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STRUCTURAL ASSIGNMENTS OF STEREOISOMERIC CYCLOBUTANONES BY SUBSTITUENT INCREMENTS ON CHEMICAL SHIFTS

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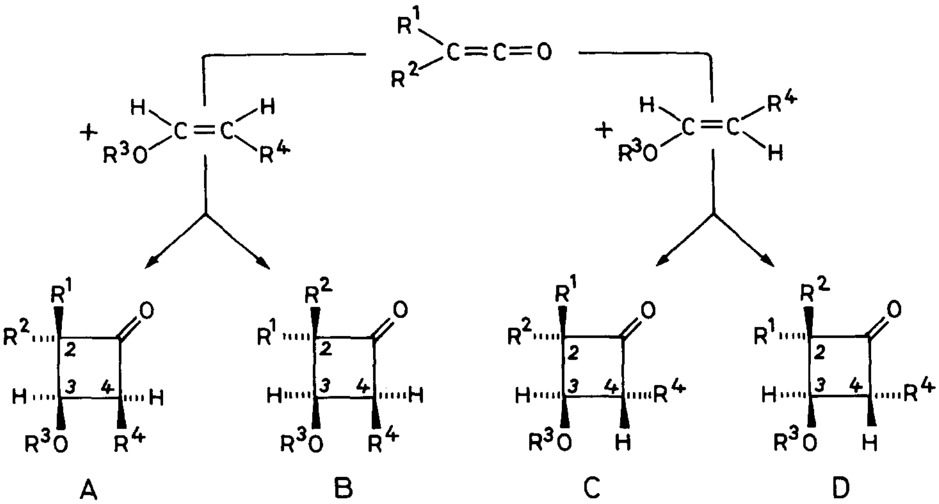
The cycloaddition of alkylphenylketenes to cis-trans isomeric enol ethers provides cyclobutanones with three chiral centers. Thus, four diastereomeric pairs of enantiomers are conceivable.



R^1, R^2 = alkyl and/or phenyl, R^3 = alkyl, R^4 = alkyl or H

Ketene cycloadditions to enol ethers proceed stereospecifically with retention of the ketenophile configuration (1). Thus, the relative configuration at the positions 3 and 4 is determined by the choice of the enol ether. A distinction between A and B or C and D is based on the chemical shift of the 3-H.

It was noticed in the nmr spectra ($CDCl_3$, 60 MHz) of the cyclobutanones with $R^1 = R^2$ that the 3-H absorbs at higher field in the cycloadducts of trans-1-alkenyl ethers (R^3O and R^4 trans) (1-3). The generalization is permissible that ring protons are more strongly shielded by cis-vic- than by trans-vic-alkyl. On the other hand, cis-vic- and trans-vic-phenyl appear to be equally effective in deshielding cyclobutanone ring protons as testified by the AA'X spectrum of the ring protons in 2,2,3-triphenylcyclobutanone (4). Therefore, one expects the 3-H of cyclobutanones A and C at higher field than in B and D for R^1 = phenyl and R^2 = alkyl ; that provides a convincing argument for the assignment of all four diastereomers.

The cyclobutanones A and C as well as B and D are interconverted by epimerization at C-4 - probably *via* the enolate - in the presence of alumina (activity 4, Woelm) in benzene. Thus, even those adducts are accessible which are not directly formed from the reactants. The equilibrated mixtures contain predominantly the diastereomers with R^3O and R^4 trans located, *i.e.*, C and D.

Additivity of substituent influences on chemical shifts is assumed for the statistical analysis. For each of the 59 cyclobutanones investigated an equation of the general type

$$8.04 + a_1T_1 + a_2T_2 + \ldots a_nT_n = \tau(3\text{-H})$$

is set up in which 8.04 is the τ(3-H) of the unsubstituted cyclobutanone (5), and a_i is the number of substituents with the effect T_i on τ(3-H) in ppm. The system of 59 equations with 17 unknown was solved by using the least squares subroutine LEASQ2 (6). Table 1 shows the calculated substituent influences and their standard deviations (7).

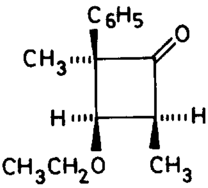
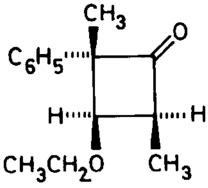
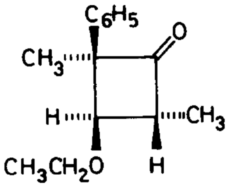
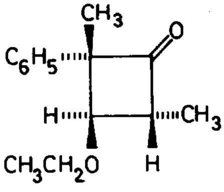
Table 1. Substituent influences on τ(3-H) of 59 cyclobutanones in $CDCl_3$ in ppm ; in brackets frequency of the substituent. Base : τ(3-H) = 8.04 for cyclobutanone.

Substituent	in 3-position	in 2- or 4-position	
		cis-vic	*trans*-vic
Methoxy (2)	-2,16 ± 0.11		
Ethoxy (40)	-2.17 ± 0.09		
Isopropoxy (3)	-2.38 ± 0.10		
Butoxy (5)	-2.10 ± 0.09		
t-Butoxy (9)	-2.34 ± 0.09		
Methyl (51)		+0.37 ± 0.03	-0.01 ± 0.03
Ethyl (20)		+0.28 ± 0.03	-0.00 ± 0.03
Propyl (4)		+0.33 ± 0.05	+0.08 ± 0.05
Isopropyl (16)		+0.12 ± 0.04	-0.06 ± 0.04
t-Butyl (5)		+0.01 ± 0.05	-0.15 ± 0.04
Phenyl (65)		-0.28 ± 0.03	-0.31 ± 0.03

Calculation of τ(3-H) with these parameters reproduces the experimental values with the standard deviation of ± 0.06 ppm ; the deviation never exceeds 0.12 ppm (some examples in Table 2).

cis-vic-Methyl shifts the 3-H signal of cyclobutanones by 0.37 ppm to higher field, while trans-vic-CH_3 is virtually without influence. With increase of branching cis-vic-alkyl loses its shielding effect and trans-vic-alkyl becomes slightly deshielding. Weitkamp and Korte (8) observed the following methyl influences on the τ values of ring-H of cyclobutanes : cis-vic +0.31, trans-vic -0.19 ppm. Sustmann, Huisgen, and Huber (9) found effects of +0.28 for cis-vic- and +0.01 ppm for trans-vic-methyl in 2-pyrazolines and 2-isoxazolines. However, in 2-pyrazolines and 2-isoxazolines cis-vic-C_6H_5 shifts τ(ring H) by -0.11 and trans-vic-C_6H_5 by -0.51 ppm, while in cyclobutanones the two effects are within the error limits (Table 1). This difference might be caused, i.a., by the spreading of bond angles in four-membered rings.

Table 2. Experimental and calculated τ values of 3-H and 3-OCH_2CH_3 in cyclobutanones

		 A	 B	 C	 D
τ(3-H)	Calcd.	5.92	5.57	6.30	5.95
	Exp.	6.00	5.62	6.30	6.01
$\tau(O\underline{CH_2})$	Calcd.	6.65	6.46	6.50	6.31
	Exp.	6.37	–	6.57	6.39
$\tau(OCH_2\underline{CH_3})$	Calcd.	9.01	8.80	8.91	8.70
	Exp.	9.11	8.76	8.98	8.76

The chemical shifts of the O-ethyl protons in 3-ethoxycyclobutanones confirm the above structural assignments. The O-ethyl protons of A and C are located in the diamagnetic shielding cone of the cis-vic-phenyl and are shifted by ~ 0.2 ppm to higher field compared with B and D (Table 2). The statistical evalution of the substituent influences furnishes τ = 6.51 ± 0.16 for $O\underline{CH_2}CH_3$ and 8.79 ± 0.09 for $OCH_2\underline{CH_3}$ of the parent compound (10). Table 3 reveals that only cis-vic-phenyl exerts a sizable effect.

Table 3. Substituent influences on the τ values of the ethoxy protons in 35 substituted 3-ethoxycyclobutanones

Substituent in 2 or 4	Δτ in $O\underline{CH_2}CH_3$	Δτ in $OCH_2\underline{CH_3}$
cis-Alkyl	+0.03 ± 0.06	+ 0.03 ± 0.03
trans-Alkyl	-0.12 ± 0.06	-0.07 ± 0.03
cis-Phenyl	+0.23 ± 0.07	+0.26 ± 0.04
trans-Phenyl	-0.11 ± 0.07	-0.05 ± 0.04

The $O\underline{CH_2}CH_3$ protons of substituted ethoxycyclobutanones are diastereotopic and, therefore, give rise to ABX_3 spectra. Only in the presence of two *cis*-vic. substituents, of which one is phenyl, are the τ values of the CH_2 protons noticeably different. On the other hand, in *cis*- and in *trans*-substituted 3-isopropoxycyclobutanones one always observes two methyl doublets.

The coupling constants of the ring protons are less useful for the structure determination of ketene cycloadducts than the substituent influences. $J_{3.4}$(cis) = 7.4 - 8.4 Hz and $J_{3.4}$(trans) = 5.9 - 6.8 Hz are the experimental ranges. It is not recommendable to base an assignment on such small differences, the less so as even examples of $J_{cis} < J_{trans}$ in four-membered rings have been described (11,12).

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