The Journal of
Organic
Chemistry

VOLUME 55, NUMBER 11 MAY 25, 1990

Communications

How Important Are Secondary Orbital Interactions in Favoring the Endo Mode in 1,3-Dipolar Cycloadditions of Nitrones?

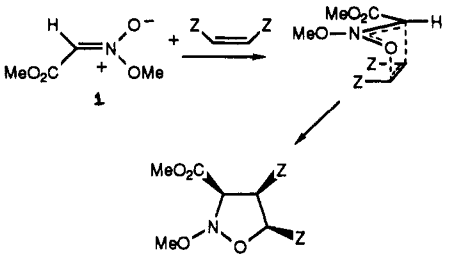
Marina Burdisso, Remo Gandolfi,* and Paolo Grünanger
Dipartimento di Chimica Organica, Università di Pavia, V.le Taramelli 10, 27100 Pavia, Italy
Augusto Rastelli*
Dipartimento di Chimica, Università di Modena, Via Campi 183, 41100 Modena, Italy

Received February 5, 1990

Summary: Experimental endo/exo selectivity data for the reaction of cyclic and open-chain nitrones with Z-disubstituted dipolarophiles as well as computational data cast serious doubt on the role of secondary overlaps as important endo orienting factors in nitrone cycloadditions.

The truly remarkable 100% endo selectivity in the reactions of (*Z*)-*N*-alkoxynitrones (nitronic esters) 1 with dimethyl maleate, maleic anhydride, and maleimides points to the presence of strong endo-orienting factors in these reactions.[1,2] At the time of this discovery, in the middle 1970s, secondary orbital interactions involving the nitrogen atom of the 1,3-dipole and the substituents on the dipolarophile (see Figure 1) lent themselves as a possible rationale for the observed selectivity.[2] Since then researchers in the field of nitrone cycloadditions seem to have, more or less tacitly, assumed that stabilizing secondary orbital overlaps are also important factors in determining endo/exo selectivity in the case of *N*-alkyl- and *N*-arylnitrone cycloadditions.[3] The experimental and theoretical data reported below clearly show that this credence must be reconsidered.

Endo/exo ratios (kinetic and thermodynamic) of the reactions of nitrones 2[4,5] with Z-disubstituted dipolarophiles[6] are reported in Table I. Kinetic ratios in benzene make it apparent that the tendency of electron-deficient dipolarophiles to enter endo addition is higher than that of electron-rich dipolarophiles. However, only one case of clear-cut dominance of endo mode was found, namely the



Endo Adduct

---

[1] Greé, R.; Carrié, R. *Bull. Soc. Chim. Fr.* **1975**, 1319.

[2] Greé, R.; Tonnard, R.; Carrié, R. *Bull. Soc. Chim. Fr.* **1975**, 1325.

[3] Tufariello, J. J. *Nitrones.* in *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley Interscience: New York, 1984; Vol. 2, p 1.

[4] Despite a widespread use of **2a** in the synthesis of natural products, in particular in the alkaloid field,[5] no systematic studies of the endo/exo selectivity of its reaction with *Z*-disubstituted dipolarophiles has so far been reported. For a very recent report on the reaction of **2a** with maleic anhydride and dimethylmaleate, see: Asrof Ali, S.; Khan, J. H.; Wazeer, M. I. M.; Penzanowski, H. P. *Tetrahedron* **1989**, *45*, 5979.

[5] Tufariello, J. J. *Acc. Chem. Res.* **1979**, *12*, 396. Confalone, P. N.; Huie, E. M. *The* [*3* + *2*] *Nitrone Olefin Cycloaddition Reaction, Organic Reactions*; J. Wiley and Sons: New York, 1988; Vol. 36, p 1. Torssell, K. B. G. *Nitrile Oxides Nitrones and Nitronates in Organic Synthesis*; VCH Publishers: New York, 1987.

[6] Total yields: ≃70% for vinylenecarbonate, ≥85% for the other dipolarophiles. The endo/exo ratios were evaluated by column chromatography (cyclohexane–AcOEt mixtures as eluants; endo adducts exhibit, as a rule, a lower R_f value than exo adducts) and/or by ^{1}H NMR. Elemental analyses as well as IR and NMR spectra support structure assignments which are based on the following criteria: (i) Exo structure was assigned to the adducts with lower $J_{3,4}$. In particular with cyclic dipolarophiles this criterion is very reliable as $J_{3,4}$ in exo adducts to these dipolarophiles is ≤1.0 Hz and is lower by ≥5.5 Hz than that in the related endo compounds (by ≥2.0 Hz in the case of open chain dipolarophiles). (ii) Exo structure was attributed to the dominant or to the sole detected product under thermodynamic control. (iii) Adducts to maleic anhydride were correlated to adducts to dimethyl maleate. Exo adducts to this latter dipolarophile could be obtained by treatment of exo adducts to maleonitrile with a saturated solution of HCl in methanol.

0022-3263/90/1955-3427$02.50/0

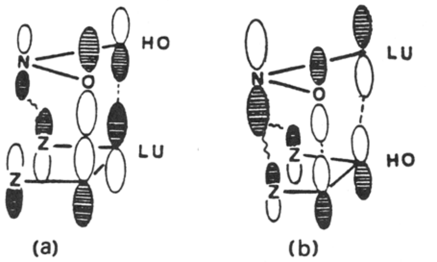


Figure 1. FO interactions between a nitrone system and a *Z*-disubstituted dipolarophile. Interaction (a) is the dominant interaction with electron-poor dipolarophiles (Z = CN, CO_2Me, etc.).

Table I. Endo:Exo Ratios of the Reactions of 2a, 2b, and 5, Respectively, with *Z*-Disubstituted Olefins[a]

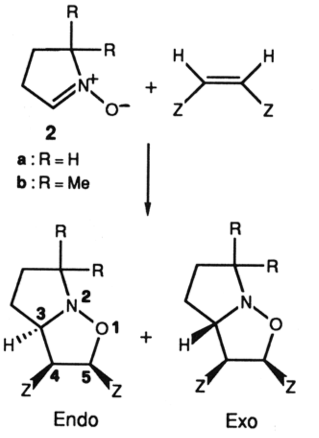
dipolarophile	**3a:4a**	**3b:4b**	**6:7**
acenaphthylene	21:79	14:86	29:71
vinylenecarbonate	26:74	<5:95	40:60
N-phenylmaleimide[b]	45:55 (30:70) [5:95]	6:94 (3:97) [0:100]	58:42 (46:54)
maleonitrile	77:23 (61:39) [20:80]	48:52 (37:63) [13:87]	62:38 (54:46)
dimethyl maleate	15:85 [10:90]	0:100 [5:95]	46:54 (37:63)
dibenzoylethylene	30:70 [≤10:90]	0:100 [0:100]	50:50
bis(phenylsulfonyl)ethylene	0:100 [0:100]	0:100 [0:100]	<10:90

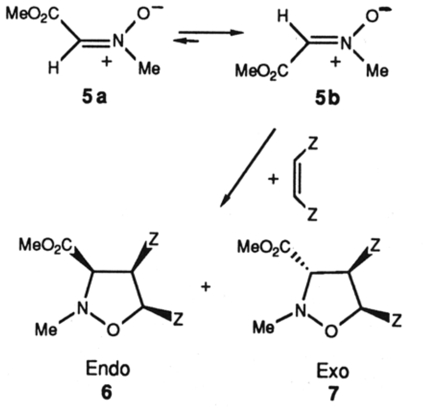
[a] In benzene at 20 °C. Values in parentheses are for reactions in acetonitrile at 20 °C. Values in brackets are for thermodynamic ratios (in C_6D_6 or $CDCl_3$). [b] Similar results were obtained for *N*-methylmaleimide and maleic anhydride.

reaction of **2a** with maleonitrile (a dipolarophile with a high dipole moment). An increase in solvent polarity, i.e., upon passing from benzene to acetonitrile, brings about a decrease in endo/exo ratio (see the table).

This effect, which if far from being dramatic, lends some support to the suggestion that the exo approach is disfavored by a worse alignment of the dipoles of the two reactants as compared to the endo mode.[7] In particular dipole–dipole interaction should favor the endo addition in the case of maleonitrile. As for thermodynamic ratios[8,9] they are certainly controlled by steric interactions in the adducts and can be taken as a rough qualitative indication of the role of steric factors in favoring exo addition. These factors, which easily explain the lower endo selectivity of **2b** as compared to **2a** (this latter relatively free of steric encumbrance), are at a minimum in the reaction of **2a** with maleonitrile.

At this point we deemed it necessary to carry out reactions of the same dipolarophiles with *C*-(methoxycarbonyl)-*N*-methylnitrone **5**, an open-chain nitrone which mimics as far as possible the nitronic esters used by Carrié et al. In fact, the *E* form **5b** is highly dominant over the *Z* form **5a** (at the equilibrium: 84:16 in benzene).[10] Moreover, it is well known that the *E* form of nitrones is more reactive than the *Z* form.[1,3] Thus, even if some ambiguity remains, it may be reasonable to assume that the stereochemical outcome of the fast equilibrating[10] **5a** ⇄ **5b** mixture is largely the result of the reaction of **5b**. Inspection of the last column of the table shows that the endo selectivity of **5** roughly parallels that of **2a** and no examples of 100% or very high endo selectivity were found.[11,12]





We can conclude that the diastereoselectivity exhibited by the nitrones **2a** and **5** stand in sharp contrast to the 100% endo selectivity observed for nitronic esters. An "endo rule" does not hold for nitrone (either cyclic or open-chain) cycloadditions with cis-disubstituted alkenes.

Our conclusion refers to reactions of disubstituted nitrones in which there is an inherent steric bias (more or less strong) against endo orientation. Formation of significant amounts of endo adducts certainly points to the fact that endo-orienting factors are far from being negligible. Can we invoke stabilizing secondary orbital overlaps (in addition to other effects such as dipole–dipole interactions) as a rationale for these factors? Preliminary semiempirical MO C-INDO calculations of the endo- and exo-oriented complexes of the parent nitrone with maleonitrile (in the geometrical structures of their isolated molecules and approached on parallel planes at a distance of 2.20 Å)[13] have been carried out. They show that sec-

---

(7) Tada, K.; Yamada, T.; Toda, F. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 1839.

(8) Thermodynamic ratios were obtained by prolonged heating of the reaction mixtures at temperatures at which the cycloreversion reaction[9] takes place readily (e.g. ≥60 °C for maleonitrile and dibenzoylethylene, ≥110 °C for maleimides, bis(phenylsulfonyl)ethylene and dimethyl maleate). Adducts from **2b** cyclorevert faster than adducts from **2a**. The cycloreversion of these latter compounds sometimes is accompanied by decomposition reactions.

(9) For reviews on 1,3-dipolar cycloreversions, see: Bianchi, G.; De Micheli, C.; Gandolfi, R. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 721. Bianchi, G.; Gandolfi, R. 1,3-Dipolar Cycloreversions. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley Interscience: New York, 1984; Vol. 2, p 451.

(10) Inouye, Y.; Takaya, K.; Kakisowa, H. *Bull. Chem. Soc. Jpn.* **1983**, 3451.

(11) The nitrone **5** was dissolved in benzene and left equilibrating for 1 h before adding portionwise the dipolarophile. Endo/exo ratios were evaluated by ^1H NMR. Structure assignments of adducts to vinylenecarbonate, maleimides, maleonitrile, and dimethyl maleate were based on ^1H NMR data and chemical correlation as in the case of nitrones **2**.[6] The endo adduct to acenaphthylene has already been reported.[12] The assignment of exo structure to the sole detected adduct with bis(phenylsulfonyl)ethylene was made by analogy and is tentative.

(12) Cerri, A.; De Micheli, C.; Gandolfi, R. *Synthesis* **1974**, 710.

ondary orbital overlaps involving the nitrogen atom of the 1,3-dipole give rise to a higher destabilization of the endo form of $\simeq 0.5$ kcal mol^{-1} with respect to the exo orientation whereas electrostatic effects appear to favor endo orientation and, on the whole, the two oriented complexes have quite similar total energies.[14] Destabilization of the endo form as a result of secondary overlap can be attributed, in PMO terms, to a prevalence of closed-shell repulsions over filled–unfilled attractive interactions.

The present data and previous findings[3–5,15] allow us to conclude that: (i) high endo diastereoselectivity cannot be achieved even in the reaction of sterically low demanding nitrones with electron-poor Z dipolarophiles, (ii) factors which favor endo orientation in 1,3-dipolar cycloadditions are still to be clearly identified.[16] In this connection it should be stressed that the very same statement seems to hold for the Diels–Alder reaction. In fact, the role of secondary orbital interaction as major endo orienting factors has recently been questioned.[17]

Additional experiments are in progress as well as more sophisticated computational studies in an attempt to shed some light on the elusive endo-orienting factors.

Acknowledgment. We thank the Ministero della Pubblica Istruzione and CNR for financial support.

---

(13) Mc Douall, J. J. W.; Robb, M. A.; Niazi, U.; Bernardi, F.; Schlegel, B. H. *J. Am. Chem. Soc.* **1987**, *109*, 4642.

(14) The parent nitrone was used in order to have a system in which the only secondary orbital interaction is that involving the nitrogen atom of the nitrone. The electrostatic effect has been estimated by the difference between the total energy of the oriented complex (where the intermolecular delocalization had been suppressed by removing all the intermolecular overlap integrals) and the energy of the separated molecules. Likewise, the effect of secondary interactions between the π-orbital of the nitrogen atom of the dipole and the π-system of the dipolarophile has been estimated by removing the corresponding overlap integrals. For C-INDO procedure, see: Momicchioli, F.; Baraldi, I.; Bruni, M. *Chem. Phys.* **1982**, *70*, 161.

(15) Burdisso, M.; Gamba, A.; Gandolfi, R.; Pevarello, P.; Oberti, R. *Tetrahedron* **1988**, *44*, 3735 and references cited therein. See also: Asrof Ali, S.; Wazeer, M. I. M. *J. Chem. Soc., Perkin Trans. 1* **1988**, 597.

(16) Aside from electrostatic and van der Waals forces, steric repulsions, and secondary overlap interactions, primary overlaps (Baldwin, J. E.; Prakash Reddy, V. *J. Org. Chem.* **1989**, *54*, 5264 and references cited therein) can also play a role in determining endo/exo selectivity in gas phase. In solution also solvent "polarity" effects (due to internal pressure, solvation ability, etc.) come into play.

(17) Loncharich, R. J.; Brown, F. K.; Houk, K. N. *J. Org. Chem.* **1989**, *54*, 1129 and references cited therein. Sodupe, M.; Oliva, A.; Bertran, J.; Dannenberg, J. J. *J. Org. Chem.* **1989**, *54*, 2488. Pitea, D.; Gastaldi, M.; Orsini, F.; Pelizzoni, F.; Mugnoli, A.; Abbondanti, E. *J. Org. Chem.* **1985**, *50*, 1853. Houk, K. N.; Loncharich, R. J.; Blake, J. F.; Jorgensen, W. L. *J. Am. Chem. Soc.* **1989**, *111*, 9172.

Mild and Stereocontrolled Synthesis of Iodo- and Bromohydrins by X_2–$Ti(O\text{-}i\text{-}Pr)_4$ Opening of Epoxy Alcohols

Eleuterio Alvarez, María Teresa Nuñez, and Victor S. Martín*

Centro de Productos Naturales Orgânicos "Antonio Gonzâlez", Instituto Universitario de Bio-Orgânica, Universidad de La Laguna, Carretera La Esperanza, 2, 38206 La Laguna, Tenerife, Spain

Received May 25, 1989

Summary: A mild procedure to obtain halo diols by opening epoxy alcohols with halogen is described. The method is based on the use of $Ti(O\text{-}i\text{-}Pr)_4$ and the suitable halogen over allylic and homoallylic epoxy alcohols, affording high regioselectivities and yields. Reaction with enantiomerically enriched epoxides leads selectively to chiral halohydrins.

In the course of our synthetic studies directed toward the enantioselective total synthesis of marine natural compounds[1] containing polyfunctionalized cyclic ethers,[2] we have been very interested in the possibility of using chiral vicinal iodo- or bromohydrins as fragments to further produce cyclization in an electrophilic manner.[3] An attractive way to achieve this goal could be the regioselective opening of epoxides, having in mind the availability of 2,3-epoxy alcohols by asymmetric epoxidation of the suitable allylic alcohol,[4] in which case chiral compounds would be obtained. Few reagents are known to convert epoxy alcohols to halohydrins.[5,6] We now report that the treatment of allylic and homoallylic epoxy alcohols with an equivalent amount of halogen (Br_2, I_2) in presence of a stoichiometric amount of $Ti(O\text{-}i\text{-}Pr)_4$ provides a mild procedure to synthesize halohydrins with a high degree of generality, mildness, and regioselectivity (Table I).[7]

The regioselectivity and purities of the resulting halo diols obtained with the addition of $Ti(O\text{-}i\text{-}Pr)_4$ are markedly greater than those obtained in the absence of the metal mediation. When epoxy alcohol 1 was treated with iodine or bromine, at room temperature, a 1:1 mixture of

---

(1) Erickson, R. E. *Marine Natural Products*; Scheuer, P. J., Ed.; Academic Press: New York, 1986; Vol. V, p 131.

(2) (a) Nuñez, M. T.; Rodríguez, M. L.; Martín, V. S. *Tetrahedron Lett.* **1988**, *29*, 1979. (b) Tonn, C. E.; Palazón, J. M.; Ruiz-Pérez, C.; Rodriguez, M. L.; Martín, V. S. *Tetrahedron Lett.* **1988**, *29*, 3149. (c) Alvarez, E.; Manta, E.; Martín, J. D. *Tetrahedron Lett.* **1988**, *29*, 2093.

(3) Bartlett, P. A. *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3, p 411.

(4) (a) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974. (b) Martín, V. S.; Woodard, S. S.; Katsuki, T.; Yamada, Y.; Ikeda, M.; Sharpless, K. B. *J. Am. Chem. Soc.* **1981**, *103*, 6237.

(5) Caron, M.; Sharpless, K. B. *J. Org. Chem.* **1985**, *50*, 1560.

(6) (a) Lu, L. D.; Johnson, R. A.; Finn, M. G.; Sharpless, K. B. *J. Org. Chem.* **1984**, *49*, 731. (b) Onaka, M.; Sugita, K.; Takeuchi, H.; Izumi, Y. *J. Chem. Soc., Chem. Commun.* **1988**, 1173. (c) While this work was being written up, a recently published communication reported that dialkylamine hydrohalides, $Ti(O\text{-}i\text{-}Pr)_4$-mediated ring openings of 2,3-epoxy alcohols at the 3-position have been performed efficiently: Gao, L.; Murai, A. *Chem. Lett.* **1989**, 357.

(7) In a typical experiment, to a stirred solution of iodine (or bromine) (1.1 mmol) in 10 mL of dry dichloromethane (methanol-fre) were sequentially added $Ti(O\text{-}i\text{-}Pr)_4$ (1.2 mmol) [smaller values on the regioselectivities have been obtained when less than 1 equiv of $Ti(O\text{-}i\text{-}Pr)_4$ was used] and the epoxy alcohol (1.0 mmol) dissolved in 2 mL of CH_2Cl_2, under inert atmosphere at 0 °C.[8] The reaction was stirred at the temperature and for the time indicated in Table I. After the reaction was completed (TLC) 15% aqueous tartaric acid solution (20 mL) [in most cases dilute H_2SO_4 (5%) equally suitable] and solid $NaHSO_3$ (500 mg) were added with vigorous stirring until clear phases were reached. The aqueous phase was extracted with CH_2Cl_2 (3×50 mL) (with some CH_2Cl_2 insoluble halo diols, EtOAc may be more convenient as extracting solvent), and the combined organic phases washed with saturated $NaHCO_3$ solution (20 mL) and saturated brine (20 mL), dried ($MgSO_4$), and concentrated to afford a crude reaction mixture containing the desired halo diols, which were purified by column chromatography.

0022-3263/90/1955-3429$02.50/0