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Facial selectivity in the reaction of dihalocarbenes with 2-substituted 4,7-dihydro-1,3-dioxepines

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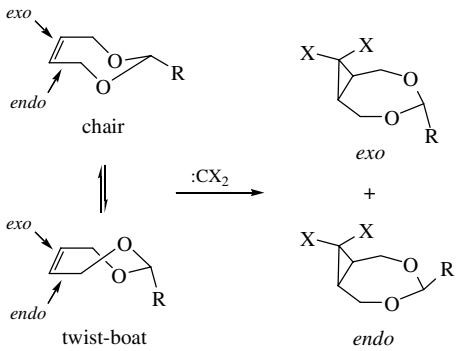
The dichloro(dibromo)cyclopropanation of conformationally heterogeneous 2-substituted 4,7-dihydro-1,3-dioxepines was found to afford a low selectivity; *endo* addition on the side of a remote alkyl substitutent is governed by the π-facial solvation of substrates.

The inspection of electronic, steric and solvation terms controlling π-facial selectivity is of great theoretical and commercial interest in organic chemistry due to diverse reactions at the sp^2 reactive centre. The role of the conformational properties of substrates in the formation of the stereochemical outcome is poorly known.[1,2] Conformationally heterogeneous 2-substituted 4,7-dihydro-1,3-dioxepines **1a–d** are suitable objects in [4 + 2] cycloaddition reactions with dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate[3,4] and hexachlorocyclopentadiene.[5] The substrates exist in solution as an equilibrium of the forms with different spacial architectures: chair with equatorial alkyl and twist-boat conformations. For acetals **1a–c**, the twist-boat form dominates (4:1), whereas for **1d** the ratio is found to be inversed.[3,6] According to Curtin–Hammet/Winstein–Holness concepts, the overall kinetic description of such reactions leading to cross products is complicated and the stereochemical outcome appeared to be a function of four reaction rate constants and the ground state conformational population.[7] Note that the chair conformation has C_s symmetry but the twist-boat one belongs to the C_2 point group. Both *endo* and *exo* approaches to the double bond of the twist-boat form are practically equal for an incoming reagent. The stereodefined environment of the double bond in the chair conformation dictates the *exo* face to be more accessible. Thus, the symmetry arguments render the stereochemical course of reactions with the participation of chair and twist-boat forms quite different. The stereochemical results of the Diels–Alder reaction above[3,4] revealed that π-facial selectivity was exclusively



1a R = Me
1b R = Et
1c R = Pr^i
1d R = Bu^t

2 X = Cl
3 X = Br

Scheme 1

Table 1 Reaction conditions of dihalocarbene cycloaddition to 2-substituted 4,7-dihydro-1,3-dioxepines and *endo*-isomers **2** and **3**, fraction (%).[a]

R	$CHCl_3$/ 50% NaOH/ BTEAC[b]	$CHBr_3$/ 50% NaOH/ BTEAC	CCl_3COOEt/ MeONa	Decomposition of CCl_3COONa[c]
Me	54	55	—	—
Et	53	56	55	54
Pr^i	54	55	—	—
Bu^t	57	58	60	—

[a]The accuracy is ±3. [b]Increasing the temperature from 298 up to 333 K did not change the product ratio. [c]In pentane and $CHCl_3$.

sensitive to the conformational equilibrium constant, the bulk of the remote substituent and, finally, the solvent effect. It seems reasonable to clarify the peculiarities of seven-membered unsaturated acetals **1a–d** in the reactions with dichloro(dibromo)-carbenes (Scheme 1). According to modern concepts, a low selectivity of dihalocyclopropanation reactions is surely a reflection of both a low activation energy and earlier transition state.[8,9]

Several methods were applied in carbene generation.[10] We have used the two-phase Makosza method for CCl_2 (CBr_2)[†] formation; ethyl[‡] and sodium[§] trichloroacetates served as a source of CCl_2. The results are collected in Table 1.

The Makosza procedure gave the highest yields (50–70%) of the products. Under ultrasonic irradiation, reaction times were

[†] A 50% solution containing 7 g of NaOH was added to a solution of 43.5 mmol of the corresponding 2-substituted 4,7-dihydro-1,3-dioxepine and 0.3 g (1 mmol) of benzyltriethylammonium chloride (BTEAC) in 28 ml of $CHCl_3$ at 278 K for 2 h. The reaction mixture was stirred for 50 h at room temperature, diluted with CH_2Cl_2 and washed with water. The organic layer was separated and dried over Na_2SO_4.

Dibromocarbene formation procedure is similar, and 30.5 ml of $CHBr_3$ was used. A UZDN-A device with a frequency of 20 kHz was used for ultrasonic activation.

[‡] 10 g (52.2 mmol) of ethyl trichloroacetate was added to the suspension of 7.3 g (135.2 mmol) of sodium methoxide and 46 mmol of 2-substituted 4,7-dihydro-1,3-dioxepine in 25 ml of pentane with stirring at 270 K for 15 min. The reaction mixture was stirred for 8 h at room temperature, diluted with CH_2Cl_2 and washed with water. The organic layer was separated and dried over Na_2SO_4; the unreacted starting material was evaporated. The same procedure was applied to the reaction in $CHCl_3$.

[§] The mixture of 3 g (23.4 mmol) of 2-ethyl-4,7-dihydro-1,3-dioxepine, 24.5 g (132.2 mmol) of sodium trichloroacetate and 0.5 g (1.6 mmol) of BTEAC in 30 ml of $CHCl_3$ was stirred at 333 K for 7 h, diluted with CH_2Cl_2 and washed with water. The organic layer was separated and dried over Na_2SO_4, and the unreacted starting material was evaporated.