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SELECTIVITY IN CYCLOADDITIONS—XII

THE DIRECTIVE EFFECT OF ENOL ETHERS AND THIOENOL ETHERS IN CYCLOADDITIONS OF NITRILE OXIDES[1]

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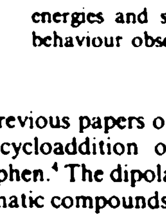
Abstract– Cycloadditions of nitrile oxides to 2,3-dihydrofuran are highly regioselective whereas the regioselectivity of the cycloadditions to 2,3-dihydrothiophen is only moderate. The directing effect of oxygen and sulfur in these cycloadditions could be evaluated at 2.8 and 1.1 Kcal mol^{-1} respectively. The related acyclic sulfur dipolarophiles, (E)-propenyl methyl and phenyl sulfides, similarly undergo cycloadditions with moderate regiochemistry.

The different regioselectivities and reactivities of the dipolarophiles can be related to differences in energies and shapes of their highest occupied orbitals, which are also responsible for the diverging behaviour observed in the electrophilic reactions and 2 + 2 cycloadditions of enol and thioenol ethers.

In previous papers of this series we have investigated the cycloaddition of nitrile oxides to furan[3] and thiophen.[4] The dipolarophilic activity of these heteroaromatic compounds is strongly diminished relatively to the isocyclic system of cyclopentadiene, by two and three powers of ten, respectively, because of the loss of aromaticity in the cycloaddition transition state. The regioselectivity of these cycloadditions remains however almost unchanged, since no sizeable changes in the shapes of the frontier orbitals (FO) occur. The α-carbon of the heteroaromatic compounds, which is the site with the highest HOMO coefficient, binds to the carbon terminus of the moderately electrophilic nitrile oxides, which is the site with the highest LUMO coefficient and cycloadducts **1** are formed with high regioselectivity.



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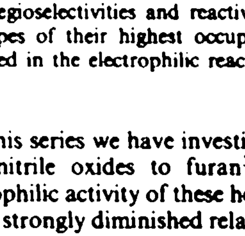

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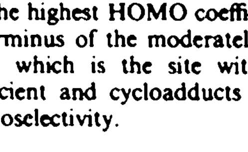

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Because of the presence of the rather reactive enol ether and thioenol ether moieties in the cycloadducts **1**, further addition occurs readily and the asymmetric bisadducts **2** are the predominant products if the cycloadditions are performed with only a moderate excess of furan and thiophene. In the case of the furan only bisadducts **2** are formed from monoadducts **1**. Somewhat surprisingly, a decreased regioselectivity was observed in cycloadditions to the thiophene monoadducts and minor amounts of the symmetrical bisadducts **3** were isolated along with the prevailing bisadducts **2**.

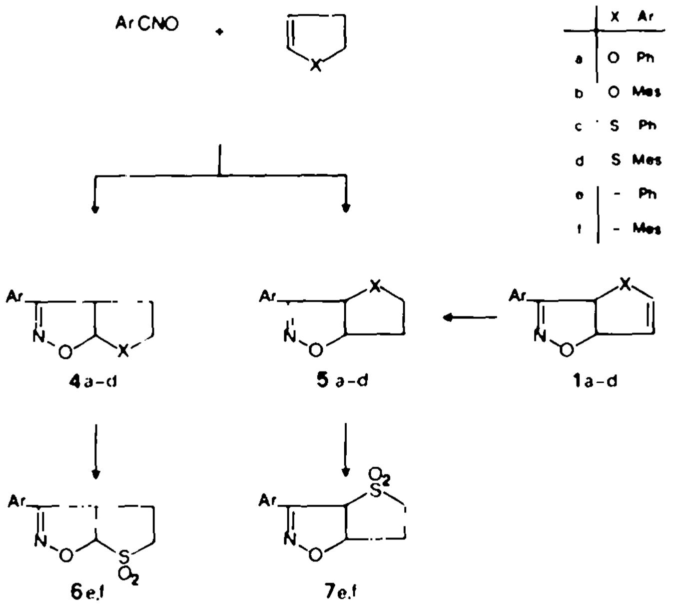
The reduced regioselectivity of the thioenol ether moiety was unexpected in view of the high directive effect of S and O substituents in electrophilic reactions. Enol ethers and thioenol ethers undergo regiospecific attack of electrophiles at the β-carbon and the same β-carbon undergoes attack of electrophilic olefins in 2 + 2 cycloadditions also.[5,6] The behaviour in electrophilic reactions is consistent with the highly polarized HOMOs of these compounds toward the β-carbon.[7] Why should the cycloadditions of the moderately electrophilic nitrile oxides to thioenol ethers be an exception? The behaviour of the thioenol ether moiety in the cycloadditions could be induced by some intrinsic features of the bicyclic system of the dipolarophiles **1**. We investigated therefore more simple systems.

The following is a careful assessment of the regioselectivity of the cycloadditions of benzo- and mesitonitrile oxides to the parent 2,3-dihydrofuran and 2,3-dihydrothiophen. A study of the cycloadditions of nitrile oxides to the related acyclic (E)-propenyl methyl and phenyl sulfides is also included.

The high directing effect of the enol ether moiety in cycloaddition reaction is well documented. Cycloadditions of enol ethers with moderately electrophilic 1,3-dipoles, like nitrile oxides,[8] azides,[9] nitrile imines[10] and nitrones[11] occur with high regioselectivity, which can be attributed to the high HOMO polarization of the dipolarophiles. Thioenol ethers did not arise interest as cycloaddition partners, in spite of the synthetic potential of a sulfide substituent.[12] Only some phenylthioalkenes[5,6] and styryl methyl sulphides[1] have been tested for their dipolarophilic activity in 1,3-dipolar cycloadditions with aromatic nitrile oxides.

RESULTS

The dipolarophilic activity of the unsubstituted 2,3-dihydrofuran and 2,3-dihydrothiophen in cycloadditions with benzonitrile oxide are comparable to that of the isocyclic cyclopentene. As shown by competition experiments, dihydrofuran is 1.8 times more reactive than cyclopentene, whereas the di-



Scheme 1.

polarophilic activity of dihydrothiophen drops to 0.6, relatively to cyclopentene.

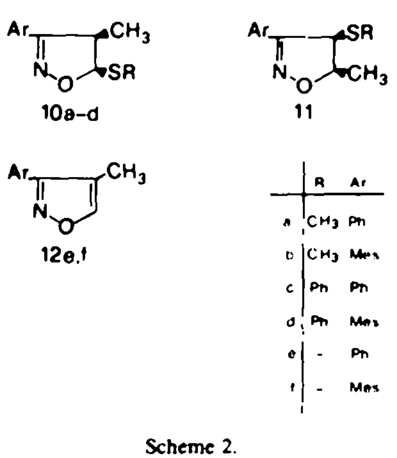
The effects of the heteroatoms upon the regioselectivity are more striking. Cycloaddition of benzo- and mesito-nitrile oxides to excess 2,3-dihydrofuran takes place with high regioselectivity and the predominant adducts **4a** and **4b** could be isolated in high yields (Scheme 1).

The regioisomeric adducts **5a, b** have been synthetized by catalytic hydrogenation of the furan adducts **1a, b**[3] and the presence of the regioisomers **5** in the mother liquors of adducts **4a, b** have been secured by NMR and TLC. The ratios of the adducts **4/5** in the cycloadditions of benzo and mesito nitrile oxides were determined by gas chromatography and are high and similar, 99.4:0.6 and 99.5:0.5 respectively.

Cycloadditions to 2,3-dihydrothiophen similarly afford cycloadducts **4c, d** as the predominant cycloaddition products as well as regioisomers **5c, d**, which are present in sizeable amounts in the reaction mixtures. The ratios of the adducts **4/5** in the cycloadditions of benzo and mesito nitrile oxides are 88:12 and 89:11, respectively, as determined by the integration of their NMR signals in the cycloaddition mixtures. The structures of adducts **4c, d** and **5c, d** have been confirmed by oxidation with m-chloroperbenzoic acid to the know sulfones **6e, f** and **7e, f**. Adducts **5c, d** have been also obtained by catalytic hydrogenation of the thiophen adducts **1c, d**.[4]

The structures of the adducts **4** and **5** are consistent with their NMR spectra (Table 1). As already observed,[3,4] the signals of the isoxazolinic protons are rather close in the spectra of adducts **5** because of some compensation of the deshielding effect of the O and X heteroatoms.

The cycloadditions to the related propenyl methyl and phenyl sulfides similarly occur with reduced regiochemistry. The dipolarophiles were obtained as 1:1 mixtures of the (E)- and (Z)-stereoisomers from the isomerization of allyl methyl and phenyl sulfides and cycloadditions were run with excess dipolarophile (3 equivalents). Column chromatography afforded fair yields of the predominant trans-adducts **8a–d** along with the regioisomers **9a–d** as well as the stereoisomeric cis- adducts **10a–d** (Scheme 2). The regioisomers **9a–d** were isolated in small amounts. In the cycloadditions to propenyl methyl sulfide the ratios **8/9** are the same for both nitrile oxides, 96:4, while lower ratios **8/9** were determined in the cy-



Scheme 2.

Table 1. Chemical shifts[a] and coupling constants[b] of cycloadducts

Compound	H_4[c]	H_5[c]	$J_{4,5}$	Others	
4a	4.1 m	6.32d	6.7	$(CH_2)_2$ 2.2m, 3.3-4.2m	
4b	3.6-4.4[d]	6.31d	6.7	$(CH_2)_2$ 3.6-4.4m	
4c	4.57m	6.45d	8.2	$(CH_2)_2$ 2.4-3 m	
4d	4.47m	6.44d	8.4	$(CH_2)_2$ 2.1-3.1m	
5a	5.78d	5.18dd	6.3	$(CH_2)_2$ 2.2m, 3.4-4m	
5b	5.53d	5.20dd	6.0	$(CH_2)_2$ 2.4m, 3.4-4.4m	
5c	5.01d	5.49m	8.2	$(CH_2)_2$ 2.6-3.1m	
5d	4.91d	5.45m	8.3	$(CH_2)_2$ 2.1-3.3m	
8a	3.59m	5.51d	3.2	4-CH_3 1.33d	SCH_3 2.51s
8b	3.35m	5.52d	4.7	4-CH_3 1.12d	SCH_3 2.31[e]
8c	3.67m	5.75d	3.3	4-CH_3 1.27d	
8d	3.31m	5.67d	5.3	4-CH_3 1.12d	
9a	4.16d	4.93m	3.3	5-CH_3 1.42d	SCH_3 2.03s
9b	3.97d	4.69m	5.9	5-CH_3 1.49d	SCH_3 1.93s
9c	4.45d	4.95m	3.3	5-CH_3 1.27d	
9d	4.39d	4.75m	6.6	5-CH_3 1.45d	
10a	3.89m	5.82d	9.2	4-CH_3 1.26d	SCH_3 2.31s
10b	3.95m	6.02d	8.7	4-CH_3 1.04d	SCH_3 2.32[e]
10c	3.91m	6.04d	9.2	4-CH_3 1.35d	
10d	3.92m	6.16d	9.2	4-CH_3 1.09d	

[a] Chemical shifts in part per million (δ) from internal Me_4Si. Multiplicity: d, doublet; dd, doublet of doublet; s, singlet; m, multiplet. Solvent: $CDCl_3$

[b] In Hz

[c] Numbering refers to the isoxazoline ring

[d] Together with methylenic protons of the ring

[e] With mesityl CH_3

cloadditions of benzo and mesito nitrile oxide to propenyl phenyl sulfides, 84:16 and 83:17, respectively., The cis adducts **10a–d** were isolated in rather consistent amount, and correspond to *ca* 1/3 of the amounts of the predominant trans adducts **8**. Because of the lower reactivity of the (Z)-dipolarophiles, as usual in 1,3-dipolar cycloadditions,[13] no attempt was made to isolate the cis-regioisomers **11** from the cycloaddition mixtures.

The structures of the adducts **8**, **9** and **10** rely upon their NMR spectra (Table 1) as well as on the behaviour under hydrolitic conditions. Adducts **8** and **10** undergo ready elimination to isoxazoles **12e, f** upon boiling with acids, because of the presence of a S, O acetalic carbon. Under the same conditions adducts **9** were recovered unchanged.

DISCUSSION

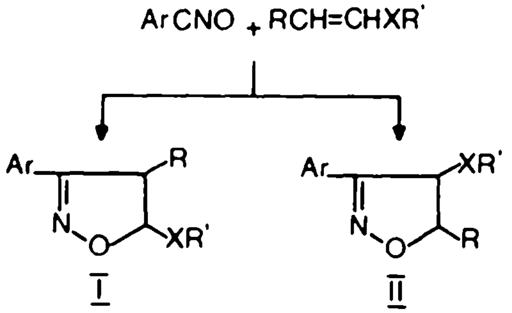
General aspects

The cycloaddition of nitrile oxides to 2,3-dihydrofuran fully conforms to the expectations. The resonance interaction between the double bond and the oxygen lone pair places a negative charge at the β-carbon of the enol-ether, thereby increasing the nucleophilic potential of the double bond and differentiating the vinylic carbons. The moderately electrophilic benzonitrile oxide does indeed react 1.8 times faster with 2,3-dihydrofuran than with the isocyclic reference cyclopentene and a highly regioselective cycloaddition takes place. The regioisomers are formed in a 99.4:0.6 ratio, which corresponds to the quite high value of 2.8 Kcal mol^{-1} for the $\Delta\Delta G^{\neq}$ between the paths leading to regioisomers I and II (Table 2).

On going to 2,3-dihydrothiophen the reactivity and the regioselectivity of the cycloaddition drop. Dihydrothiophen is less reactive than cyclopentene (K_{rel} 0.6) and both the regioisomers could be readily isolated in a 9:1 ratio. The $\Delta\Delta G^{\neq}$ between the regioisomeric paths falls to 1.1 Kcal mol^{-1}. Similar attenuated regioselectivities are observed in the cycloadditions to the acyclic analogs, (E)-propenyl methyl and phenyl sulfides. The acyclic (E) propenyl methyl sulfide undergoes more regioselective cycloadditions than dihydrothiophen, while the regioselectivity is lesser with (E) propenyl phenyl sulfide, because of the lesser donating ability of the SC_6H_5 substituent caused by the inductive and competing conjugative effects of Ph.

The partial rates of formation of the regioisomers

Table 2. Regioisomer distribution in the cycloadditions of nitrile oxides to 2,3-dihydrofuran, 2,3-dihydrothiophen and propenyl methyl and phenyl sulfides



	I/II		ΔΔG$^{\ne}$ I/II[a]	
Dipolarophile	Ph	Mes	Ph[b]	Mes[c]
2,3-Dihydrofuran	99.4:0.6	99.5:0.5	2.8	3.1
2,3-Dihydrothiophene	88:12	89:11	1.1	1.2
(E) Propenyl methyl sulfide	96:4	96:4	1.7	1.9
(E) Propenyl phenyl sulfide	84:16	83:17	0.9	0.9

[a] Kcal/mole
[b] 0°, ether
[c] 25°, benzene

which can be obtained from the relative rates of cycloadditions to dihydrofuran, dihydrothiophen and cyclopentene and from the regioisomer ratios, allow for a more detailed analysis of the effect of the heteroatoms upon the reactivity and regiochemistry. The partial rate factors are given in Fig. 1, which displays the changes of the reaction barriers leading to the regioisomers relatively to the two equivalent directions of addition of cyclopentene.

As shown in Fig. 1, the rate of formation of regioisomer I is moderately increased by substitution of CH_2 with oxygen (the barrier lowers) while S substitution has an almost negligeable effect. On the other hand the heteroatoms strongly affect the rate of formation of regioisomers II, which decreases sharply in the order $CH_2 > S > O$ (the barrier rises). Since regioselectivity is the difference between the rates of formation of the regioisomers, the large effect of the

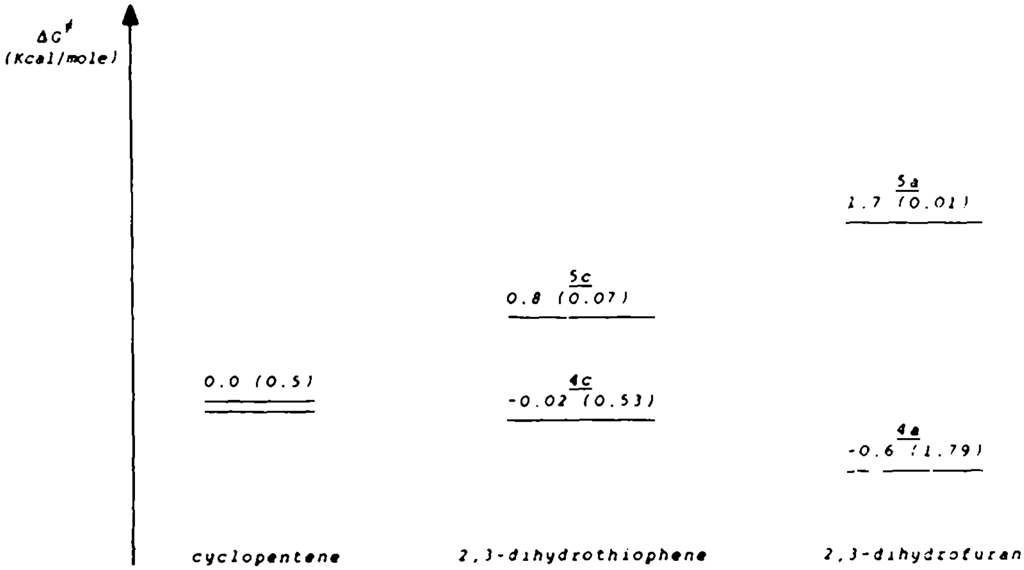
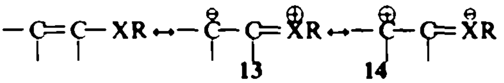


Fig. 1. The barriers of the predominant regioisomers **4a, c** are lowered while those leading to the minor regioisomers **5a, c** are sharply raised, relatively to the two equivalent directions of addition of cyclopentene. Numbers above levels are the changes in activation energies, as obtained from the relative rates of formation of regioisomer given in parentheses

heteroatoms on the regioselectivity depends only marginally upon the increase of the rate of formation of regioisomers I and is mainly determined by the sharp decrease of the rate of formation of regioisomer II.

The only moderate changes in the reactivity of the dipolarophiles follow simply because the total reactivity refers to the sum of the rates of formation of both regioisomers. In the case of dihydrothiophen the increase of the rate of formation of regioisomer I is almost negligeable and the sharp decrease of II determines its lower dipolarophilic activity relative to cyclopentene. In the case of dihydrofuran the rate of formation of regioisomer I more than doubles and a dipolarophilic activity higher than cyclopentene results.

The trends shown by the partial rate factors and by the regioselectivities point out that the mechanism of action of the two heteroatoms is at least qualitatively similar as far as the assistance to regioisomer I and opposition to regioisomer II are concerned, and that an alkoxy substituent is much more effective than a thioalkoxy substituent in affecting the dipolarophilic activity of a double bond. In VB terms, this behaviour corresponds to a less effective resonance of sulfur with the double bond. This view agrees indeed with the pi delocalization parameters derived from the Hammett equation. These indicators of conjugation ability, i.e. σ_R,[14] places a thiomethoxy substituent ($\sigma_R = -0.20$) between methyl (-0.11) and methoxy (-0.45). Thus, the different behaviour of enol and thioenol ethers can be ascribed to a reduced importance of the resonance formula **13** when X = S, or it may be the consequence of second pi interaction mechanism indicated in **14**, where the pseudo unsaturated SCH$_3$ substituent accepts charge by using its d orbitals.



$$-\underset{|}{C}=\underset{|}{C}-XR \leftrightarrow -\underset{|}{\overset{\ominus}{C}}-\underset{|}{C}=\overset{\oplus}{X}R \leftrightarrow -\underset{|}{\overset{\oplus}{C}}-\underset{|}{C}=\overset{\ominus}{X}R$$

13 **14**

The latter mechanism is invoked to account for the wild changes of σ_R. observed for alkyl thio substituents[14] and could account also for the addition of nucleophiles to thioenol ethers.[6]

The effect of the heteroatoms in the cycloadditions appears therefore small and well behaved and precedented. In reactions where charged intermediates are formed the influence of the heteroatom increases enormously, since the charge stabilization potential of the heteroatom is fully exploited. The replacement of an alkyl with alkoxy or thioalkoxy substituent causes enormous rate enhancement in electrophilic additions to olefins as well as the exclusive attack of the electrophile at the β position. In hydrations, for instance, the rate of enol ethers and thioenol ethers are enhanced by 10 to 8 powers of ten, respectively, relative to the corresponding alkyl substituted alkenes.[15,16]. Alkoxy and thioalkoxy substituents similarly activate olefins toward 2 + 2 cycloadditions with TCNE. At variance with hydrations, however, thioalkoxy substituents are more effective than alkoxy in promoting the 2 + 2 cycloadditions of TCNE.[17,18] The origin of this different behaviour has hitherto remained unexplained, in spite of the importance of these reactions as models for late transition state reactions.[19] In principle differences in solvations of the intermediates or in their transition structures could be devised to account for the diverging behaviours.

A crude understanding of the main features involved in selectivity and reactivity of enol ethers and thioenol ethers can then be based on the lower resonance of thioenol ethers according the VB formalism. An alternate description of the chemistry of these compounds can be provided in the framework of the frontier orbitals (FO) theory.[20-22] The FO description is much more rich in details and affords a more flexible model to account for the subtleties in their chemistry.

The orbitals

The ab initio STO-3G[23] eigenvectors and eigenvalues of the two highest occupied and the lowest unoccupied orbitals of the cyclic dipolarophiles and those of the propenyl and vinyl methyl ethers and sulfides are given in Table 3 along with the polarization of the orbitals defined as the difference between the squares of the coefficients at the β and α carbons of the double bonds. Also given in Table 3 are the corresponding MINDO/3[24] eigenvalues. The two methods of calculations give similar trends as far as the shapes of the orbitals and the changes in the orbital energies along the series are concerned. The MINDO/3 energies compare however more favourably with available PES data. Thus, the two lowest vertical IPs of vinyl methyl ether (9.05, 12.0 eV)[25] and vinyl methyl sulfide (8.45, 11 eV)[25] are fairly well reproduced by MINDO/3. Similarly the IPs of 3,4-dihydro-2H-pyran (8.56, 12.06 eV)[26] and 4.4 - dimethyl- 3,4 - dihydro - 2H - thiopyran (8.06, 10.85 eV)[27] compare favourably with the orbital energies of dihydrofuran and dihydrothiophene. Estimates of the LUMO energies of vinyl methyl ether and sulfide, based upon the empirical relation[22] (1)

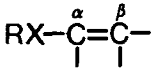
$$E(\mathrm{LUMO}) = E(\mathrm{HOMO}) + \Delta E(\pi \rightarrow \pi^*) + (J_{ij} - 2K_{ij}) \quad (1)$$

and using the transition energies of the unsatured ether (6.60 eV)[27] and sulfide (5.50 eV)[27] and a $J_{ij} - 2K_{ij}$ values of 5 eV[22], also compare favourably with their MINDO/3 LUMO energies.

The shapes of the FMOs of the cyclic dipolarophiles are displayed in Fig. 2. Also given in Fig. 2, near the drawings of the orbitals, are the polarization as well as, in parentheses, the difference and the sum of the absolute value of the coefficients on the β and α carbons of the double bonds. These latter indexes will be referred to hereafter as asymmetry (difference) and π-density (sum) of an orbital.

The general changes of the cyclopentene MOs upon substitution with the heteroatoms are as predicted for the formation of an heteroallyl anion. Thus, the HOMO becomes somewhat non bonding and raises in energy, being polarized toward the β carbon. The LUMOs and SHOMOs become more antibonding and bonding, respectively and polarize toward the α carbon. Aside from these general characteristics, however, the HOMOs of the two heterodipolarophiles are significantly different in energies, polarizations and compositions. When compared to dihydrofuran HOMO, the HOMO of dihydrothiophen

Table 3. STO-3G eigenvectors and eigenvalues for the frontier orbitals[a]



$$RX-\overset{\alpha}{C}=\overset{\beta}{C}-$$

Compound	SHOMO						HOMO						LUMO					
	X	C_α	C_β	ϵ,eV	ϵ,eV[b]	P[c]	X	C_α	C_β	ϵ,eV	ϵ,eV[b]	P[c]	X	C_α	C_β	ϵ,eV	ϵ,eV[b]	P[c]
2,3-Dihydrofuran	.60	.43	.27	-11.61	-11.87	-.12	-.59	.43	.59	-6.82	-8.86	.17	.24	-.81	.76	8.75	2.03	-.09
2,3-Dihydrothiophene	.50	.50	.38	- 9.76	-10.97	-.11	-.82	.29	.46	-5.91	-8.55	.13	.18	-.80	.77	8.67	1.77	-.06
Cyclopentene							-.13	.60	.60	-7.74	-9.39	.00	.06	-.79	.79	8.82	1.53	.00
(E) Propenyl methyl ether	.66	.41	.18	-11.65	-11.90	-.13	-.56	.45	.62	-6.96	-8.92	.18	.29	-.82	.76	9.10	2.13	-.08
(E) Propenyl methyl sulfide	.53	.56	.41	- 9.66	-10.86	-.15	-.84	.30	.48	-5.95	-8.57	.14	.25	-.81	.78	8.90	1.84	-.05
Vinyl methyl ether	.63	.42	.22	-11.84	-11.97	-.13	-.58	.43	.64	-7.36	-9.21	.22	.30	-.83	.77	9.02	2.32	-.09
Vinyl methyl sulfide	.49	.57	.46	-10.00	-11.15	-.11	-.86	.26	.48	-6.20	-8.72	.16	.25	-.82	.78	8.83	2.02	-.06

[a] Experimental geometries were used for the calculations of 2,3-dihydrofuran and 2,3-dihydrothiophene (T. Ueda and T. Shimanouchi, J. Chem. Phys. **47**, 5018 (1967)), cyclopentene (G.W. Rathjens, J. Chem. Phys. **36**, 2401 (1962)) and vinyl methyl ether and sulfide (S. Samdal and H.M. Seip, J. Molecular Structure **28**, 193 (1975). A standard methyl was used for the propenyl dipolarophiles (J.A. Pople and J.L. Beveridge, Approximate Molecular Orbital Theory, McGraw-Hill, N.Y. (1970)).

[b] MINDO/3 eigenvalues

[c] Polarization defined as $C_\beta^2 - C_\alpha^2$

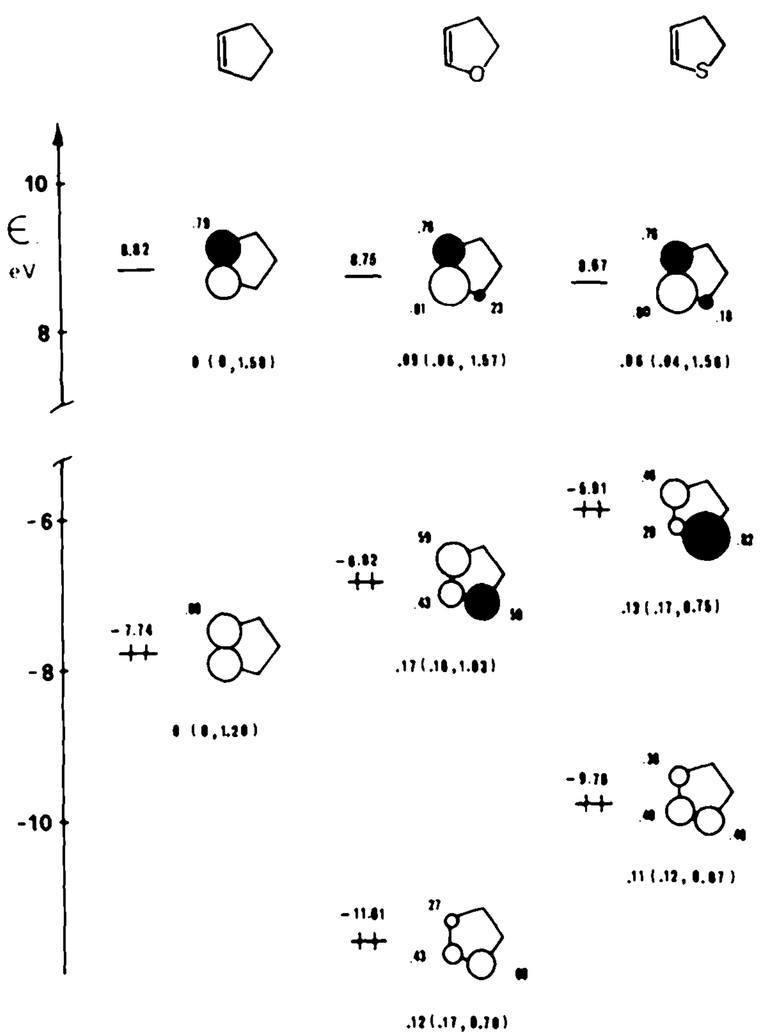


Fig. 2. STO-3G frontier molecular orbitals of cyclopentene, dihydrofuran and dihydrothiophen. Numbers above the levels and near the lobes represent STO-3G energies and coefficients. The polarization and, in parentheses, asymmetry and π-density of the orbitals are given below the drawings

clearly shows up higher in energy, heavily localized at the heteroatom and less polarized. Only the asymmetry, as defined above, is similar in the two dipolarophiles. The difference arises because of the different sets of component orbitals as summarized in the interaction diagrams of Fig. 3.

As shown in Fig. 3(a) the enol ether system of dihydrofuran derives by interaction of the π and π*MOs of cyclopentene with a lower lying lone pair orbital. According to the mixing rules,[28] orbitals split apart. The π MO mixes in the lone pair in an antibonding fashion, raises in energy, polarizes in second order and becomes the HOMO of the enol ether. The thioenol ether system of dihydrothiophen derives instead by interaction of the π and π*MOs of cyclopentene with a sulfur lone pair, which is higher in energy than the π orbital (Fig. 3b). The sulfur lone pair mixes in the π* and π orbitals in a bonding and antibonding fashion, respectively, raises in energy and becomes the HOMO of dihydrothiophen. Since the HOMO retains a more strict parentage with the highest of the occupied orbitals of the fragments, as shown in Fig. 3, the HOMOs of dihydrofuran and dihydrothiophen result mainly localized on the C=C and X portions of the heteroallylic system, respectively, as displayed in drawings of Fig. 2. As a consequence the sum of the absolute values of the coefficients of the HOMO, i.e. the HOMO π density, is lower in dihydrothiophen than in dihydrofuran, whereas the reverse is true for the SHOMO π density (Fig. 2, second number in parentheses).

The asymmetry of the orbitals on the C=C portion of the system arises as a second order correction to the alkene orbitals, as described for π in Fig. 3(a), or as a first order correction to the heteroatom lone pair orbital, as described for X in Fig. 3(b), and could be evaluated with the aid of the appropriate formulas.[28] In general, asymmetry increases in both cases, albeit differently, with the increase of some intrinsic conjugating ability of the fragments, namely the resonance integral H_{ij}, and with the decrease of the energy gaps between the fragments. The resonance integrals depend upon the type of the atoms connected and on their overlap.[29] Since the overlaps of the pi orbitals of carbon with those of oxygen and sulfur are similar at the C-O and C S bond lengths, the resonance inte-

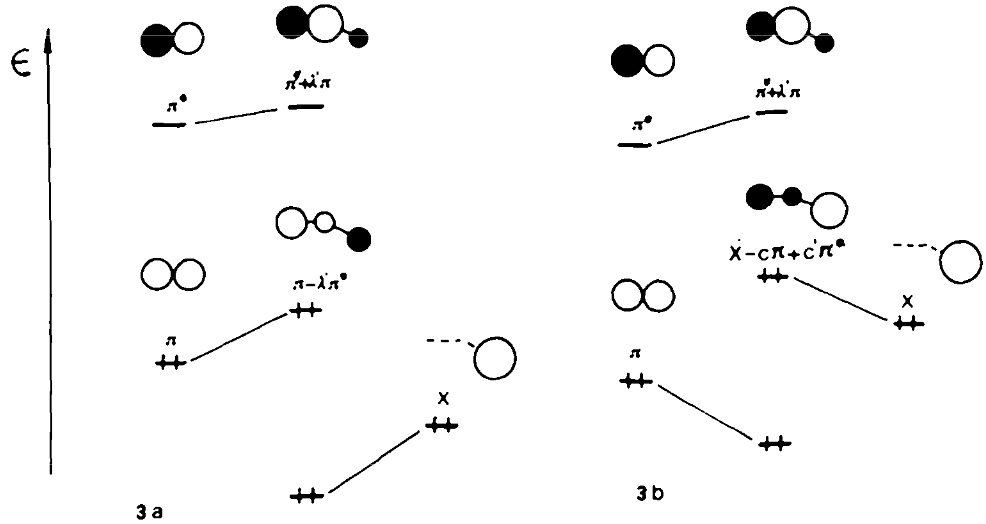


Fig. 3. Derivation of enol ether and thioenol ether orbitals by interactions of oxygen and sulfur lone pairs with alkene π and π* orbitals. First and second order mixing coefficients are represented by c and λ, respectively.

gral is mainly determined from the type of the atoms. Thus, resonance integrals are larger for C–O connections that for C-S connections,[29] in keeping with the strong and weak character of the C–O and C–S bonds, respectively. The asymmetries of the C–C portion of the dihydrothiophene MOs are therefore usually smaller than the corresponding ones of dihydrofuran. Only in the case of the HOMOs the more favourable energy gaps of sulfur almost compensate for its smaller resonance integral and a similar asymmetry results in dihydrofuran and dihydrothiophen HOMOs (Fig. 2, first number in parentheses).

The reasons of the reduced polarization in dihydrothiophen HOMO can then be grasped. Polarization is the difference of the squares of the coefficients and can be expressed as a product of the π density and the asymmetry of the orbitals. Since the HOMO asymmetries are similar, reduced polarization follows from the reduced π density

Reactivity and regioselectivity

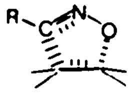
The shapes and the energies of the orbitals we have described above are the basis for the understanding of the reactivity and regioselectivity in the framework of the FO theory. In the cycloadditions of the moderately electrophilic nitrile oxides[7] with the electron rich enol ethers and thioenol ethers the predominant interaction is that between the LUMO of the dipole and the HOMO of the dipolarophile. The remaining FO and the other occupied vacant MO interactions do not change the overall consequence of the dominating one and will be considered only when specifically required.

The energy gain of an interaction (ΔE) is given by expression[20-22]

$$\Delta E = 2\frac{H_{ij}^2}{E_{HO} - E_{LU}^{dipole} - Q} = 2K^2\frac{S_{ij}^2}{E_{HO} - E_{LU} - Q} \qquad (2)$$

where the initial energy gap between the FO orbitals has been reduced by factor Q to account for the narrowing of the gap during the reaction. Within the Mulliken approximation ($H_{ij} = KS_{ij}$), reactivity (log K) is then proportional to the square of the overlap between the interacting orbitals and inversely proportional to their energy gap.

As far as the formation of the regioisomer I is concerned, on going from cyclopentene to dihydrofuran an increase of reactivity is observed, since the dihydrofuran HOMO increases in energy (lower gap) while overlap decreases only slightly. This follows because of the negligible change of the β coefficient, which leaves the large C... C bond formaton almost unaffected, while the sharp decrease of the α coefficient affects the smaller C... O bond formation of the concerted and slightly asynchronous transition state of nitrile oxide cycloadditions,[30,31] sketched in **15**.



15

In the case of dihydrothiophen, however, the definite drop of the HOMO β and α coefficients—due to the composition of this orbital —completely offsets the benefits of its higher energy and some intervention of SHOMO, which is highly π populated, could be necessary to account for the almost unchanged rate of formation of I.

The faster drop in reactivity for the orientation leading to regioisomers II can be similarly accounted for, since the larger drops of the HOMO α coefficients significantly reduce the C... C bond formation in TS **15**. In the case of dihydrofuran the large decrease of the HOMO α coefficient (0.43) and the negligeable change of the HOMO β coefficient (0.59) with respect to cyclopentene HOMO coefficients (0.60) follow from the renormalization of the orbitals.[28]

The comparison of the regioselectivities can be made more thoroughly with the aid of the analytical expression of the regioselectivity effect (ΔΔE) of the orbital interaction shown in eqn. (3)[22]

$$\Delta\Delta E = A\,\frac{P_{HO}}{E_{HO} - E_{LU}^{dipole} - Q} \qquad (3)$$

The regioselectivity effect is proportional to the polarization of the orbital of the dipolarophile (P_{HO}) and inversely proportional to the energy gap between the interacting orbitals after correction with Q. The quantity A, E_{LU}(dipole) and Q, which depends upon the dipole and the transition state structure, can be taken as constant when comparing the selectivities of the same dipole

Thus, the lower regioselectivity observed with dihydrothiophen follows immediately from the low polarization of its HOMO, which more than compensates the opposing effect of its higher energy. Numerical proof can be obtained from eqn (3) using the estimated EA of benzonitrile oxide (0.5 eV)[7] and the MINDO/3 HOMO energies of the dipolarophiles. Even using the largest recommended values of Q (3–5 eV),[22] the decrease of P_{HO} remains by far ahead the increase caused by the gap factor.

The regioselectivity effect of the HOMO (dipolarophile)-LUMO(dipole) interaction is somewhat decreased by the SHOMO(dipolarophile)-LUMO(dipole). The influence of the latter interaction upon the regioselectivity is however small because of the smaller SHOMO polarization and its lower energy. On the other hand the other FO interaction, i.e. HOMO(dipole)-LUMO(dipolarophile), still favours slightly regioisomer I, as a result of the union of the nucleophilic nitrile oxide oxygen to the α carbon, which is the site of the highest LUMO coefficient.

On going from benzonitrile oxide to the more nucleophilic mesitonitrile oxide no changes in regioselectivity are observed (Table 2). This follows because the FO interactions favour the same regioisomer. Sizeable changes in regioselectivity show up instead in those cycloadditions where FO interactions privilegiate different regioisomers.[1,4,32]

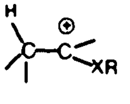
In summary the cycloadditions of enol ethers and thioenol ethers with nitrile oxides nicely obey to FO prescriptions. The regioselectivity parallels the polarizations of the dipolarophile HOMOs, while the rates of formation of the regioisomers depend more subtly upon the magnitude of the HOMO coefficients as well as on the HOMO energies.

Further subtleties clarified

The simple picture of the opposing influence of HOMO coefficients and energy in determining the reactivity of dihydrothiophen lends itself to further applications to the chemistry of enol and thioenol ethers. The two classes of compounds offer different opportunities to attacking species. Enol ethers possess a high negative charge at the β carbon (*cf* ^{13}C spectra)[33,34] and their HOMOs have the highest lobe at the β carbon. These compounds are therefore biased toward electrostatic as well as orbital mixing interactions. Thioenol ethers possess a less charge-polarized C=C double bond (*cf* ^{13}C spectra),[16a] and their HOMOs are higher but less π-populated. These compounds are therefore inclined to offer mainly energy gap advantage to attacking species.

Thus, charged and relatively high lying LUMO reactants, like proton or nitrile oxides, prefer attack at the β carbon of enol ethers, while uncharged and low lying LUMO reactants, like TCNE, attack faster the thioenol ether double bond. TCNE seems indeed ideally suited as a partner of a thioenol ether. The TCNE LUMO has a very low energy (EA = 2.88 eV)[35] and relatively low coefficients on the double bond,[36] a fact which further disadvantages its union with enol ethers. The low separation of the FOs of TCNE and thioenol ethers and their low overlap, because of the low coefficients on their double bonds, could even induce a change in the mechanism. The reaction could take place through radical ion pairs intermediates, formed by single electron transfer (SET) between the reactants. A change of mechanism in 2 + 2 reactions has been envisaged for reactants with small FO gaps[22] and some evidence has been gained from selectivity studies of TCNE cycloadditions to complex trienes.[37]

Aside from the question of mechanism, the different opportunities model correctly accomodates the higher reactivity of enol ethers in hydration and the higher reactivity of thioenol ethers in TCNE 2 + 2 cycloadditions. Both of these reactions are believed to involve the rate determining formation of the charged intermediates depicted in **16**[6] and **17**.[19]



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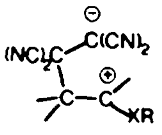


17

The donor ability of the heteroatoms accounts for the exclusive β attack observed. The stability of the intermediates *alone* cannot however accounts for the diverging reactivities, since hydration requires oxygen as a better donor than sulfur, whereas the reverse, i.e. sulfur better than oxygen, is implied in TCNE cycloadditions. In spite of wide discussion and controversy, consensus has been reached that oxygen is, in solution, a better donor than sulfur in stabilizing an adjacent carbenium ion.[38] Thus the reactivity trend observed in hydration can be ascribed either to the stability of the charged intermediates or to charge and FO interactions, which also favour oxygen over sulfur. Factors other than the stability of the intermediates must be involved in the enhanced reactivity of thioenol ether toward TCNE! In FO terms these enhancing factors can be easily identified as a very favourable energy gap. Higher lying LUMO π^2 components, such as diethyl acetylenedicarboxylate, do indeed enter 2 + 2 cycloadditions with enol ethers preferentially.[39]

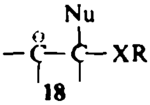
The recognition of the involvement and importance of FO interactions in accounting for the reactivity trends of enol and thioenol ethers suggests some limitations in the use of late transition state models for hydrations and TCNE cycloadditions. Late TS models appear suitable as long as no significant changes in the FO interactions occur. The apparent success[19] of the late TS model in relying the reactivity of cyano alkenes toward enol ethers to the stability of the intermediates may derive in part from a parallelism between FO density effects and the stability of the intermediates.

The different types of interactions involved in TCNE and hydration reactions show up again quite clearly in the puzzling response of thioenol ethers to substituent effect. Thus, upon increasing the donor ability of the alkyl substituents at sulfur (inductive order: Me < Et < iPr < tBu), the reactivity of thioenol ethers increases in TCNE cycloadditions[17,18] and decreases in hydrations.[16] This perplexing behaviour follows quite naturally from Fig. 3(b). Donor substituents raise the sulfur lone pair.[40] This causes the HOMOs of thioenol ethers to raise and to lose π density because of the increased π/SR separation. As a consequence higher reactivity toward TCNE and retardation in hydration are observed, since diverging energy and density effects are reflected. The same set of alkyl substituents promotes in the inductive order the reactivity of enol ethers in hydrations[41] and TCNE cycloadditions,[42] since the HOMO energies increase in that order (Fig. 3a), while the β coefficients are only slightly affected.

Substitution on the double bond causes again distressingly dissimilar results.[18] The higher sensitivity of thioenol ethers to steric effects in TCNE cycloadditions[18] is probably related to their low HOMO π density, which restrict somewhat the transition state flexibility because of the poorer overlap.

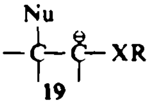
The FOs clarify other aspects of the reactivity of these interesting classes of compounds. Thus, the FOs of thioenol ethers nicely account for the site selectivity observed in reactions with carbenes. These species undergo with similar ease 2 + 1 cycloadditions to the double bond as well as 1,1-cycloadditions at sulfur, yielding ylides and insertion products.[43,44] High lying LUMO carbenes (CCl_2) attack preferentially the thioenol double bond,[43] whereas low lying LUMO carbenes (dicarbalkoxy carbenes) attack at sulfur,[44] where the highest coefficient of the thioenol ether HOMO is located.

Finally, the striking different orientations[6] of nucleophilic additions to enol and thioenol ethers can be understood. Nucleophiles add to the α carbon of enol ethers, which is the site of highest LUMO coefficient, yielding adducts **18**, in spite of the larger thermodynamic stability[45] of the regioisomeric anions **19**. On the other hand thioenol ethers yield the β addition anions **19**.



$-\overset{\ominus}{\underset{|}{C}}-\overset{Nu}{\underset{|}{C}}-XR$

18



$-\overset{Nu}{\underset{|}{C}}-\overset{\ominus}{\underset{|}{C}}-XR$

19

The large and well-known ability of sulfur in stabilizing adjacent anionic centres[46] causes probably a predominance of late transition state effects over the opposing and feeble FO effects, as a consequence of the low LUMO polarization of thioenol ethers. Predominance of late transition state effects may be not required even in this case. Our STO 3G LUMOs of thioenol ethers are not above any suspicion, since inclusion of d orbitals in the basis set has been shown to stabilize significantly sulfonium ylides[47] and is expected to reduce or even to reverse the LUMO polarizations of thioenol ethers, as discussed at length earlier.[1] In VB terms a negligeable or reversed LUMO polarization would correspond to some weight of the otherwise unnecessary formula **14**.

CONCLUSIONS

With respect to the isocyclic cyclopentene, dihydrofuran shows a slightly increased reactivity in the cycloaddition with nitrile oxides whereas in the case of dihydrothiophen a slight retardation is observed. This mild effect of the heteroatoms upon the reactivity stands in marked contrast with the enormous rate enhancement observed in reaction where ionic intermediates are formed and are consistent with the concerted nature of cycloaddition reactions.[48] The regioselectivity of the cycloadditions are more heavily affected by the heteroatoms and could be evaluated at 2.8 and 1.1 Kcal/mol for cycloadditions of benzonitrile oxide to dihydrofuran and dihydrothiophen, respectively.

The reactivity and regioselectivity trends observed in the cycloadditions can be accounted for in terms of FO interactions, taking into account both orbital energy and coefficient changes. Because of the heavy localization at sulfur of the HOMOs, the low IPs of thioenol ethers are not reliable indexes of reactivity since the low π density of the HOMOs offsets the benefits of their higher energies. A further consequence of the low π density of the HOMOs is a reduced polarization, which shows up in a reduced regioselectivity.

The FO description of the dipolarophiles encompasses their VB formulation and allows for a more flexible model in accounting for the chemistry of these important classes of electron rich dipolarophiles. The varying reactivity of thioenol ethers, with respect to enol ethers, can be related to the composite nature of their high energy HOMOs. High lying LUMO or charged ractants attack thioenol ethers slower than ethers because of their lower HOMO π density and lower charge polarization. Rate enhancement are however observed in reaction with low LUMO reactants, which take advantage of the higher HOMO energies of thioenol ethers.

Aside from accounting for the main differences of the chemistry of enol and thioenol ethers, the scheme developed above is amenable to experimental verification and should promote more detailed experimental work and refined theoretical analyses of these important representatives of electron rich reactants.

EXPERIMENTAL

All m.ps are uncorrected. IR spectra: Perkin–Elmer mod. 197 spectrophotometer, Nujol mulls. NMR spectra: Perkin–Elmer R12 spectrometer. Microanalyses were performed by Dr. L. Maggi Dacrema on a Elemental Analyzer 1106, Carlo Erba. Satisfactory analytical data (± 0.4% for C, H, N) were obtained for all new compounds (Table 4). Gas chromatographic analyses were performed on a Hewlett Packard instrument, with a glass column packed with a 2.5% OV 17 and 3% Carbowax 20 M. Column chromatography and qualitative TLC: silica gel H and GF_{254} (Merck) respectively, eluent cyclohexane: AcOEt 9:1 to 7:3, unless otherwise specified. Samples from different experiments were identified by mixed m.ps and superimposable IR spectra.

Starting materials. 2,3-Dihydrofuran was obtained by alkaline isomerization of 2,5-dihydrofuran.[49]

Table 4. Analytical data for all new compounds

Compound	Formula	Found %			Required %		
		C	H	N	C	H	N
4b	$C_{14}H_{17}NO_2$	72.48	7.42	6.27	72.70	7.41	6.06
4c	$C_{11}H_{11}NOS$	64.55	5.60	6.76	64.35	5.40	6.82
4d	$C_{14}H_{17}NOS$	68.30	7.05	5.71	67.97	6.92	5.66
5a	$C_{11}H_{11}NO_2$	69.95	5.93	7.31	69.82	5.86	7.40
5b	$C_{14}H_{17}NO_2$	72.73	7.42	6.05	72.70	7.41	6.06
5c	$C_{11}H_{11}NOS$	64.55	5.71	6.64	64.35	5.40	6.82
5d	$C_{14}H_{17}NOS$	67.85	6.87	5.71	67.97	6.92	5.66
8a	$C_{11}H_{13}NOS$	63.50	6.26	6.73	63.75	6.32	6.76
8b	$C_{14}H_{19}NOS$	67.77	7.75	5.67	67.44	7.68	5.62
8c	$C_{16}H_{15}NOS$	71.35	5.57	5.18	71.36	5.61	5.20
8d	$C_{19}H_{21}NOS$	72.91	6.76	4.56	73.29	6.80	4.50
9a	$C_{11}H_{13}NOS$	63.61	6.37	6.71	63.75	6.32	6.76
9b	$C_{14}H_{19}NOS$	67.66	7.62	5.71	67.44	7.68	5.62
9c	$C_{16}H_{15}NOS$	71.24	5.73	5.15	71.36	5.61	5.20
9d	$C_{19}H_{21}NOS$	73.18	6.71	4.55	73.29	6.80	4.50
10a	$C_{11}H_{13}NOS$	63.50	6.33	6.73	63.75	6.32	6.76
10b	$C_{14}H_{19}NOS$	67.39	7.67	5.74	67.44	7.68	5.62
10c	$C_{16}H_{15}NOS$	71.56	5.62	5.23	71.36	5.61	5.20
10d	$C_{19}H_{21}NOS$	73.03	6.78	4.52	73.29	6.80	4.50
12f	$C_{13}H_{15}NO$	77.63	7.72	6.85	77.58	7.51	6.96

2,3-Dihydrothiophen was prepared by treatment of tetrahydrothiophen-oxide with benzoic anhydride.[50] Propenyl methyl sulfide[51] and propenyl phenyl sulfide[52] were obtained by alkaline isomerization of allyl methyl and phenyl sulfides, respectively, as 1:1 mixtures of (E) and (Z) stereoisomers (NMR).

General cycloaddition procedures. To a stirred, ice cooled soln of benzhydroximic acid chloride and of dipolarophile in anhyd ether, Et_3N (1.1 eq) was added dropwise. After keeping 2 days at rt, the triethylammonium salt was filtered off and the filtrate was evaporated at reduced pressure.

In cycloadditions with mesitonitrile oxide, a soln of the dipole and the dipolarophile was stored at room temp for 1 month. Evaporation of the solvent left a residue.

Catalytic hydrogenation of adducts **1a–d**

A soln of 187 mg (1 mmole) **1a**[3] in 10 ml HOAc and 40 ml AcOEt adsorbed in the presence of 50 mg Pd/C 10% 1 mmole of H_2 in 10 min. The catalyst was filtered off and the soln was evaporated. Crystallization from petroleum ether afforded 150 mg (79%) of **5a**, colorless crystals, m.p. 45–46°.

Catalytic hydrogenation of adducts **1b**[3] and **1c, d**[4] similarly yielded **5b**, colorless crystals from hexane, m.p. 65–66°, **5c**, colorless crystals from isopropyl ether, m.p. 92–93° and **5d**, colorless crystals from ethanol, m.p. 100–101°, respectively.

Cycloadditions to 2,3-dihydrofuran

5 g (32 mmole) benzhydroximic acid chloride were reacted with 7 g (100 mmole) 2,3-dihydrofuran in 100 ml anhyd ether. Crystallization of the residue from diisopropyl ether afforded 6.46 g (98%) of adduct **4a**, colorless crystals, m.p. 104–105° (lit[46] 105–106°). TLC and NMR examination of the mother liquors show the presence of adducts **4a** and **5a** (in a ratio **4a**/**5a** 9:1). The ratio of the adducts in the cycloaddition mixture was determined by gas chromatography as 99.4:0.6.

Mesitonitrile oxide (1.61 g, 10 mmole) and 2,3-dihydrofuran (2.1 g, 30 mmoles) in benzene (50 ml) for 3 days afforded **4b** (2.21 g, 96%), colorless crystals from diisopropyl ether, m.p. 117–118°. The presence of a few percent of **5b** with **4b** in the mother liquors was ascertained by NMR and TLC. The ratio of the adducts **4b** and **5b** in the cycloaddition mixture was found 99.5:0.5 by gas chromatography.

Cycloadditions to 2,3-dihydrothiophen

155 mg (1 mmole) benzhydroximic acid chloride and 300 mg (3.5 mmole) 2,3-dihydrothiophen afforded a 88:12 mixture of adducts **4c** and **5c**, as determined by NMR integration of the reaction mixture. Crystallization from ethanol gave 0.13 g (63%) of adduct **4c**, colorless crystals m.p. 110°.

A solution of 161 mg (1 mmole) mesitonitrile oxide and 300 mg (3.5 mmole) 2,3-dihydrothiophen in benzene (10 ml) was kept for a week and afforded at 89:11 mixture of adducts **4d** and **5d**, as determined by NMR. Crystallization from ethanol gave 0.15 g (61%) of adduct **4d**, colorless crystals, m.p. 75–76°.

Oxidation of the adducts **4c, d** *and* **5c, d**

A soln of cycloadduct **4c** (0.13 g, 0.5 mmole) in 10 ml CH_2Cl_2 was treated with excess m-chloroperbenzoic acid (2 mmole). After 1 night at room temp the mixture was poured into 10% of Na_2SO_3 aq. The soln was extracted with $CHCl_3$, washed with $NaHCO_3$ aq. and with water. The organic layers were dried on Na_2SO_4. Evaporation at reduced pressure afforded sulfone **6e**, almost quantitatively, colorless crystals from ethanol, m.p. 175–176°, identical with an authentic specimen.[53]

Similarly, oxidation of **4d**, **5c** and **5d** afforded sulfones **6f**, **7e** and **7f**, available from a previous study.[53]

Cycloadditions to propenyl methyl and phenyl sulfides

5 g (32 mmole) benzhydroximic acid chloride were reacted

with 8.5 g (96 mmole) propenyl methyl sulfide. Column chromatography gave, besides the dimerization products of BNO, 75 mg (1.2%) of **9a**, white crystals from EtOH, m.p. 58 59°, 2.1 g (31%) of **8a**, white crystals from diisopropyl ether, m.p. 55° and 0.75 g (11%) of **10a**, white crystals m.p. 40–41° from diisopropyl ether. Cycloadditions to propenyl phenyl sulfide similarly yielded **8c** (25%), colorless oil b.p. 100° (bath)/0.1 mm, and a mixture of **9c** (5%), colorless crystals from EtOH, m.p. 104–105° and **10c** (7%), white crystals from EtOH, m.p. 83-84°. The mixture of **9c** and **10c** was separated by column chromatography, benzene serving as eluent. **10c** is eluted first.

Mesitonitrile oxide (5 g, 31 mmole) and propenyl methyl sulfide (8.5 g, 96 mmole) afforded by column chromatography 4.18 g (54%) of **8b**, white crystals from ethanol, m.p. 64°, and a mixture of 0.16 g (2%) of **9b**, white crystals from ethanol, m.p. 79–80° and 1.55 g (20%) of **10b**, white crystals from ethanol, m.p. 47–48°. Fractional crystallization of the mixtures afforded **10b**. Pure **9b** was obtained by converting a sample of the mixture into a mixture of **9b** and isoxazole **12f** upon boiling with H_2SO_4 20%/HOAc 1:1 for 2 h. Crystallization from EtOH afforded **9b**. Cycloaddition to propenyl phenyl sulfide similarly yielded **8d** (40%), white crystals from ethanol, m.p. 49–50° and a mixture of **9d** (8%), white crystals from ethanol, m.p. 55° and **10d** (13%), white crystals from ethanol, m.p. 96°. The mixture was separated by column chromatography, benzene serving as eluent. **10d** is eluted first.

The ratios of the trans-adducts **8** and **9** in the cycloaddition mixtures have been determined by NMR and are given in Table 2.

Acidic cleavage of adducts **8** *and* **10**

A solution of adduct **8a** (100 mg) in a 1:1 mixture of H_2SO_4 20% and HOAc (4 ml) was boiled 2 h. After cooling, dilution with water and extraction with ether, the organic phase was washed with $NaHCO_3$, H_2O, dried on Na_2SO_4 and evaporated, leaving a residue of 3-phenyl-4-methylisoxazole **12e**, pale yellow liquid, b.p. 100° (bath)/0.1 mm (lit.[34] 100°, 0.6 mm). NMR ($CDCl_3$): δ 2.15 (4-CH_3, d, J 1.2 Hz), δ 8.27 (5-H, q, J 1.2 Hz).

Adducts **8c**, **10a** and **10c** similarly afforded isoxazole **12e**.

The adducts of mesitonitrile oxide **8b, d** and **10b, d** yielded the 3 - mesityl - 4 - methylisoxazole **12f** colorless oil b.p. 130° (bath)/0.1 mm. NMR ($CDCl_3$): δ 1.75 (4-CH_3, d, J 1.2 Hz), δ 8.33 (5-H, q, J 1.2 Hz).

Competition experiments

BNO (0.2 mmole) was generated in diethyl ether soln at 0° in the presence of 2,3-dihydrofuran or 2,3-dihydrothiophen (10 mmole) and cyclopentene (5 20 mmole). After keeping two days at 0°, the ratio of the adducts **4** and the cyclopentene adduct[35] was determined by NMR. With respect to cyclopentene a relative rate of 1.8 and 0.6 ± 0.2 were determined for dihydrofuran and dihydrothiophen, respectively.

Calculations

The calculations were executed with GAUSSIAN 70[23] and MINDO/3[24] programs on a CDC 6600 computer available at the university of Catania.

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REFERENCES

[1] Part XI: P. Caramella, E. Albini, T. Bandiera, A. Corsico Coda, P. Grünanger and F. Marinone Albini, *Tetrahedron* **39**, 689 (1983).

[2a] University of Catania; [b] University of Pavia.

[3] P. Caramella, G. Cellerino, A. Corsico Coda, A. Gamba Invernizzi, P. Grünanger, K. N. Houk and F. Marinone Albini, *J. Org. Chem.* **41**, 3349 (1976).

[4] P. Caramella, G. Cellerino, P. Grünanger, F. Marinone Albini and M. R. Re Cellerino, *Tetrahedron* **34**, 3545 (1978).

[5] P. Fischer, in The Chemistry of Ethers, Crown Ethers, Hydroxyl Group and their Sulphur Analogues, Supplement E (Edited by S. Patai), Part 2, p. 761. Wiley, New York (1980).

[6] L. Brandsma and J. F. Arens, In The Chemistry of the Ether Linkage. (Edited by S. Patai), p. 553. Wiley, New York (1967).

[7] K. N. Houk, J. Sims, R. E. Duke, R. W. Strozier and J. K. George, *J. Am. Chem. Soc.* **95**, 7287 (1973).

[8a] R. Paul and S. Tchelitcheff, *Bull. Chem. Soc. France* 2215 (1963); [b] I. Adachi and H. Kano, *Chem. Pharm. Bull.* **16**, 117 (1968).

[9] R. Huisgen, L. Möbius and G. Szeimies, *Chem. Ber.* **98**, 1138 (1965).

[10] R. Huisgen, R. Sustmann and G. Wallbillich, *Ibid.* **100**, 1786 (1967).

[11a] R. Huisgen, R. Grashey, H. Seidl and H. Hauck, *Ibid.* **101**, 2559 (1968); [b] L. Fisera, J. Kovac and J. Poliacikova, *Heterocycles* **12**, 1005 (1979); [c] C. M. Dicken and P. DeShong, *J. Org. Chem.* **47**, 2047 (1982).

[12] L. Field, *Synthesis* 713 (1978).

[13] R. Huisgen, *Angew. Chem. Int. Ed. Engl.* **2**, 565, 633 (1963).

[14] S. Ehrenson, R. T. C. Brownlee and R. W. Taft, *Prog. Phys. Org. Chem.* **10**, 1 (1973).

[15a] G. Melloni, G. Modena and U. Tonellato, *Acc. Chem. Res.* **14**, 227 (1981); [b] V. J. Nowlan and Th. Tidwell, *Ibid.* **10**, 252 (1977).

[16a] T. Okuyama, M. Nakada and T. Fueno, *Tetrahedron* **32**, 2249 (1976); [b] T. Okuyama, M. Masago, M. Nakada and T. Fueno, *Ibid.* **33**, 2379 (1977).

[17a] H. Graf and R. Huisgen, *J. Org. Chem.* **44**, 2594 (1979); [b] R. Huisgen and H. Graf, *Ibid* **44**, 2595 (1979); [c] S. Fries and K. Gollnick, *Angew. Chem. Int. Ed. Engl.* **19**, 831 (1980).

[18] T. Okuyama, M. Nakada, K. Toyoshima and T. Fueno, *J. Org. Chem.* **43**, 4546 (1978).

[19] R. Huisgen and R. Schug, *J. Am. Chem. Soc.* **98**, 7819 (1976).

[20] K. Fukui, *Angew. Chem. Int. Ed. Engl.* **21**, 801 (1982).

[21] I. Fleming, *Frontier Orbitals and Organic Chemical Reactions*, Wiley, New York (1976).

[22] K. N. Houk, In *Pericyclic Reactions* (Edited by A. P. Marchand and R. E. Lehr) Vol. 2, p. 181. Academic Press, New York (1977).

[23] W. J. Hehre, R. F. Stewart and J. A. Pople, *J. Chem. Phys.* **51**, 2657 (1969); *QCPE Program No.* 236 by W. J. Hehre, W. A. Lathan, R. Ditchfield, M. D. Newton and J. A. Pople.

[24] R. C. Bingham, M. J. S. Dewar and D. H. Lo, *J. Am. Chem. Soc.* **97**, 1285, 1294, 1302, 1307 (1975); *QCPE program No.* 279 by M. J. S. Dewar, P. J. Student, A. Brown, R. C. Bingham, D. H. Lo, C. A. Ramsden, H. Kollmar, P. Weiner and R. K. Bischof.

[25] H. Bock, G. Wagner, K. Wittel, J. Sauer and D. Seebach, *Chem. Ber.* **107**, 1869 (1964).

[26] M. Block, F. Brogli, E. Heilbronner, T. B. Jones, H. Prinzbach and O. Schweikert, *Helv. Chim. Acta* **61**, 1388 (1978).

[27] A. A. Planckaert, J. Doucet and C. Sandorfy, *J. Chem. Phys.* **60**, 4846 (1974).

[28] L. Libit and R. Hoffmann, *J. Am. Chem. Soc.* **96**, 1370 (1974).

[29a] S. P. McGlynn, L. G. Vanquickenborne, M. Kinoshita and D. G. Carrol, *Introduction to Applied Quantum Chemistry*, Holt, Rinehart and Winston, New York (1972); [b] F. Bernardi, I. G. Csizmadia and N. D. Epiotis, *Tetrahedron* **31**, 3085 (1975).

[30] P. Caramella, K. N. Houk and L. N. Domelsmith, *J. Am. Chem. Soc.* **99**, 4511 (1977).

[31] A. Komornicki, J. D. Goddard and H. F. Schaefer, *Ibid.* **102**, 1763 (1980).

[32a] P. Caramella, G. Cellerino, K. N. Houk, F. Marinone Albini and C. Santiago, *J. Org. Chem.* **43**, 3006 (1978); [b]P. Caramella, A. Coda Corsico, A. Corsaro, D. Del Monte and F. Marinone Albini, *Tetrahedron* **38**, 172 (1982).

[33] G. P. Ford, A. R. Katritzky and R. D. Topsom, in *Correlation Analysis in Chemistry* (Edited by N. B. Chapman and J. Shorter), p. 269. Plenum Press, New York (1978).

[34a] H. Yuki, K. Hatada and M. Takeshita, *J. Polimer Sci. A*-1 7, 667 (1969); [b]K. Hatada, K. Nagata and H. Yuki, *Bull. Chem. Soc. Jpn* **43**, 3195 (1970).

[35] E. C. M. Chen and W. E. Wentworth, *J. Chem. Phys.* **63**, 3183 (1975).

[36] K. N. Houk and L. L. Munchausen, *J. Am. Chem. Soc.* **98**, 937 (1976).

[37] L. T. Scott, I. Erden, W. R. Brunsvold, Th. H. Schultz, K. N. Houk anbd M. N. Paddon-Row, *Ibid.* **104**, 3659 (1982).

[38] J. R. Larson and N. D. Epiotis, *Ibid.* **103**, 410 (1981) and refs therein.

[39] K. Gollnick and S. Fries, *Angew. Chem. Int. Ed. Engl.* **19**, 832 (1980).

[40a] G. Wagner and H. Bock, *Chem. Ber.* **107**, 68 (1974); [b]B. J. Cocksey, J. H. D. Eland and C. J. Danby, *J. Chem. Soc.* (*B*) 790 (1971).

[41] A. Ledwith and H. J. Woods, *Ibid.* 753 (1966).

[42] R. Huisgen and G. Steiner, *Tetrahedron Letters* 3763 (1973).

[43a] W. E. Parham, L. Christensen, S. H. Groen and R. M. Dodson, *J. Org. Chem.* **29**, 2211 (1964); [b]W. E. Parham, S. Kajigashi and S. H. Groen, *Bull. Chem. Soc. Jpn* **45**, 509 (1972).

[44a] W. Ando, H. Higuchi and T. Migita, *J. Org. Chem.* **42**, 3365 (1977); [b]W. Ando, K. Nakayama, K. Ichibori and T. Migita, *J. Am. Chem. Soc.* **91**, 5164 (1969).

[45] T. Clark, H. Kômer and P. v. R. Schleyer, *Tetrahedron Letters* 743 (1980).

[46a] A. Streitwieser and J. E. Williams, *J. Am. Chem. Soc.* **97**, 190 (1975); [b]N. D. Epiotis, R. L. Yates, F. Bernardi and S. Wolfe, *Ibid.* **97**, 5435 (1975); [c]J. M. Lehn and G. Wipff, *Ibid.* **98**, 7498 (1976).

[47a] D. J. Mitchell, S. Wolfe and H. B. Schlegel, *Can. J. Chem.* **59**, 3280 (1981); [b]G. D. Andreetti, F. Bernardi, A. Bottoni and A. Fava, *J. Am. Chem. Soc.* **104**, 2176 (1982).

[48] R. Huisgen, *J. Org. Chem.* **41**, 403 (1976).

[49] R. Paul, M. Fluchaire and G. Collardeau, *Bull. Soc. Chim. France* 668 (1950).

[50] G. E. Wilson and R. Albert, *J. Org. Chem.* **38**, 2156 (1973).

[51] D. E. O'Connor and W. I. Lyness, *J. Am. Chem. Soc.* **86**, 3840 (1964).

[52] D. S. Tarbell and M. A. McCall, *Ibid.* **74**, 48 (1952).

[53] F. Marinone Albini, P. Ceva, A. Mascherpa, E. Albini and P. Caramella, *Tetrahedron* **38**, 3629 (1982).

[54] I. Adachi and H. Kano, *Chem. Pharm. Bull.* **17**, 2201 (1969).

[55] N. Barbulescu and P. Grünanger, *Gazz. Chim. Ital.* **92**, 138 (1962).

[56] G. Bianchetti, D. Pocar, C. Torricelli, E. Arlandini and B. Gioia, *Gazz. Chim. Ital.* **111**, 315 (1981).