concentrated without heating on a vacuum rotoevaporator. The isomer distribution was determined by nmr and vpc during the addition of reagents, after the 2-hr stirring period, and on the concentrated reaction mixture. No variation was ever observed in the isomer distributions. The concentrated reaction mixture was vacuum distilled through a 6- or 12-in. Vigreux column. The yields were based on the total *endo*- and *exo*-methyl isomers from the fractional distillation. The *endo*- and *exo*-methyl isomers were separated by vpc in almost every case.

8-Chloro-8-methylbicyclo[4.2.0]octan-7-one (I). Distillation of the concentrated reaction mixture afforded a 26% yield of crude product at 55–67° (1.0 mm). Successive fractionations of the isomer mixture yielded a fraction at 57–58° (1.0 mm) that had an *endo*:*exo*-methyl distribution of >10: ir both isomers, 1800 cm^{-1} (C=O); nmr (CCl_4) *endo*-methyl isomer, δ 1.45 (s, 3 H), 1.8 (m, 8 H), 2.8 (m, 1 H), 4.1 (m, 1 H). The *exo*-methyl isomer had a singlet at δ 1.72 but this higher boiling fraction was contaminated with side reaction products.

Anal. Calcd for $C_9H_{13}ClO$: C, 62.60; H, 7.55. Found: C, 62.37; H, 7.41.

8-Chloro-8-methylbicyclo[4.2.0]oct-2-en-7-one (II). This compound was prepared using 1/10th of the quantities described in the general procedure above. Consequently, the yield was estimated by vpc. The isomers were separated by vpc: ir, both isomers, 1800 (C=O) and 1607 cm^{-1} (C=C); nmr (CCl_4) *endo*-methyl isomer, δ 1.47 (s, 3 H), 1.6–2.6 (m, 4 H), 3.71 (m, 1 H), 4.23 (m, 1 H), and 5.95 (m, 2 H). The *exo*-methyl appeared as a singlet at δ 1.77.

Anal. Calcd for $C_9H_{11}ClO$: C, 63.34; H, 6.45. Found: C, 63.51; H, 6.53.

10-Chloro-10-methylbicyclo[6.2.0]decan-9-one (III). The isomers distilled at 122–129° (0.5 mm). Careful fractionation yielded a fraction at 122–124° (0.5 mm) with an *endo*:*exo*-methyl isomer distribution of >10: ir, both isomers, 1800 cm^{-1} (C=O); nmr (CCl_4) *endo*-methyl isomer, δ 1.43 (s, 3 H), 1.2–1.7 (m, 12 H), 2.8 (m, 1 H), 3.6 (m, 1 H). A singlet at δ 1.72 was attributed to the *exo*-methyl isomer. The product was contaminated with some unidentified decomposition products and a 2,4-dinitrophenylhydrazone derivative was prepared.

Anal. Calcd for $C_{17}H_{21}N_4O_4Cl$: C, 53.60; H, 5.52; N, 14.72. Found: C, 53.34; H, 5.64; N, 14.51.

8-Chloro-8-methyl-2-oxabicyclo[4.2.0]octan-7-one (IV). The crude adduct distilled at 45–67° (0.8 mm) but successive fractionations yielded a fraction at 56–57° (0.8 mm) with an *endo*:*exo*-methyl ratio of >20 and a fraction at 66–67° (0.8 mm) with an *endo*:*exo*-methyl distribution of <0.1: ir, both isomers, 1800 cm^{-1} (C=O); nmr (CCl_4) *endo*-methyl isomer, δ 1.51 (s, 3 H), 1.6 (m, 4 H), 3.5 (m, 2 H), 3.9 (m, 1 H), 4.28 (d, 1 H); *exo*-methyl isomer, δ 1.68 (s, 3 H), 1.6 (m, 4 H), 3.5 (m, 2 H), 3.7 (m, 1 H), 3.89 (d, 1 H).

Anal. Calcd for $C_8H_{11}ClO_2$: C, 55.02; H, 6.32. Found: C, 54.87; H, 6.39.

8-Bromo-8-methylbicyclo[4.2.0]oct-2-en-7-one (V). The reagents were reduced by $^1/_{10}$th that described in the general procedure. Consequently, the yield of cycloadduct was estimated by vpc. The isomers were separated by vpc: ir, both isomers, 1800 (C=O) and 1607 cm^{-1} (C=C); nmr (CCl_4) *exo*-methyl isomer, δ 1.92 (s, 3 H), 1.6–2.6 (m, 4 H), 3.6 (m, 1 H), 4.05 (m, 1 H), 5.95 (m, 2 H); *endo*-methyl isomer revealed a singlet at δ 1.59.

Anal. Calcd for $C_9H_{11}BrO$: C, 50.23; H, 5.12. Found: C, 50.34; H, 5.25.

8-Bromo-8-methyl-2-oxabicyclo[4.2.0]octan-7-one (VI). Distillation of the concentrated reaction mixture yielded the crude product at 75–88° (1.0 mm). Successive fractionations of this isomer mixture yielded a fraction at 76–77° (1.0 mm) which had an *endo*:*exo*-methyl isomer distribution of >10 and a fraction at 86–88° (1.0 mm) with an endo:exo distribution of <0.2: ir, both isomers, 1800 cm^{-1} (C=O); nmr (CCl_4) *endo*-methyl isomer, δ 1.60 (s, 3 H), 1.6 (m, 4 H), 3.5 (m, 2 H), 3.9 (m, 1 H), 4.35 (d, 1 H); *exo*-methyl isomer, δ 1.85 (s, 3 H), 1.6 (m, 4 H), 3.5 (m, 2 H), 3.7 (m, 1 H), 4.03 (d, 1 H).

Anal. Calcd for $C_8H_{11}BrO_2$: C, 43.84; H, 5.02. Found: C, 43.71; H, 5.14.

2-Bromo-2-methyl-3-ethoxycyclobutanone (VII). The mixture of isomers distilled at 39–45° (0.4 mm) with some decomposition occurring during distillation. An analysis of the fractions from successive fractionations indicated that the adducts were unstable to heat as one of the decomposition products was found to be the starting vinyl ether. A rapid vacuum distillation afforded a fraction at 39–40° (0.4 mm) with an *endo*:*exo*-methyl isomer ratio of 0.9. The starting ethyl vinyl ether, which appeared as a decomposition product in this fraction, was removed by rotoevaporation prior to elemental analysis: ir, both isomers, 1800 cm^{-1} (C=O); nmr (CCl_4) both isomers, δ 1.25 (t, 3 H), 1.73 (s, 1.5 H), 1.80 (s, 1.5 H) 3.2 (m, 2 H), 3.6 (q, 2 H), 4.3 (m, 1 H).

Anal. Calcd for $C_7H_{11}BrO_2$: C, 40.51; H, 5.32. Found: C, 40.37; H, 5.34.

7-Iodo-7-methylbicyclo[3.2.0]hept-2-en-6-one. An 80% yield of cycloadduct was obtained which distilled at 77–80° (1.6 mm): ir, both isomers, 1780 (C=O) and 1640 cm^{-1} (C=C); nmr (CCl_4) both isomers, δ 1.77 (s, 1 H), 2.14 (s, 2 H), 2.6 (m, 2 H), 4.2 (m, 2 H), 5.9 (m, 2 H).

Anal. Calcd for C_8H_9IO: C, 38.75; H, 3.63. Found: C, 39.06; H, 3.93.

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The 4-Dechlorination of 4,6-Disubstituted Steroids

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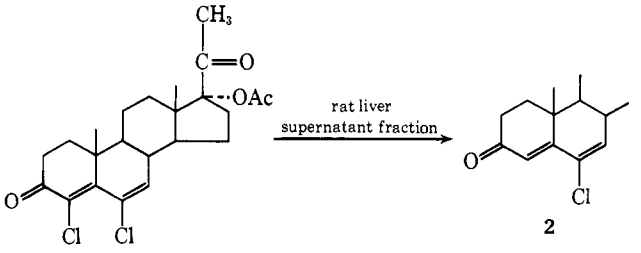
Abstract: Treatment of a steroid incorporating the 4,6-dichloro-4,6-dien-3-one system with various mercaptans results in 4-dechlorination. The 4-chloro-6-methyl and 4-monochloro analogs are also dechlorinated but to a lesser extent. Possible mechanisms for these transformations are discussed.

Earlier work from these laboratories[1] has shown that the major *in vitro* metabolite of the 4,6-dichloro steroid **1**[2] using 105,000 *g* rat liver supernatant fraction is the 6-chloro compound **2**.[3] It was also demonstrated that conditions which usually suffice to denature an enzyme (boiling, acidification) did not completely inhibit the dechlorination reaction.[1] This led us to suspect that the *in vitro* dechlorination of **1** is not necessarily an enzymatic process.



1 **2**

Hydride transfer was initially considered as a possible mode of 4-dechlorination, but no dependence on the pyridine nucleotides NADPH or NADH could be demonstrated. Sulfhydryl compounds, functioning in an oxidation–reduction reaction, were then considered as 4-dechlorinating agents. We first investigated the heat-stable, ubiquitous tripeptide, glutathione (GSH, **3**),[4] which is the most abundant sulfhydryl compound in most mammalian tissues. Incubation of **1** with 100 mol equiv of GSH at 37° in pH 7.4 buffer afforded an 80% yield of **2**. The dechlorination could also be carried out on a preparative scale at 25° using 2.5 mol equiv of GSH in methanol containing dilute sodium hydroxide. The product was identified by spectral data and by mixture melting point with authentic **2**.[3] No dechlorination of **1** was observed using oxidized GSH. The GSH-mediated 4-dechlorination in buffer was pH dependent and gave better yields at pH's higher than 7.4. Complete inhibition by a 10% molar excess of the known sulfhydryl group inhibitors, *N*-ethyl maleimide and iodoacetamide,[5] demonstrated that the sulfhydryl group of GSH is essential for the dechlorination.

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