Face selectivity in electrophilic additions to methylenenorsnoutanes: relative importance of through-space, through-bond and electrostatic interactions

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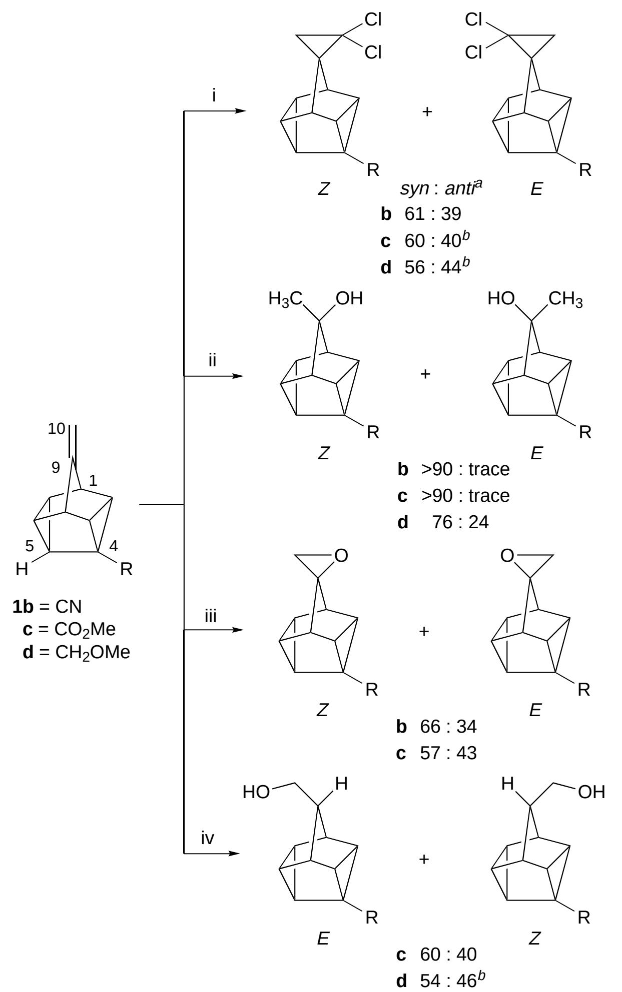
4-Substituted 9-methylenenorsnoutanes undergo a variety of electrophilic additions with a small but consistent *syn* preference; *ab initio* MESP maps indicate that electrostatic factors and through-space interaction between the double bond and cyclopropane Walsh orbitals are unimportant in determining the face selectivity, while AM1 transition state energetics suggest that the observed preferences are determined primarily by through-bond interactions.

The origin of π-face selectivity in sterically unbiased substrates continues to be a challenging problem in spite of many innovative experimental[1a–d] and theoretical investigations.[1c–e] While the importance of hyperconjugative interactions has been clearly demonstrated in electrophilic additions in several olefinic substrates,[2a–c] the competing role of electrostatic effects has been equally well established in nucleophilic additions to related carbonyl derivatives.[1d–e,2d] However, the mode by which some substituents, like the vinyl and aryl groups, induce face selectivity is often complex.[1a,2d] Recently, the cyclopropyl ring has also been shown to exhibit unusual trends in selectivity. Three-membered ring fusion causes *anti* selectivity in electrophilic additions to 7-methylenenorbornanes, but a *syn* preference in isomeric bicyclo[2.2.2]octenes.[3] This reversal is especially surprising because through-space interaction between the olefinic bond and a cyclopropane Walsh orbital is strong in both substrates on the basis of photoelectron spectral studies.[4] In order to critically evaluate the relevance of such orbital interactions in the context of alternative models, we now report the results of a combined experimental and computational examination of face selectivity in electrophilic additions to 4-substituted 9-methylenenorsnoutanes **1**. These substrates enable a comparison of the effect of two subtly different cyclopropyl units in a truly sterically unbiased environment. This study complements our earlier investigation of nucleophilic additions to the corresponding ketones,[5] in which significant face selectivity was observed and attributed to effective transmittal of orbital and electrostatic effects through three-membered rings.

The 9-methylenenorsnoutanes **1b**–**d**, readily synthesized from the corresponding ketones[5] *via* Wittig olefination ($Ph_3P^+MeBr^-$, Bu^tOK, 80%), were subjected to dichlorocarbene addition, oxymercuration, epoxidation and hydroboration reactions (Scheme 1). The structures of the *E*,*Z*-diastereomers were deduced on the basis of ^1H and ^{13}C NMR data, but more specifically from (i) the greater deshielding of H-5 in the *E*-series compared to *Z*-series, (ii) the relative deshielding of H-2 and H-3 in the *Z*-series compared to the *E*- series and (iii) the deshielding of the quaternary C-4 carbon resonances in the *Z*-series compared to *E*-series. These observations could be further confirmed through selected lanthanide-induced shift (LIS) studies.

All the derivatives **1b–d** show a consistent preference for *syn* face addition. As noted in earlier studies[1,2] on remotely substituted 7-methylenenorbornanes and 2-methyleneadamantanes, oxymercuration shows the highest facial preference. Neutral electrophiles exhibit modest selectivity.

In order to interpret the above results, the topographical features of the molecular electrostatic potentials (MESP) of methylenenorsnoutane **1a** and its cyano analog **1b** were examined at the *ab initio* HF/6-31G(d,p)//HF/3-21G level using the program INDMOL.[6] Typically, a $R_2C{=}CH_2$ unit has MESP minima above and below the π cloud, shifted towards the methylene group, while a cyclopropyl ring has three minima in the CCC plane about 1.4 Å away from each C–C bond.[7] In **1a**,



Scheme 1 *Reagents and conditions*: i, $CHCl_3$, 50% *aq*. NaOH, Et_3BnNCl, room temp., 75–80%; ii, $Hg(OAc)_2$, aq. THF, $NaBH_4$–NaOH, 80%; iii, MCPBA, CH_2Cl_2, Na_2CO_3, 5–10 °C, 75%; iv, B_2H_6–THF, H_2O_2–aq. NaOH, 80%. [a] Ratios based on ^1H NMR integration of crude reaction mixture (±5%). [b] *E* : *Z* mixture could not be separated. However, ^1H NMR data enabled identification of each isomer.

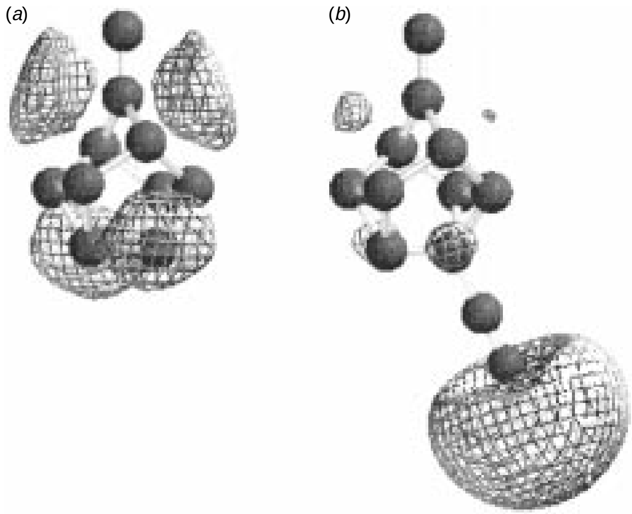


Fig. 1 MESP isopotential surfaces (contour level = −0.024 au) of (*a*) **1a** and (*b*) the cyano analogue **1b**

all the (3, +3) critical points (CPs at which the gradient of the potential vanishes and all the three eigen values of the Hessian are positive)[8] expected for the double bond and cyclopropyl rings are found. The pairs of CPs which share large negative regions [and are linked through (3, +1) saddle points] offer graphic proof of strong interactions between each of the cyclopropyl units and the olefinic π-bond as well as between the two cyclopropyl rings (see Fig. 1). These interactions were quantified earlier using photoelectron (PE) spectroscopy. In particular, σ–π interactions raise the π MO energy to 9.0 eV, compared to the value of 9.4 eV found in 7-methylenenorbornane.[4a]

The above interactions are substantially reduced by the introduction of a cyano group. The MESP minima due to the π-bond become shallow (−0.029 au compared to −0.047 au in the parent), while the CPs due to the cyclopropyl bonds are all virtually eliminated. There are no common negative regions indicative of σ–π interactions (see Fig. 1). These results are consistent with the PE spectrum of **1b**.[9] The first ionization potential, assigned to the π-bond, corresponds to 9.53 eV, fairly close to that of 7-methylenenorbornane.[4a] In the absence of electrostatic bias as well as through-space σ–π interactions in the substrate, the observed face-selectivities must have a different origin.

The activation energies for singlet :CCl_2 addition to substrates **1b–d** computed at the AM1 level with a modified version of MOPAC[10] provide further insights. As pointed out earlier,[2a,b] transition state geometries for carbene addition to olefins are unsymmetrical, with one C–C bond being formed to a greater extent. Hence, four sets of transition states were computed for each substrate, with facial approach being *syn* or *anti*, and the initial site of attack being C-9 or C-10.

As expected, no facial preference is computed for the transition states corresponding to initial approach towards the distal carbon (Table 1). However, in the higher energy structures in which the carbene attacks at the C-9 center, the substituents are computed to exert a small face selectivity. Consistent with the experimental data, both cyano and ester groups lead to a *syn* preference. The prediction for the methoxymethyl derivative is ambiguous since the relative activation energies are sensitive to the conformation of the substituent. These results, especially the absence of selectivity for initial approach at C-10 and *syn* selectivity for approach at C-9 for strongly electron-withdrawing groups, suggest the operation of a relay of hyperconjugative interactions, which makes the *syn* face C–C bonds relatively electron deficient. Stabilization due to interactions between electron-rich C–C bonds and the σ*-orbital of the newly formed bond with the electrophile is greater for *syn* face approach.[11]

Table 1 AM1 activation energies for :CCl_2 addition to **1b**–**d**

Site of attack	Activation energy/kcal mol^{-1}							
	1b		**1c**		**1d** (C_s)		**1d** (C_1)	
	syn	*anti*	*syn*	*anti*	*syn*	*anti*	*syn*	*anti*
C-9	13.59	13.90	13.55	13.85	13.61	13.22	13.19	13.48
C-10	7.02	7.02	6.92	6.92	6.56	6.39	6.41	6.52

In summary, 4-substituted 9-methylenenorsnoutanes show *syn* selectivity in a variety of electrophilic additions. Electrostatic effects and through-space σ-π mixing are both unimportant in these substrates, as confirmed through MESP topographical analyses. The observed selectivities are primarily due to Cieplak-type hyperconjugative interactions[11] in the transition states, whose energetics are fairly correctly reproduced using AM1 calculations.

Notes and References

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