Pergamon

Tetrahedron Letters, Vol. 37, No. 8, pp. 1321-1324, 1996

0040-4039/96 $15.00 + 0.00

0040-4039(95)02384-4

π-Facial Diastereoselectivity in Electrophilic Additions and 1,3-Dipolar Cycloadditions to Bicyclo[2.2.2]oct-2-enes 5,6-cis,exo-Disubstituted with Electron Withdrawing Groups.

Remo Gandolfi,*[a] Mirko Sarzi Amade',[a] Augusto Rastelli[b] and Marisa Bagatti[b]

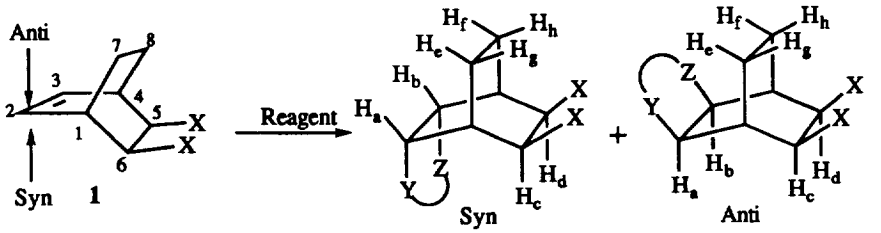
[a]Dipartimento di Chimica Organica, V.le Taramelli 10, Università di Pavia, 27100 Pavia (Italy)

[b]Dipartimento di Chimica , Via Campi 183 , Università di Modena, 41100 Modena (Italy)

The high syn selectivity (e.g., syn/anti ≥ 83:17) observed in epoxidation of the torsionally and sterically unbiased 5,6-cis,exo-disubstitutedbicyclo[2.2.2]oct-2-enes (bearing electron withdrawing groups) progressively decreases on going to dihydroxylation and 1,3-dipolar cycloadditions, with practically no selectivity in the case of nitrones and dominance of anti attack in the reactions of diazomethane (syn/anti ≤ 32:68), in contrast with predictions based on Cieplak's theory.

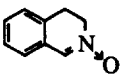
The ever-increasing pressure to achieve higher levels of stereochemical control in the attack to a plane non-symmetric double bond or diene is paralleled by the need to better understand factors which determine this π-facial diastereoselectivity and to assess their relative importance in different substrates.[1,2] Hyperconjugative interactions between the π bond and the allylic σ bonds present in the reactant progressively transform, on going to transition state, into hyperconjugative interactions between the incipient bonds and the allylic σ bonds.[3] These interactions are certainly involved in determining selectivity of attack to stereoelectronically biased π faces, however, their role is a matter of lively controversial debate.[1-5] Cieplak has proposed that at the transition state, electron donation by the filled σ orbitals of the allylic σ bonds into the vacant σ* of the forming bonds should dominate, no matter whether the attacking reagent is a nucleophile or an electrophile. This stabilizing interaction owes its importance, in Cieplak's opinion, to the high intrinsic electron deficiency of incipient bonds and it is at its maximum when these bonds bear an antiperiplanar relationship to the more electron donating allylic σ bonds.[4] As a result, the dominant attack to a plane non-symmetric π bond should always take place as anti with respect to the more electron rich allylic σ bonds.

5,6-Cis,exo-disubstituted-bicyclo[2.2.2]oct-2-enes **1** lend themselves as appealing substrates to make Cieplak's effect clearly emerge for i) the diastereotopic faces of **1** are not only sterically but also torsionally unbiased; in fact, staggering[5a,5i] between the forming bonds and allylic σ bonds in the anti attack is almost exactly the same as that in the syn attack as a consequence of the rigid symmetric bicyclo[2.2.2] carbon skeleton of **1** ii) both centers of the π bond of **1** are equivalently controlled iii) the presence of strong electron attracting substituents at positions 5 and 6 significantly decrease (through inductive effects) the electron donating power of C_1-C_6/C_4-C_5 bonds thus substantially unbalancing the power of hyperconjugative electron donation by these bonds with respect to that of C_1-C_7/C_4-C_8 bonds.[6]



a: X = CN; **b**: X = OH; **c**: X = OAc; **d**: X = OSO_2Me; **e**: X-X = $OCMe_2O$; **f**: X-X = OCOO

Table. Syn/anti ratios of electrophilic and 1,3-dipolar reactions of bicyclooctenes **1**.

X	CN	OH	OAc	OSO_2Me	X-X	$OCMe_2O$	OCOO
Reagent	syn:anti	syn:anti	syn:anti	syn:anti		syn:anti	syn:anti
m-$ClC_6H_4CO_3H$	95:5	83:17	82:18	96:4		90:10	96:4
OsO_4	68:32						80:20
PhCNO		70:30	50:50	45:55		75:25	71:29
PhCOCNO	53:47	64:36	54:46			73:27	71:29
	52:48	48:52	46:54			58:42	51:49
CH_2N_2	31:69			30:70			38:62

Some years ago we claimed that the 1,3-dipolar cycloaddition of 3,4-dihydroisoquinoline-N-oxide with the dihydroxy **1b** (X = OH) and diacetoxy **1c** (X = OAc) derivatives is unselective[7a] whereas more recently Jones and Vogel reported good facial selectivity in electrophilic additions to the dimethoxycarbonyl derivative (**1**, X = COOMe; e.g., epoxidation: syn/anti = 83:17) in agreement, as they stressed, with Cieplak's theory.[7b]

Our paper aims i) at confirming these two apparently contrasting results ii) at demonstrating that very high levels of diastereoselectivity can be achieved through long range (stereoelectronic and/or electrostatic) substituent effects iii) at demonstrating that diastereoselectivity of the reactions of **1**, as a whole, does not conform to predictions based on Cieplak's model.

Compound **1a** was obtained as the minor product from the reaction of maleonitrile with cyclohexadiene and compounds **1c-1f** were prepared by standard procedures from the known dihydroxyderivative **1b**.[8] Epoxidation (some days, ≥95%) was performed at r.t. in CH_2Cl_2 with excess m-chloroperbenzoic acid and catalytic OsO_4 dihydroxylation (24 h, ≥70%) at r.t. in acetone/water (6:1) in the presence of excess N-methylmorpholine-N-oxide. Good yields (12 h, ≥80%) of adducts in the reactions of mildly electrophilic nitrile oxides (PhCNO and PhCOCNO) with **1** were obtained by liberating the 1,3-dipole in situ from the corresponding hydroximic acid chloride in boiling toluene. The mildly nucleophilic 3,4-dihydroisoquinoline-N-oxide was reacted at 120 °C (toluene, 36 h, ≥60%). The reaction of "electron-rich" diazomethane (high excess in ethyl ether, r.t.) was very sluggish and reasonable yields (≥ 30%) could be obtained only after long reaction times (e.g., 30 days). Adducts proved stable under reaction conditions. Their ratios (see Table) were evaluated by high field ^1H NMR spectra and confirmed by column chromatography. Syn/anti stereochemistry was assigned mostly on the basis of the

following reliable diagnostic ^1H NMR features : i) a long range W couplings (1.0-2.0 Hz) between H_a/H_b and H_g/H_h was present in the anti adducts which consistently was missing in the syn adducts ii) irradiation of H_a/H_b brought about significant NOE enhancements (2-4%) in intensity of signals of H_e/H_f in the syn adducts and of H_c/H_d in the anti adducts iii) H_c and H_d in the anti adducts from nitrile oxide cycloadditions resonated at very similar field [$\Delta\delta$ ($CDCl_3$) $\leq$ 0.15 ppm] while in the syn adducts one of them was shifted upfield and the other downfield ($\Delta\delta$ ($CDCl_3$) $\geq$ 0.4 ppm) by shielding effects of the aryl group and deshielding effect of the oxygen atom, respectively, of the former nitrile oxide. Adducts with different X groups were correlated each other by standard chemical transformations.

Inspection of the Table shows that substituents can induce a syn selectivity as high as 96% [i.e., epoxidation of **1d** (X = OSO_2Me) and **1f** (X-X = OCOO), $\Delta\Delta G^{\#}$ = 1.9 kcal mol^{-1}]. This is a remarkable observation for a long range substituent effect. It is certainly interesting from a synthetic point of view as well the finding that the sign of diastereoselectivity can be reversed upon changing the reagent (i.e., the anti attack is dominant in the reactions of diazomethane, syn:anti $\leq$ 38:62).

From a mechanistic standpoint it should be emphasized that there is a progressive decrease in syn selectivity on going from epoxidation to dihydroxylation and 1,3-dipolar cycloadditions. As for the latter reactions, there is a tendency for prevalence of syn attack in the case of nitrile oxides, but all the reactions of 3,4-dihydroisoquinoline-N-oxide are practically unselective and a clear-cut reversal of selectivity was observed in the reactions of diazomethane. Noteworthy also the finding that the diacetoxy derivative **1c** exhibits a definitely lower syn selectivity than the carbonyldioxy derivative **1f** (X-X = OCOO) and even slightly lower than the dihydroxy derivative **1b**. Thus, facial selectivity in the reactions of compounds **1** is highly dependent on the type of reagent used. Very roughly, syn selectivity seems to decrease as the electrophilicity of the reagent decreases and cyclic substituents seem to be more efficient in promoting syn attack than their acyclic counterparts. It is quite evident that these findings, as a whole, can not be rationalized on the basis of the "Cieplak effect" which predicts that the preferred attack will always (no matter which reagent is used) take place as anti with respect to the more electron donating σ allylic bond(C_1-C_7/C_4-C_8 in **1**, the syn attack should always be favored). Moreover, Cieplak's theory can not explain the difference between cyclic and acyclic substituents

Thus, even in substrates that are completely free from stereodirecting steric and torsional strains the stereoelectronic Cieplak's effect does not emerge clearly. This observation may be the result of the fact that hyperconjugative delocalizations are overshadowed by other effects and/or that Cieplak's model does not properly accounts for the effect of hyperconjugative delocalizations. As for the first point, several authors have emphasized that facial selectivity induced by electron attracting substituents is better rationalized on the basis of electrostatic factors.[2e,5a,5c,5f,5g] In compounds **1** a variable blend of hyperconjugative and electrostatic interactions might be at work to determine the complicate scenery of their facial selectivity. As for the second point, certainly all hyperconjugative interactions, not only the $\sigma^*_{\text{forming bonds}}$-$\sigma_{\text{allylic bonds}}$ interactions of the Cieplak's model, between the incipient bonds and the allylic σ bonds must be taken into account [1a,3] even if their stereodirecting influence is not easy to evaluate on qualitative grounds.

To conclude, at present we are not able to advance a convincing simple qualitative explanation for the synthetically interesting π-facial selectivity observed in the reactions of compounds **1** and, as a consequence, we are actively addressing this problem with semiempirical and ab-initio MO calculations by using our model of analysis of chemical interactions[3] which, we hope, will allow us to evaluate the relative role of electrostatic and hyperconjugative interactions.[9]

Acknowledgments. This work was financially supported by CNR and MURST

References

1. (a) Li, H.; le Noble, W. J. *Recl. Trav. Chim. Pays-Bas*, **1992**, *111*, 199-210; (b) Fallis, A. G.; Lu, Y.-F in *Advances in Cycloaddition*, Curran, D. P., Ed., JAI Press, 1993, Vol. 3, ch. 1; (c) Mander, L. N. *Stereoselective Synthesis*, ch. 12 in Eliel, E. E.; Wilen, S. H. *Stereochemistry of Organic Compounds*, Wiley-Interscience, New York, 1994.
2. For very recent papers see: (a) Ishida, M.; Kakita, S.; Inagaki, S. *Chem. Lett.*, **1995**, 469-470; (b) Adam, W.; Jacob, U.; Prein, M. *J. Chem. Soc., Chem. Commun.*, **1995**, 839-840; (c) Metha, G.; Uma, R. *Tetrahedron Lett.*, **1995**, *36*, 4873-4875; (d) Rastelli, A.; Bagatti, M.; Gandolfi, R. *J. Am. Chem. Soc.*, **1995**, *117*, 4965-4975; (e) Paquette, L. A.; Branan, B. M.; Rogers, R. D.; Bond, A. H.; Lange, H.; Gleiter, R. *J. Am. Chem. Soc.*, **1995**, *117*, 5992-6001; (f) Poirier, R. A; Pye, C. C.; Xidos, J. D.; Burnell, D. J. *J. Org. Chem.*, **1995**, *60*, 2328-2329.
3. Rastelli, A.; Bagatti, M.; Gandolfi, R.; Burdisso, M. *J. Chem. Soc. Faraday Trans*, **1994**, *90*, 1077-1082 and references therein.
4. Cieplak, A. S.; Tait, B. D.; Johnson, C. R. *J. Am. Chem. Soc*, **1989**, *111*, 8447-8462.
5. (a) Wu, Y.-D.; Tucker, J. A.; Houk, K. N. *J. Am. Chem. Soc.*, **1991**, *113*, 5018-5027; (b) Halterman, R. L.; McEvoy, M. A. *J. Am. Chem. Soc.*, **1992**, *114*, 980-985; (c) Paddon Row, M. N.; Wu, Y.-D.; Houk, K. N. *J. Am. Chem. Soc.*, **1992**, *114*, 10638-10639; (d) Ishida, M.; Aoyama, T.; Beniya, Y.; Yamabe, S.; Kato, S.; Inagaki, S. *Bull. Chem. Soc. Jpn*, **1993**, *66*, 3430-3439; (e) Metha, G.; Gunasekaran, G.; Gadre, S. R.; Shirsat, R. N.; Ganguly, B.; Chandrasekhar, J. *J. Org. Chem.*, **1994**, *59*, 1953-1955; (f) Williams, L.; Paddon-Row, M. N. *J. Chem. Soc., Chem. Commun.*, **1994**, 353-356; (g) Wipf, P.; Kim, Y. *J. Am. Chem. Soc.*, **1994**, *116*, 11678-11688; (h) Werstiuk, N. H.; Ma, J. *Can. J. Chem.*, **1994**, *72*, 2493-2505; (i) Martinelli, M. J.; Peterson, B. C.; Khau, V. V.; Hutchinson, D. R.; Leanna, M. R.; Audia, J. E.; Droste, J. J.; Wu, Y.-D.; Houk, K. N. *J. Org. Chem.*, **1994**, *59*, 2204-2210.
6. Moreover the syn and anti transition structures (both AM1 and STO-3G) of the reaction of HCNO with **1f** clearly show that the allylic anti σ bonds bear an almost exact antiperiplanar relationship to the incipient bonds. That is, at least in 1,3-dipolar cycloadditions, Cieplak's effect should be at its maximum.
7. (a) Burdisso, M.; Gandolfi, R.; Pevarello, P.; Rastelli, A. *Tetrahedron Lett.*, **1987**, *28*, 1225-1228; (b) Jones, G. R.; Vogel, P. *J. Chem. Soc., Chem. Commun.*, **1993**, 769-771.
8. Lambert, J.; Holcomb, G. A. *J. Am. Chem. Soc*, **1971**, *93*, 3952-3956.
9. Preliminary analysis of vicinal interactions in the transition structures of the reaction of formonitrile oxide with **1f** suggests that hyperconjugative delocalizations slightly favor the syn attack (by 0.3 kcal mol^{-1}, STO-3G calculations). Hyperconjugative effects are also reflected in the observation that forced bending of the olefinic hydrogens of **1f** in the anti direction is easier than that in the syn direction (by 0.8 kcal mol^{-1} for an angle of 20°, AM1). The component of the dipole moment (AM1) of compounds **1a**, **1e** and **1f** orthogonal to the plane of the π bond (namely, in a direction almost parallel to that of attack by reagents on the double bond) is small (< 1 D) suggesting that also the stereodirecting power of electrostatic factors should not be strong. Net charges are only slightly more positive on the C_5H-C_6H bridge than on the C_7H-C_8H bridge.

(*Received in UK* 8 *December* 1995; *accepted* 15 *December* 1995)