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Non-Steric Facial Selectivity in Nucleophilic 1,4-Conjugate Additions

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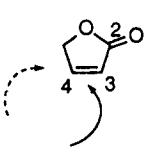
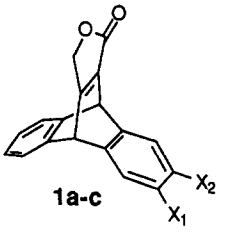
Abstract The effect of a remote substituent on the facial selectivity in a nucleophilic 1,4-conjugate addition was investigated in the dibenzobicyclo-[2.2.2]octatriene skeleton. A nitro substituent favored *syn*-addition of ethanethiol toward the embedded 2(5*H*)-furanone moiety. Polar solvents increased the magnitude of the selectivity.

In 1,4-conjugate additions toward cyclic unsaturated lactones, facial selectivity is generally determined by the stereochemistry of the substituents on the ring. [1] Other effects such as stereoelectronic effects are also important in some cases. [2,3] In this paper, we present an example that can not be accounted for in terms of the classical steric effect: we designed and synthesized several lactones with 2(5*H*)-furanone (**A**) embedded in a dibenzobicyclo[2.2.2]octatriene frame (**1a-c**). In this system, the aromatic substituent is far from the reaction center, and the π-face is considered to be free from conventional steric effects. Furthermore, the use of the cyclic lactone moiety fused to the bicyclo skeleton avoids complexity arising from *cis/trans* protonation of the intermediate adduct. [4] Thus, these compounds will be substrates with minimal bias close to the reacting sp^2-carbon, allowing us to separate steric, torsional and stereoelectronic variables.



A



1a-c

1a: (X_1=X_2=H)
1b: (X_1=H, X_2=NO_2)
1c: (X_1=NO_2, X_2=H)

We carried out the base-catalyzed 1,4-addition of ethanethiol to **1a-c** in a variety of aprotic solvents at 23°C for 75 hrs. [5] The results are summarized in Table 1. The *syn/anti* ratios were determined from signal integration values in the ^{1}H-NMR, the structures being confirmed by detection of proton NOEs. The 3-nitro lactone (**1b**) favors *syn*-addition rather than *anti*-addition in all cases. The 2-nitro lactone (**1c**) also favors *syn*-addition, though the ratio obtained in a neat condition is smaller than that of **1b**. The adduct **3c** did not change into **2c** at 23°C during 94 hrs in a mixture of ethanethiol and sodium thioethoxide without solvent. In DMF as a solvent, the isomerization was observed to only a small extent (**3c**:**2c**=93:7). These results indicate that the distributions of products are kinetically determined. In both cases (**1b** and **1c**) it was found that the magnitude of the *syn*-preference increased with increasing solvent polarity: the *syn/anti* ratio of **1b** and that of **1c** reached 79:21 and 75:25 in DMF, respectively. On the other hand, the reaction in a non-polar solvent such

as *n*-hexane shows a smaller selectivity than those in polar solvents, though *syn*-preference is still observed. These results indicate intrinsic *syn*-preference of attack of the nucleophilic reagent on **1b** and **1c**.

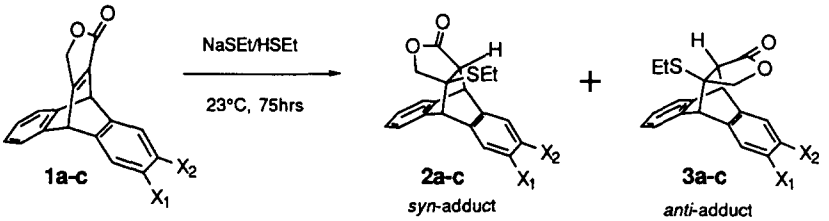


Table 1 Facial Selectivity in Nucleophilic 1,4-Conjugate Addition of Ethanethiol. [a,b,c]

	X_1	X_2	solvent	yield(%)	*syn* : *anti*
1a	H	H	*neat*	84	50 : 50
1b	H	NO_2	*neat*	100	63 : 37
1b	H	NO_2	*n*-hexane	73 [d]	61 : 39
1b	H	NO_2	CCl_4	16 [e]	62 : 38
1b	H	NO_2	benzene	90 [f]	62 : 38
1b	H	NO_2	Et_2O	93	69 : 31
1b	H	NO_2	DMF	94	79 : 21
1b	H	NO_2	DMSO	91	77 : 23
1c	NO_2	H	*neat*	92	54 : 46
1c	NO_2	H	DMF	95	75 : 25
1c	NO_2	H	DMSO	98	73 : 27

a) These reactions were carried out at 23°C for 75 hrs. b) *Anti*/*syn* ratios were determined from signal integration values in the ^1H NMR spectrum. c) EtSH was used at 307-357 equiv.(*neat*), or 64-67 equiv.(other solvents). NaSEt was used in catalytic amount. d-f) Recovery of substrate: d) 20%, e) 76%, f) 10%.

The *syn*-preference of **1b** and **1c** is similar to those observed in the reduction of the related ketones, 9,10-dihydro-9,10-ethanoanthracen-11-ones (dibenzobicyclo[2.2.2]octadienones) and in the epoxidation and dihydroxylation of the related olefins, 9,10-dihydro-9,10-ethenoanthracenes (dibenzobicyclo[2.2.2]-octatrienes). [6] Although the trajectories of the attacking reagents are considered to be different in these reactions, [2] all three types of reactions favor *syn*-addition, which excludes a predominant role of divergent trajectories in these dibenzobicyclic systems.

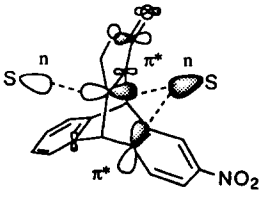


Figure 1 Unsymmetrization of LUMO of lactone **1b**

The substituent effect of the aromatic nitro group can be accounted for in terms of π-orbital unsymmetrization. [6,7] The LUMO of the dibenzobicyclic lactone can be analyzed as an in-phase combination

of three vacant π* orbitals, i.e., those of benzene, nitrobenzene and the 2(5*H*)-furanone moiety. The energetically lower-lying π* orbital of the nitrobenzene fragment contributes significantly to the LUMO of the whole molecule rather than the π* orbital of the non-substituted benzene. Thus the LUMO of the 2(5*H*)-furanone is unsymmetrized (Figure 1). Therefore the *syn*-attack of the nucleophilic reagent is favored because of the additional *in-phase* interaction of the π* lobe of the nitrobenzene motif. [8]

The predominant component of the LUMO of the whole molecule is the π* orbital of the nitrobenzene fragment rather than that of the reaction center. However, the orbital being perturbed to generate the *syn*-preference is the LUMO and not the next LUMO, which contains the π* orbital of the reaction center as a main component. This is similar to the selectivity we reported previously. [6,7,16]

References and Notes

1) Trost, B. M., Fleming, I. Eds.; Semmelhack, M. F., Volume Ed. *Comprehensive Organic Synthesis*; Pergamon Press: Oxford, U.K., 1992; Vol. 4, Chapter 1.
2) Sato, M.; Murakami, M.; Sunami, S.; Kaneko, C.; Furuya, T.; Kurihara, H. *J. Am. Chem. Soc.*, **1995**, *117*, 4279-4287.
3) Gung, B. W.; Francis, M. B. *J. Org. Chem.* **1993**, *58*, 6177-6179.
4) In general Michael reactions, involvement of *cis/trans* paths and their interconversion in the reaction make the analysis of mechanisms complicated. For example, see ref 1.
5) After the specified time, the volatile solvent and ethanethiol were distilled off with an argon flow, and the residue was flash-chromatographed to give the product mixture. In DMF and DMSO, the reaction mixture was poured into ether, and the organic layer was washed with dilute aqueous hydrochloric acid, dried over magnesium sulfate, and the solvent was evaporated and then the residue was flash-chromatographed.
6) a) A similar selectivity is observed for both 2-nitro and 3-nitro-9,10-dihydro-9,10-ethanoanthracen-11-ones in the reduction of sodium borohydride in a protic *polar* solvent, methanol. Ohwada, T.; Okamoto, I.; Haga, N.; Shudo, K. *J. Org. Chem.* **1994**, *59*, 3975-3984. b) Haga, N.; Ohwada, T.; Okamoto I.; Shudo, K. *Chem. Pharm. Bull.*, **1992**, *40*, 3349-3351.
7) a) Ohwada, T. *J. Am. Chem. Soc.*, **1992**, *114*, 8818-8827. b) Okamoto, I.; Ohwada, T.; Shudo, K. *J. Org. Chem.*, **1996**, *61*, 3155-3166.
8) In order to interpret enhanced *syn*-additions in polar solvents, it is considered that polar solvents can modify the reaction at least in two ways: polar solvents increase the concentration of free thioethoxide anion in the solution from the aggregated anion cluster (in non-polar solvents), and they activate the nucleophilicity [10] (i.e., raise the HOMO of the reagent), resulting in a strong orbital interaction. Another effect is polarization of the furanone moiety to be activated as the Michael acceptor. Indeed, experimental and calculational studies showed the polarization of carbonyl functionalities arising from dipole and donor-acceptor interactions of the carbonyl oxygen atom with a polar solvent. [11,12,13] Consequently, the polar solvent has a similar effect on protonation of the carbonyl group, lowering the energy of the LUMO of the 2(5*H*)-furanone moiety and increasing the amplitude at the 4-position rather than the 3-position (**A**). [14] Therefore the π* lobe at the reaction center preferentially interacts with the π* orbital of the aromatic fragment and the HOMO of the reagent. This enhanced orbital interaction between the LUMO of the acceptor and the HOMO of the nucleophile results in a larger bias. [15]

Interestingly, **1c** shows an apparently smaller *syn*-preference than **1b** in the neat condition. The coefficients of the LUMO of nitrobenzene are localized on the *para*-position rather than the *meta*-position. So the π*(the olefin of the furanone)-π*(nitrobenzene) overlap of **1c** is smaller than that of **1b**

(Figure 2), while the energy difference of the two fragments is the same in magnitude. Therefore the interaction of these two fragment's π* orbital in **1c** is smaller than that in **1b**, and **1c** shows a smaller *syn/anti* ratio than **1b**. On the other hand, modification of the enhanced orbital interactions by polar solvents hides this minute difference of interactions to give comparable selectivities in polar solvents.

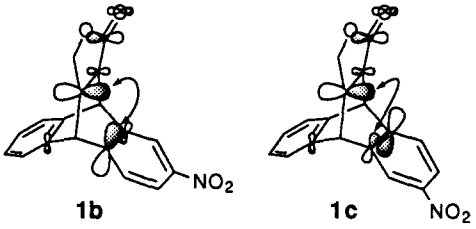


Figure 2 Divergent magnitude of π*(furanone)-π*(nitrobenzene) overlap in **1b** and **1c**

The facial preference described here may also be accounted for in terms of the Cieplak postulate. However, the interpretation of the solvent effect requires modification of the original Cieplak postulate. [9]

9) Cieplak, A. S. *J. Am. Chem. Soc.*, **1981**, *103*, 4540-4552.
10) The thioethoxide anion is not externally solvated in these non-protic solvents, and is a strong nucleophile. See: Abramovitch, R. A.; Struble, D. L. *Tetrahedron*, **1968**, *24*, 357-380.
11) a) Nyquist, R. A.; Putzig, C. L.; Hasha, D. L. *Appl. Spectrosc.*, **1989**, *43*, 1049-1053. b) Nyquist, R. A.; Settineri, S. E. *Appl. Spectrosc.*, **1991**, *45*, 1075-1084.
12) DMSO and DMF have higher acceptor ability than other solvents in terms of AN (acceptor number) values.: Gutmann, V. *The Donor-Acceptor Approach to Molecular Interactions;* Plenum: New York, 1978.
13) Wong, M. W.; Frisch, M. J.; Wiberg, K. B. *J. Am. Chem. Soc.*, **1991**, *113*, 4776-4782.
14) Houk, K. N.; Strozier, R. W. *J. Am. Chem. Soc.*, **1973**, *95*, 4094-4096.
15) It is also possible to consider that the dipole moment of the transition structure of *syn*-addition is larger than that of *anti*-addition. However, this hypothesis can not account for the intrinsic *syn*-preference even in non-polar solvents.
16) One of the referees pointed out the possible predominant complex formation on the *syn* side of the ethanethiol prior to reagent attack because of a favorable electrostatic interaction and this will determine the facial selectivity. In this case, however, the nucleophile on the *syn* side is stabilized and less reactive, and therefore, the nucleophile would attack on the *anti* side.

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