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ROLE OF STERIC, ELECTROSTATIC AND HYDROGEN BONDING EFFECTS AS FACE SELECTIVITY CONTROLLING FACTORS IN NITRONE CYCLOADDITIONS

Marina Burdisso, Remo Gandolfi*, Paolo Pevarello
Dipartimento di Chimica Organica, Università di Pavia, V.le Taramelli 10, 27100 Pavia, Italy
Augusto Rastelli*
Dipartimento di Chimica, Università di Modena, Via Campi 183, 41100 Modena, Italy

Summary: A highly selective syn-attack is promoted by hydrogen bonding effects in the reaction of nitrones with endo-5-hydroxybicyclo[2.2.2]oct-2-enes. By contrast repulsive interactions (steric and electrostatic) between other kinds of substituents and the attacking nitrone result in an almost exclusive anti selectivity.

The way the allylic substituent effectively controls or directs π-facial selectivity in nucleophilic, electrophilic, radical and cycloaddition reactions has recently attracted considerable interest.[1] The substituent can act either via direct intermolecular interaction (steric, electrostatic and secondary orbital interactions) with the incoming reactant or by perturbing the π-bond via intramolecular interactions: both mechanisms render the two faces chemically non equivalent. Thus, for example, in cis-3,4-dimethoxy, diacetoxy, dichloro etc. cyclobutenes the intrinsic asymmetry of the double bond is disclosed by a small syn pyramidalization, able to anticipate that the bending of the olefinic hydrogens towards the TS will be definitively easier in anti than in syn direction. According to our results this factor can explain the preferred syn attack of 1,3-dipoles to these dipolarophiles.[2]

Endo-cis-5,6-disubstituted bicyclo[2.2.2]oct-2-enes (**1**) were chosen as the most appropriate substrates where the substituents can exploit their direct effect without strongly perturbing the π-bond. Due to the symmetry of the parent compound, there is no carbon skeleton imposed facial diastereotopicity and MO calculations showed that the bending asymmetry of the olefinic hydrogens in these compounds is either small or negligible (e.g. **5-7**)[3]. Moreover the reaction of **2** with exo-cis-5,6-disubstituted derivatives **10** gave rise to an equimolar mixture of syn and anti products thus ruling out any through bond effect on face selectivity.

Compounds **1** showed a low dipolarophilic activity, but high yields (87-95%) of cycloadducts could be obtained by carrying out the reaction with excess (30%) 3,4-dihydroisoquinoline-N-oxide (**2**) in refluxing toluene for three days.[4] Anti specificity was found not only in the case of compounds **1a-c**, but also in the presence of the small but highly polar cyano groups (i.e. **1d**) and of the methoxy groups (i.e. **1e**). Trace amounts of syn adduct could be detected in the reaction of diacetoxy derivative **1f** (syn/anti $\leq$ 2/98).

Use of the dihydroxy derivative **1g** as dipolarophile caused an increase in reactivity and a complete reversal of selectivity. Indeed, **1g** is at least 8 times more reactive than **1a** and **1e** and the syn attack is now highly dominant (syn/anti=93/7). The reactions of t-butyl nitrone (at 80°C), 5,5-dimetyl pyrroline-N-oxide (at 110°C) and C-phenyl-N-methyl nitrone (at 140°C) confirmed both the different selectivity of **1g** [only syn adducts were isolated, e.g., **11**)] as compared with **1f** [only anti adducts were isolated, e.g., **12**] and the role of hydroxy groups in enhancing the reaction rate.[5a]

High syn selectivity was also observed for the monohydroxy derivative **13** (96%; syn:anti = 80:20) and the methoxy-hydroxy derivative **14** (95%; syn:anti = 72:28).[5b] In these cases the syn attack was also regiospecific, with the oxygen atom of the isoxazolidine ring facing the OH group, whereas the anti attack gave rise to a mixture of regioisomers ($\simeq$ 1:1). By contrast, only anti adducts were isolated from the reactions of **15** and **16**.

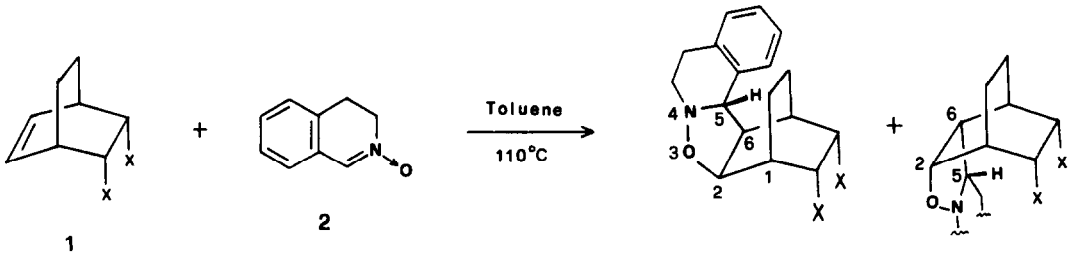
Finally, the face selectivity data for peracid epoxidation of **1g** (CH_2Cl_2, r.t., 84%; syn/anti=83/17) and **1f** (95%; syn/anti $\leq$ 5/95) clearly show that the syn orienting effect of the hydroxy group in nitrone cycloadditions compares favourably with the well established role of this group in peracid epoxidation.[6]

The rationalization of the foregoing data is straightforward: steric and electrostatic effects cooperate in dictating the dominant anti selectivity observed for compounds **1a-f**. In particular dipole-dipole repulsive interactions clearly show up in the anti specificity promoted by the cyano groups. Moreover our experimental findings rule out a relevant effect for the stabilizing interaction between the 1,3-dipole LUMO and the n_+ combination of the lone pairs of the methoxy and acetoxy groups.[7]

A hydrogen bonding effect (shown in **17**) explains the syn-face selectivity exhibited by **1g**, **13** and **14**. In fact the syn/anti ratios of the reaction of **2** with **1g** are solvent dependent, changing from 93/7 in toluene to 73/27 and 59/41 in the good hydrogen bond acceptors DMF and methanol, respectively.

It should be added that in conformations of the type **6** or **9** the OH group is already ideally oriented to be involved in a hydrogen bond with the attacking nitrone. Conformation **6** is calculated to be more stable (by 1.05 Kcal mol^{-1}) than conformation **7** (STO-3G calculations: molecule constrained to C_s symmetry) whilst the I.R. spectrum of **1g** displays only one stretching band at 3559 cm^{-1} in agreement with a symmetric structure where both OH groups are involved in hydrogen bonding with the π system, i.e., **6** or with structure **9** where the two OH strecthings accidentally merge into one band.[8,9] The small anti-bending of H-2 and H-3 in the conformation **6** of **1g** could also help enhance syn selectivity.

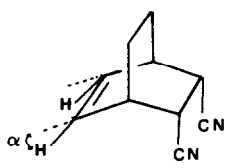
In the case of 5,6-dihydroxy-norbornene (**15**, X = OH) the carbon skeleton imposed asymmetry of the π bond is still large even in conformation **8** (α = 2.21°) although smaller than in norbornene itself (α =4.34°) and this factor along with staggering effects[10] wins over hydrogen bonding. Finally, when the OH groups are located too close over the bond, their



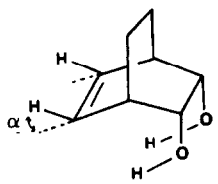
1 + 2 → 3 (anti) + 4 (syn)

a : X = CO_2Me **c** : X - X = OCOO **e** : X = OMe **g** : X = OH

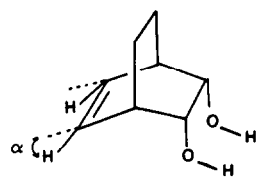
b : X = CH_2OH **d** : X = CN **f** : X = OAc



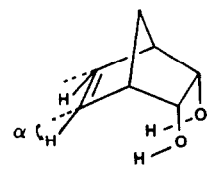
5 (α = + 0.27°)



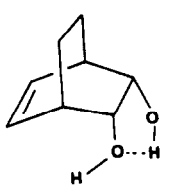
6 (α = −0.98°)



7 (α = +0.35°)



8 (α = + 2.21°)



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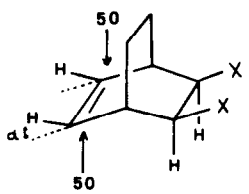
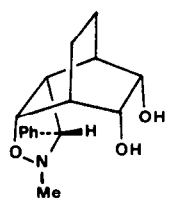


10 : X = OH (α = −0.51°), OAc



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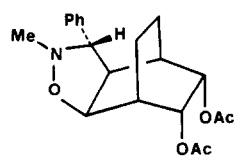

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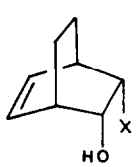
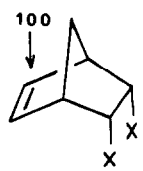
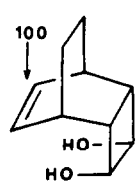


13 : X = H

14 : X = OMe



15 : X = OH, OAc, CO_2Me



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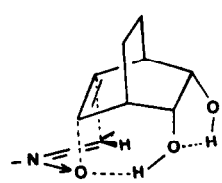

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steric effect prevails as in **16** leading to anti selectivity and to a decrease in reactivity.[11]

To conclude, for the first time, the role of hydrogen bonding in 1,3-dipolar cycloadditions of nitrones to cyclic dipolarophiles has been precisely assessed.[12] We are now investigating the role of this effect in the reaction of nitrones with acyclic substrates.

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References and Notes

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3. Standard ab-initio (STO-3G) calculations have been performed by the use of the Gaussian 82 package.[13] Bicyclo[2.2.2]oct-2-ene geometry (C_{2v}) was optimized under the following constraints: C=C 1.341Å, $C(sp^3)$-H 1.094Å, $C(sp^2)$-H 1.083Å. All of the optimized parameters are well consistent with experimental ones[14] (Δ_{max} = 0.01Å, 1.0 deg). In compound **5**, optimization concerned the angles of the hydrogen atoms bonded to C_2, C_3, C_5, C_6 and the substituent C≡N; dihedral angles were allowed to vary, whereas all the other parameters were held fixed at their values in the parent compound. Dihedral angles were found to vary less than 0.5 deg. In dihydroxy derivatives **6-8** and **10** geometries were assumed from **5** and norbornene: only the dihedral angles involving C-O-H and the angles of olefinic hydrogens (C_s symmetry imposed) were allowed to vary. Additional parameters were C-CN 1.468Å, C≡N 1.159Å, C-OH 1.431Å, O-H 0.971Å, COH 105.4°.
The reliability of the theoretical results is heavily limited by the above assumptions, but we feel that the essentials for the qualitative discussion of our problem are correct.
4. Dipolarophiles were prepared according to literature methods; **1b** (m.p. 90-2°C), **1e** (oil), **1f** (m.p. 101-2°C), **10** (X=OAc, oil), **14** (oil) and **16** (m.p. 152-4°C) are new compounds. Syn-anti ratios were evaluated by column chromatography and ^{1}HNMR data. Adducts **3a,b,3c,e-g** and **4c,f, g** were correlated by standard chemical reactions. All new compounds gave satisfactory elemental analyses and their ^{1}HNMR data were fully consistent with the assigned structures. LIS studies allowed structure determination of hydroxy derivatives; in particular H-5 moved more rapidly (slowly) to lower fields than H-2 and H-6 upon progressive additions of $Eu(fod)_3$ in the case of syn (anti) adducts. The relative rate constants of **1a**, **1e** and **1g** were evaluated by competition reactions of **1a**, **1e** and **1g**, **1e** mixtures with **2**.
5. a) The reactions were conducted in benzene, toluene and xylene respectively. For example excess t-butyl nitrone reacted with **1g** and **1f** to give 94% syn adduct (after four days) and 40% anti-adduct (after ten days), respectively. b) In toluene at 110°C.
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9. By contrast compound **10** (X=OH) exhibits two absorptions at 3625 (free OH) and 3540 (OH involved in the intramolecular hydrogen bond) cm^{-1}. I.R. spectra of **1g** and **10** were recorded for dilute ($\simeq 5\times10^{-3}$ M) CCl_4 solutions.
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11. After ten days at 110°C in toluene only 14% of anti-adduct could be isolated.
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