

The High Reactivity of the CS Double Bond in 1,3-Dipolar Cycloadditions of Nitrones: A Molecular Orbital Theoretical Analysis

Reiner Sustmann,^{*,†} Willi Sicking,[†] and Rolf Huisgen[‡]

Contribution from the Institut für Organische Chemie der Universität Essen, D-45117 Essen, Germany, and Institut für Organische Chemie der Universität München, D-80333 München, Germany

Received May 23, 1995[Ⓢ]

Abstract: The CS double bond displays an unusually high reactivity in a number of 1,3-dipolar cycloadditions. Ab-initio calculations on different levels are performed for cycloadditions of the parent nitron to thioformaldehyde and ethylene, respectively. An orientation complex (OC) is found for both cycloadditions. In the case of thioformaldehyde, the nature of the complex is of charge-transfer type as revealed by a perturbational analysis, whereas for ethylene as dipolarophile, the van der Waals character predominates. The transition structures (TS) for cycloaddition resemble closely the OC with a shorter separation and a stronger distortion of the reactants. A negative energy of activation relative to the reactants (e.g., $-2.5 \text{ kcal mol}^{-1}$ (Becke3LYP)) and a small positive barrier ($+1.2 \text{ kcal mol}^{-1}$) relative to the OC is calculated for thioformaldehyde as dipolarophile; the corresponding values for ethylene are $+13.7$ and $+15.5 \text{ kcal mol}^{-1}$ respectively. The perturbational analysis shows a strong $\text{HOMO}_{\text{nitron}} - \text{LUMO}_{\text{thioformaldehyde}}$ interaction as the principal reason for the high thione reactivity. The observed equilibria in the cycloadditions of *N*-methyl-*C,C*-diphenylnitron to 2,2,4,4-tetramethyl-3-thioxocyclobutanone and of *N*-methyl-*C*-phenylnitron to 2,2,6,6-tetramethylcyclohexanethione are found to be well reproduced by PM3 calculations.

Introduction and Methods of Calculation

Reactivity in 1,3-dipolar cycloadditions varies considerably from system to system and is best explained by the FMO model.¹ According to this interpretation, 1,3-dipoles belong, depending on the number and nature of heteroatoms and on their substitution pattern, to one of three types with respect to HOMO–LUMO interactions.² This classification determines whether a high reactivity is observed toward electron-deficient or electron-rich olefins, or to both of them.

N-Methyl-*C*-phenylnitron and *N*-methyl-*C,C*-diphenylnitron are nucleophilic–electrophilic 1,3-dipoles which show a U-shaped reactivity profile but react preferentially with electron acceptor-substituted CC double bonds.³ Whereas many kinetic measurements have been performed for cycloadditions of substituted alkenes, comparable rate data on 1,3-dipolar cycloadditions to hetero-double bonds, especially those involving elements of the second long period, are scarce. It was observed in the Munich laboratory that, for example, thiofluorenone reacts faster than tetracyanoethylene with thiobenzophenone-*S*-methylide⁴ or diphenyldiazomethane,⁵ both nucleophilic 1,3-dipoles. The C=S double bond was called *superdipolarophilic*, and its high polarizability was supposed to be responsible. The pre-eminence of thiones as dipolarophiles toward *N*-methyl-*C*-phenylnitron was recently confirmed.⁶

In 1968 Ochiai et al.⁷ observed cycloadditions of formaldoxime to methyl acrylate, acrylonitrile, etc., giving rise to

isoxazolidines in poor yield. The parent of the class of nitrones, i.e., formaldimine *N*-oxide, may well be the reactive species, formed by 1,2-prototropy in small concentration. Mobile tautomeric equilibria of similar kind have since been demonstrated to be a pathway to 1,3-dipoles.⁸



Explanations of reactivity scales based on perturbational molecular orbital arguments have to be substantiated by good semiempirical or ab-initio calculations on ground states and transition structures. Here we present a combination of both for cycloadditions of the nitron parent to the CS double bond. We use the 6-31G* basis set and different ab-initio levels, including the QCISD(T) and Becke3LYP procedures implemented in the GAUSSIAN 92 program package,⁹ for unsubstituted molecules. In order to unveil the special character of the CS double bond as compared to an unsubstituted CC double bond, calculations are also reported for the model reaction of the unsubstituted nitron with ethylene. PM3 calculations are carried out for substituted nitrones and thiones; here experimental rate and equilibrium data are available.

Calculations were performed with the Gaussian 92 program package⁹ on a CRAY-Y-MP-864. For the MNDO-PM3 calculations¹⁰ we used the program SCAMP.¹¹ All energies, ab-initio and semiempirical, correspond to optimized structures, except for the QCISD(T) values which were obtained from

(8) Review: Huisgen, R. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley, New York, 1984; Vol. 1, p 148.

(9) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Gill, P. M. W.; Johnson, B. G.; Wong, M. W.; Foresman, J. B.; Robb, M. A.; Head-Gordon, M.; Replogle, E. S.; Gomperts, R.; Andres, J. L.; Raghavachari, K.; Binkley, J. S.; Gonzalez, C.; Martin, R. L.; Fox, D. J.; Defrees, D. J.; Baker, J.; Stewart, J. J. P.; Pople, J. A.; *Gaussian 92/DFT*, Revision G.2, Gaussian, Inc.: Pittsburgh PA, 1993.

(10) Stewart, J. J. P. *J. Comput. Chem.* **1989**, *61*, 109, 221.

(11) We thank Dr. T. Clark, University of Erlangen, for a copy of the program SCAMP.

[†] Universität Essen.

[‡] Universität München.

[Ⓢ] Abstract published in *Advance ACS Abstracts*, September 1, 1995.

(1) Sustmann, R. *Pure Appl. Chem.* **1974**, *40*, 569.

(2) Sustmann, R. *Tetrahedron Lett.* **1971**, *27*, 2717.

(3) Huisgen, R.; Seidl, H.; Brüning, I. *Chem. Ber.* **1969**, *102*, 1102.

(4) Huisgen, R.; Li, X. *Tetrahedron Lett.* **1983**, *24*, 4185.

(5) Huisgen, R.; Langhals, E. *Tetrahedron Lett.* **1989**, *30*, 5369.

(6) Huisgen, R.; Fiserá, L.; Giera, H.; Sustmann, R. *J. Am. Chem. Soc.* **1995**, *117*, 9671.

(7) Ochiai, M.; Obayashi, M.; Morita, K. *Tetrahedron Lett.* **1967**, *23*, 2641.

Table 1. Ab-Initio Energies (hartrees) of Ground States, Orientation Complexes, Transition Structures, and Adducts for Cycloadditions of Nitron to Thioformaldehyde and Ethylene

	RHF/6-31G*	ZPVE ^a	MP2/6-31G*	ZPVE	QCISD(T)// MP2/6-31G*	Becke3LYP/ 6-31G*	ZPVE	Becke3LYP/ 6-31G* (ε = 8.9)	ZPVE (ε = 8.9)
H ₂ C=NH-O	-168.809 206 4	31.09	-169.292 899 5	28.71	-169.328 078 9	-169.793 487 4	28.46	-169.797 612 8	28.52
H ₂ C=S	-436.506 456 8	16.84	-436.755 113	15.99	-436.791 311 6	-437.462 371 0	15.64	-437.463 599 4	15.66
H ₂ C=CH ₂	-78.031 718 1	34.37	-78.285 027 5	32.65	-78.322 152 5	-78.587 448 60	32.14		
OC ^b (3)	-605.322 462 4	49.13	-606.058 610 8	46.73	-606.126 599 6	-607.264 591 4	45.90	-607.266 823 3	46.05
OC (4)	-246.843 1 ^c	65.91	-247.581 499 6	62.04	-247.653 011 8	-248.385 5 ^c	61.65		
TS ^d (5)	-605.313 440 9	50.80	-606.057 728 9	47.29	-606.122 119 7	-607.263 583 3	46.48	-607.266 151 8	46.51
TS (6)	-246.796 673 9	67.94	-247.565 520 1	63.96	-247.628 466 4	-248.362 744 8	62.89		
OC (7)			-606.055 744 8	46.61	-606.119 895	-607.258 460 8	45.38		
TS (8)	-605.285 028 95	50.57	-606.055 628 6	46.93	-606.116 583 8	-607.254 566 1	46.48		
CA ^{e,f}	-605.383 858 2	53.62	-606.107 018 9	50.27	-606.174 723 5	-607.309 437 7	49.23		
CA ^g	-605.365 441 1	53.20	-606.091 346 4	49.85	-606.160 581 9	-607.293 874 9	48.89		
CA (1 + 3)	-246.910 073 2	71.67	-247.639 366 5	67.67	-247.707 635 6	-248.433 106 6	66.41		

^a ZPVE = zero point vibrational energy (kcal mol⁻¹). ^b OC = orientation complex. ^c Slow convergence, terminated at the limit of 10⁻⁵. ^d TS = transition structure. ^e CA = cycloadduct. ^f 1,4,2-Oxathiazolidine. ^g 1,2,5-Oxathiazolidine.

Table 2. Relative Ab-Initio Energies (kcal mol⁻¹) of Orientation Complexes, Transition Structures, and Adducts for Cycloadditions of Nitron to Thioformaldehyde and Ethylene (Reference = Sum of the Energies of the Reactants)

	RHF/ 6-31G*	ΔZPVE ^a	MP2/ 6-31G*	ΔZPVE	QCISD(T)// MP2/6-31G*	Becke3LYP/ 6-31G*	ΔZPVE	Becke3LYP/ 6-31G* (ε = 8.9)	ΔZPVE (ε = 8.9)
OC ^b (3)	-4.27	+1.20	-6.65	+2.03	-4.52	-5.48	+1.78	-3.52	+1.89
OC (4)	-1.37	+0.45	-2.24	+0.68	-1.75	-2.88	+1.05		
TS ^c (5)	+1.39	+2.87	-6.10	+2.59	-1.71	-4.85	+2.38	-3.10	+2.33
TS (6)	+27.77	+2.48	+7.79	+2.60	+13.66	+11.41	+2.29		
OC (7)			-4.85	+1.91	-0.32	-1.63	+1.28		
TS (8)	+19.22	+2.64	-4.78	+2.23	+1.76	+0.81	+2.38		
CA ^{d,e}	-42.79	+5.69	-37.03	+5.57	-34.72	-33.62	+5.13		
CA ^f	-31.24	+5.27	-27.19	+5.15	-25.53	-23.86	+4.79		
CA (1 + 3)	-43.39	+6.21	-38.55	+6.31	-36.02	-32.73	+5.81		

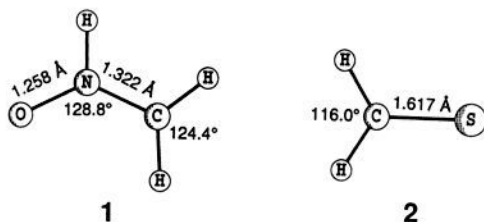
^a ΔZPVE = difference (Δ) in zero point vibrational energy (kcal mol⁻¹). ^b OC = orientation complex. ^c TS = transition structure. ^d CA = cycloadduct. ^e 1,4,2-Oxathiazolidine. ^f 1,2,5-Oxathiazolidine.

single point calculations on the MP2/6-31G* structures. Transition structures are characterized by one imaginary frequency in the Hessian matrix.

The interpretation of the results obtained by the ab-initio calculations is done by the semiempirical (MNDO-PM3) perturbation program PERVAL,¹² which evaluates the interaction of two molecules in a given geometry. It allows a partitioning of the total interaction energy in polar, covalent, and noncovalent contributions. In this way a direct reference to the FMO model is possible.

Nitron and Thioformaldehyde (Ethylene): Orientation Complex

The relevant structural features of nitron and thioformaldehyde, as obtained from the MP2/6-31G* optimization, are displayed in **1** and **2**. The geometrical parameters of nitron



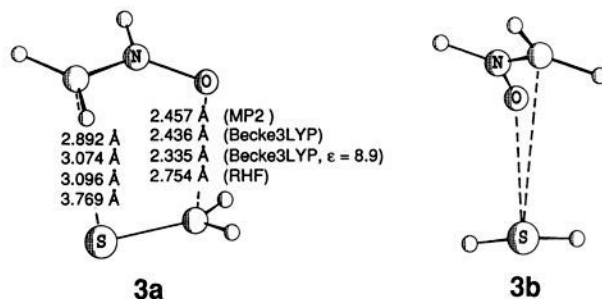
differ slightly from earlier STO-3G values.¹³ The calculated dipole moment of nitron is 3.35 D. The structure of thioformaldehyde corresponds closely to that of earlier calculations.

(12) (a) Sustmann, R.; Sicking, W. *Chem. Ber.* **1987**, *120*, 1323. (b) *Ibid.* **1987**, *120*, 1471. (c) *Ibid.* **1987**, *120*, 1653. (d) *Tetrahedron* **1988**, *44*, 379. (e) *Ibid.* **1990**, *46*, 783. (f) *Tetrahedron Lett.* **1988**, *29*, 4699.

(13) Leroy, G.; Nguyen, M. T.; Sana, M. *Tetrahedron* **1978**, *34*, 2459.

Vedejs and Houk et al.¹⁴ calculated with the split valence 3-21G basis set 1.638 Å for the CS bond length and 116.5° for the HCH angle. Our r_{CS} comes closer to 1.611 Å determined by microwave spectroscopy.¹⁵ Our new calculation of the dipole moment of thioformaldehyde, 1.71 D, is somewhat lower than the RHF/6-31G* value of 2.23 D.¹⁶ The experimental value of 1.64 D¹⁵ is closer to a CAS(2,2)/3-21G* calculation (1.69 D).¹⁶ Energies for ground states, orientation complexes (OC), transition structures (TS), and products are collected in Table 1, relative energies in Table 2.

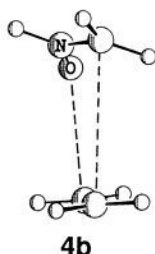
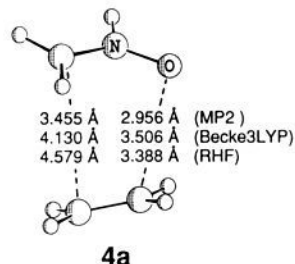
When we searched the potential energy surface for transition structures of the reaction of nitron with thioformaldehyde to form 1,4,2-oxathiazolidine, we noticed an initial decrease in total energy as compared with the isolated molecules at large separation. This was barely seen in the RHF/6-31G* calculation but clearly recognizable in the MP2/6-31G*, the QCISD(T)/6-31G*//MP2/6-31G*, and the Becke3LYP/6-31G* calculations. In **3a,b** the structure of minimal energy, as obtained by



optimization with the Becke3LYP/6-31G* density functional approach, is displayed. For the purpose of comparison the

separation of the reacting atoms is also given for the RHF/6-31G* and the MP2/6-31G* calculations. Distances of 3.074 Å for CS and of 2.436 Å for CO are outside of the range of noticeable covalent bonding and point to other forces as the origin of these *orientation complexes* (OC). It is interesting to note that there is a remarkable difference in structure between the RHF/6-31G* calculation and those including correlation. The latter ones are more symmetrical. Binding energies of -4.3 to -6.7 kcal were obtained by the four methods which decrease somewhat when the zero point vibrational energy (ZPVE) correction is made (Table 2). The structures of nitron and thioformaldehyde in **3** are almost identical to those of their ground states which follows also from the minimal energy differences between ground state structures and those in the orientation complex: $\Delta E_{\text{nitron}} = +0.61$ (MP2) and $+0.43$ (QCISD(T)) kcal mol $^{-1}$, and $\Delta E_{\text{thioformaldehyde}} = +0.17$ (MP2) and $+0.007$ (QCISD(T)) kcal mol $^{-1}$.

In order to see whether the orientation complex is due to the special character of the CS double bond in thioformaldehyde, we performed a similar calculation for the reaction of nitron with the CC double bond of ethylene. Indeed, at larger separations of the reactants, an orientation complex is also found for *ethylene* as dipolarophile. Structural information is given in **4**, and stabilization energies of -1.4 to -2.9 kcal mol $^{-1}$ are found by the different procedures (Table 2). Due to the flat energy minima only a slow convergence of the calculations is achieved.



As shown above, the corresponding thioformaldehyde complex **3** was stabilized by -4.3 to -6.7 kcal mol $^{-1}$, values which are almost three times as high as in **4**. It is suggested that the different stabilization in the orientation complexes **3** and **4** might be explained in terms of a weak van der Waals complex for nitron and ethylene and a charge-transfer type of complex for nitron and thioformaldehyde. Molecular complexes, due to van der Waals interactions, have recently been found for ozone and ethylene in the gas phase and were confirmed by ab-initio calculations.¹⁷

The separation of the reactants in the orientation complexes is such that perturbation theory can be applied in order to delineate salient bonding features. We used PERVAL¹² to dissect the energy in covalent bonding, coming from the interaction of occupied MOs of one molecule with unoccupied MOs of the other, in polar interactions and noncovalent repulsions. The calculations were performed for the MP2/6-31G* structures **3** and **4**. PM3 wave functions of the reactants in the structures which they assume in **3** and **4** are the basis for

the calculation of the interaction. This approach is taken even though PM3 does not suggest complex formation for the geometry found by the ab-initio procedures, probably due to an overestimation of repulsive interactions at longer distances. The partitioning of the perturbation energy, however, can be used to recognize similarities and differences in the orientation complexes of thioformaldehyde and ethylene. Qualitative rather than quantitative conclusions are intended.

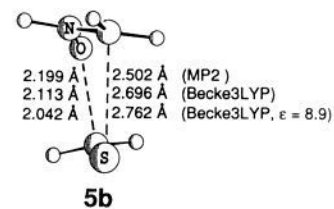
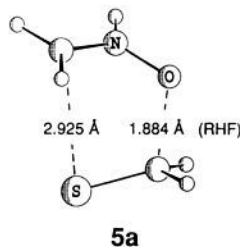
For **3** PERVAL analysis indicates that -4.6 kcal mol $^{-1}$ out of the -7.5 kcal mol $^{-1}$ of total covalent bonding derives from the interaction HOMO_{nitron}-LUMO_{thioformaldehyde} and -0.61 kcal mol $^{-1}$ from HOMO_{thioformaldehyde}-LUMO_{nitron}; the sum of the two FMO interactions equals 69% of the covalent stabilization. The stabilization due to polar interactions is -3.9 kcal mol $^{-1}$. The noncovalent repulsion of 19.4 kcal mol $^{-1}$ leads to $+7.9$ kcal mol $^{-1}$ of the total interaction. The covalent contribution to the bonding is unexpectedly high in the OC in view of the large separation of the individual molecules. It even exceeds the polar interactions. The latter were anticipated to dominate as they decrease less rapidly with distance than overlap which determines covalent bonding. The high covalent stabilization may be due to the greater spatial extension of the sulfur 3p orbital. The covalent contribution supports the hypothesis that the orientation complex is of a charge transfer and not purely of a van der Waals type. The analysis gives a hint that the reactivity in this cycloaddition will be mainly controlled by the HOMO_{dipole}-LUMO_{dipolarophile} interaction (see below).

The same perturbational analysis was carried out for **4**. The result is a total covalent stabilization of -0.6 kcal mol $^{-1}$, with no indication of a special FMO contribution. The charge interaction is -0.4 kcal mol $^{-1}$ and the noncovalent repulsion 3.0 kcal mol $^{-1}$ in the PM3-PERVAL calculation for the MP2/6-31G* structure of the complex. As no significant covalent contribution is noticed we suggest that **4** is held together mainly by van der Waals forces. Another difference between **3** and **4** is the smaller polar interaction in the orientation complex between nitron and ethylene.

It is amusing to note that one of us¹⁸ used the term *orientation complex* in 1963 to characterize the spatial arrangement of the reactants at the beginning of the bonding interaction. It was left open whether these complexes should be regarded as secondary minima, dips in the energy profiles, or not.

Nitron and Thioformaldehyde (Ethylene): Transition Structure

The transition structures (TSs) for the cycloaddition of nitron to thioformaldehyde were like the OC's determined by the three procedures mentioned above. The most significant difference is found for the length of the two forming bonds. The RHF/6-31G* TS **5a** displays separations of 1.884 Å for CO and 2.925



Å for CS, i.e. Δr is 1.04 Å, suggesting almost a two-step reaction. In contrast, MP2/6-31G* shows a $\Delta r = 0.303$ Å, the distance of 2.502 Å for CS being only moderately greater than

(14) Vedejs, E.; Perry, D. A.; Houk, K. N.; Rondan, N. G. *J. Am. Chem. Soc.* **1983**, *105*, 6999.

(15) Johnson, D. R.; Powell, X. F.; Kirchhoff, W. H. *J. Mol. Spectrosc.* **1971**, *39*, 136.

(16) Sustmann, R.; Sicking, W.; Huisgen, R. *J. Org. Chem.* **1993**, *58*, 82.

(17) (a) Gillies, C. W.; Gillies, J. Z.; Suenram, R. D.; Lovas, F. J.; Kraka, E.; Cremer, D. *J. Am. Chem. Soc.* **1991**, *113*, 2412. (b) Gillies, J. Z.; Gillies, C. W.; Lovas, J. J.; Matsumura, K.; Suenram, R. D.; Kraka, E.; Cremer, D. *J. Am. Chem. Soc.* **1991**, *113*, 6408.

(18) Huisgen, R. *Angew. Chem.* **1963**, *75*, 742; *Angew. Chem., Int. Ed. Engl.* **1963**, *2*, 633.

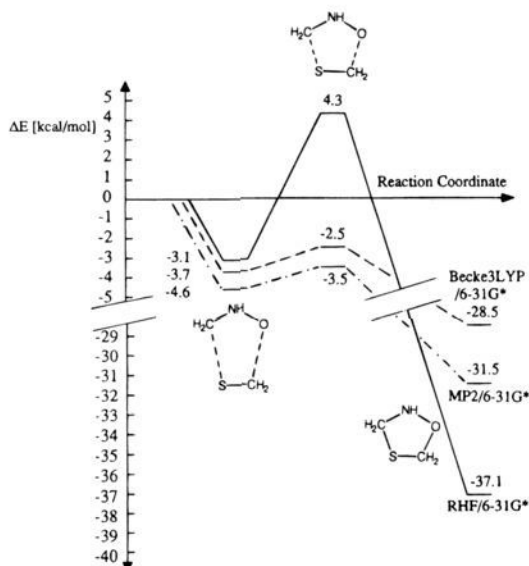


Figure 1. Reaction profile for the cycloaddition of nitron to thioformaldehyde in kcal mol⁻¹ according to three ab-initio procedures.

that of 2.199 Å for CO. The structure resulting from Becke3LYP/6-31G* (**5b**) is slightly more distorted, $\Delta r = 0.583$ Å. Thus, the use of correlated wave functions indicates that inclusion of correlation not only influences the energy but also changes the structure. Even a good basis set does not guarantee a reliable TS if correlation is not included.

The cycloaddition occurs out of the structure of the orientation complex. A comparison between the structures of the OC **3** and the TS **5** on the MP2/6-31G* level reveals remarkable similarities. The shortening of the CS distance by 0.39 Å and of the CO distance by 0.26 Å is the main difference between **3** and **5**. We are still dealing with an "early" TS.

The energies of the TS depend also critically on the approximation. In Figure 1 the energy profiles are shown for the cycloaddition of nitron to thioformaldehyde with inclusion of ZPVE. The RHF/6-31G* approximation leads to an activation energy of +4.3 kcal mol⁻¹ relative to the reactants. Starting from the OC this number increases to +7.4 kcal mol⁻¹. For MP2/6-31G* and Becke3LYP, the TSs are below the energy of the reactants but less negative than the energy of the orientation complex. The same holds true for the single-point QCISD(T) calculation which is not shown in Figure 1. Thus, a small activation of ca. 1 kcal mol⁻¹ is required to go from the OC to the TS. The different behavior of the calculational procedures has been noticed before. RHF/6-31G* tends to give the highest activation energies, normally exceeding the experimental numbers.¹⁹ MP2/6-31G* seems to overestimate the effect of correlation which is corrected when more advanced procedures like Becke3LYP or QCISD(T) are applied.

The observed *superdipolarophilic* reactivity of thiones is confirmed to a surprising extent by the ab-initio calculations. Concerted 1,3-dipolar cycloadditions show high negative activation entropies. The free energy of activation determines the rate of cycloaddition. When we accept the calculated activation energy as an approximate measure of ΔH^\ddagger , then the inclusion of the entropy term will lead to a positive free energy of activation. However, the temperature dependence of the rate constant should be slightly negative.

A similar analysis of the cycloaddition of nitron to ethylene has been performed for the purpose of comparison. Here we

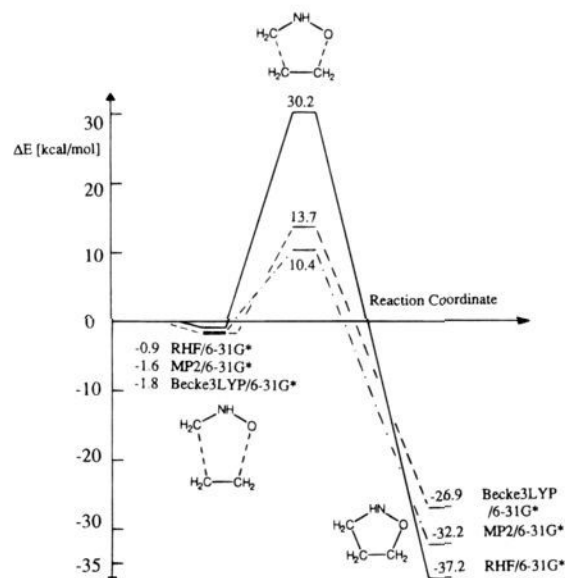
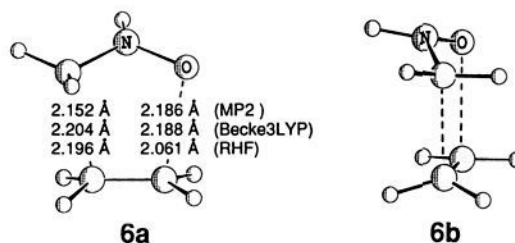


Figure 2. Reaction profile for the cycloaddition of nitron to ethylene in kcal mol⁻¹ according to three ab-initio procedures.

display the TS of the MP2/6-31G* search (**6**). In **6** we indicate also the results of the RHF and Becke3LYP calculations.

Almost equal separations for CC and CO (see **6**) are calculated for the two forming bonds; a nearly synchronous concerted process constitutes a major difference between **6** and



5. The RHF/6-31G* activation energy including ZPVE amounts to 30.2 kcal mol⁻¹, which is lowered to +10.4 kcal mol⁻¹ (MP2/6-31G*) and raised again to 13.7 kcal mol⁻¹ (Becke3LYP) (Figure 2). A single-point calculation on the MP2/6-31G* TS by QCISD(T) gives an activation energy of 13.7 kcal mol⁻¹. There is a difference of +15.4 kcal mol⁻¹ in the single-point QCISD(T) calculation on the MP2/6-31G* TS between the cycloaddition of thioformaldehyde and ethylene to nitron, indicating an enormous reactivity difference. With Becke3LYP this difference amounts to 16.3 kcal mol⁻¹. Part of the high reactivity of thioformaldehyde may derive from the biradical character of this molecule which amounts to 12% according to a CAS(2,2)/3-21G* calculation.¹⁶ With the assumption of identical activation entropies, the difference in rate for the cycloaddition of nitron to thioformaldehyde and to ethylene should amount to a factor of ca. 10¹¹.

Perturbation Calculations on the Transition Structures

Although TSs **5** and **6** are not the TS structures calculated by PM3, we subjected both to an analysis by PERVAL, in order to get a qualitative insight into the important contributions to the activation energies. For this purpose we dissected the TS into the two distorted structures of the reactants, determined their wave function by separate PM3-calculations, placed the two molecules in the geometry of MP2/6-31G* TS, and calculated the interaction by PERVAL. Because of rather strong

(19) Houk, K. N. *Pure Appl. Chem.* **1989**, *61*, 643.

perturbations present in the TS, it is not expected that PERVAL yields an interaction energy which in combination with the heats of formation of the distorted reactants leads to exactly the same ΔH_f° value as the PM3 calculation of the TS.

For **5**, the situation is as follows: $\Delta H_f^\circ(\text{TS } \mathbf{5}) = 70.0 \text{ kcal mol}^{-1}$, $\Delta H_f^\circ(\text{distorted thioformaldehyde}) = 43.0 \text{ kcal mol}^{-1}$, $\Delta H_f^\circ(\text{distorted nitrene}) = 19.6 \text{ kcal mol}^{-1}$, sum of perturbation energies = $6.4 \text{ kcal mol}^{-1}$. The difference in total energy of the TS as obtained by the two procedures is only $1.0 \text{ kcal mol}^{-1}$, underscoring the quality and validity of the perturbational approach. Information concerning the salient covalent interactions in **5** comes from the energy splitting: The perturbation total of $6.4 \text{ kcal mol}^{-1}$ is composed of $-30.0 \text{ kcal mol}^{-1}$ covalent contribution, $-6.4 \text{ kcal mol}^{-1}$ polar interactions, and $42.9 \text{ kcal mol}^{-1}$ noncovalent repulsion. The biggest portion of the covalent contribution ($-20.5 \text{ kcal mol}^{-1}$) stems from the interaction $\text{HOMO}_{\text{nitrene}}-\text{LUMO}_{\text{thioformaldehyde}}$; the second $\text{HOMO}-\text{LUMO}$ interaction provides an additional $-3.3 \text{ kcal mol}^{-1}$. As found in many calculations of this type,¹² the FMO interactions contribute the dominant covalent stabilization of the TS, in our case 79%.

The following information can be extracted from a PERVAL analysis of the MP2/6-31G* TS for the cycloaddition of nitrene to ethylene (**6**). The relevant PM3 heats of formation are: $\Delta H_f^\circ(\text{TS } \mathbf{6}) = 62.3 \text{ kcal mol}^{-1}$, $\Delta H_f^\circ(\text{distorted ethylene}) = 23.9 \text{ kcal mol}^{-1}$, $\Delta H_f^\circ(\text{distorted nitrene}) = 28.0 \text{ kcal mol}^{-1}$, sum of perturbation energies = $16.9 \text{ kcal mol}^{-1}$. The perturbation energy is $10.5 \text{ kcal mol}^{-1}$ higher than for the cycloaddition of thioformaldehyde, indicating a stronger interaction of the reactants at the transition state. As a consequence the deviation between $\Delta H_f^\circ(\text{TS})$ and the sum of the ΔH_f° values for distorted reactants and the perturbation energy is higher than for TS **5** ($6.5 \text{ kcal mol}^{-1}$). The partitioning of the total perturbation energy in its components is of interest: $-26.1 \text{ kcal mol}^{-1}$ covalent stabilization, $-1.9 \text{ kcal mol}^{-1}$ polar interaction, and $44.9 \text{ kcal mol}^{-1}$ noncovalent repulsion.

A comparison of TSs **5** and **6** shows for the latter a $2.0 \text{ kcal mol}^{-1}$ higher noncovalent repulsion, a decrease of $4.5 \text{ kcal mol}^{-1}$ in polar stabilization, and a lowering of $3.9 \text{ kcal mol}^{-1}$ in covalent stabilization. All of these contributions favor **5**. The difference in covalent stabilization can exclusively be traced back to smaller FMO interactions in **6**. As expected for an unsubstituted CC double bond, the two FMO interactions, $\text{HOMO}_{\text{nitrene}}-\text{LUMO}_{\text{ethylene}} = -12.5$ and $\text{HOMO}_{\text{ethylene}}-\text{LUMO}_{\text{nitrene}} = -7.3 \text{ kcal mol}^{-1}$, are not as different as in the case of thioformaldehyde (-20.5 and $-3.3 \text{ kcal mol}^{-1}$, see above). The high reactivity of thioformaldehyde derives thus from a dominant $\text{HOMO}_{\text{nitrene}}-\text{LUMO}_{\text{thioformaldehyde}}$ interaction, due to a low-lying LUMO of the thione. The FMO energies for the two dipolarophiles are in the PM3 approach: HOMO and LUMO of ethylene -10.64 and $+1.23 \text{ eV}$, HOMO and LUMO of thioformaldehyde -12.22 and -1.43 eV . The RHF/6-31G* calculation provides -10.19 and $+5.01 \text{ eV}$ for ethylene as well as -11.39 and $+1.54 \text{ eV}$ for thioformaldehyde.

An additional non-negligible contribution to the reactivity of the CS double bond is derived from a difference in polar interactions between the CC ($-1.9 \text{ kcal mol}^{-1}$) and the CS ($-6.4 \text{ kcal mol}^{-1}$) systems. A reason for the smaller number in the case of ethylene is its nonpolar nature. The PM3 (MP2/6-31G* geometry)-calculated dipole moments provide some insight. The dipole moments of the reactants in their ground states are as follows: nitrene, 3.37 D ; $\text{H}_2\text{C}=\text{S}$, 2.08 D . In the structure of the orientation complex **3**, they change to 3.57 D for nitrene and 2.43 D for $\text{H}_2\text{C}=\text{S}$. A total dipole moment of 2.64 D is calculated for the OC. In the distorted structures of the TS **5**,

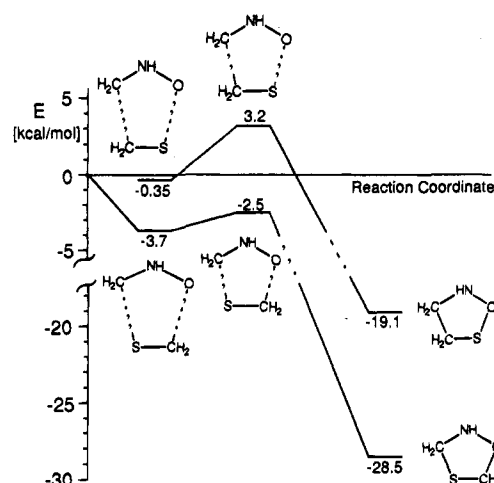


Figure 3. Reaction coordinate for the formation of 1,4,2- and 1,2,5-oxathiazolidine from the parent nitrene and thioformaldehyde.

they become 3.80 D for nitrene and 2.50 D for $\text{H}_2\text{C}=\text{S}$. For **5** a value of 3.33 D is determined. For ethylene as dipolarophile the same analysis shows for the orientation complex **4**: nitrene, 3.48 D ; C_2H_4 , 0.0 D ; OC, 3.30 D . TS **6**: nitrene, 3.98 D ; C_2H_4 , 0.44 D ; TS, 3.12 D . Although even ethylene becomes slightly polar in the distorted structure of **6**, the dipolar interactions between nitrene and thioformaldehyde in **5** must be more significant, which is substantiated by the perturbation calculation.

Solvent Effect on Orientation Complex and Transition State

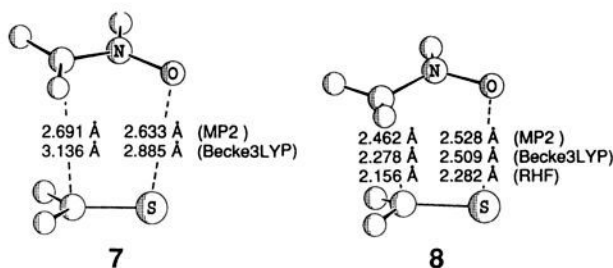
The Gaussian 92 program package allows the calculation of solvent effects by the SCRF method²⁰ where the solvent is approximated by a dielectric continuum in which the molecules are placed in spheres of appropriate size. We applied this model to the OC and the TS for the cycloaddition of nitrene and thioformaldehyde using the density functional approach (Becke3LYP). For total and relative energies see Tables 1 and 2. The goal is to see whether the OC is only a gas-phase phenomenon or whether it should exist also in solution.

A solvent of $\epsilon = 8.9$, corresponding to dichloromethane, was selected. The dielectric continuum causes a small change to less symmetrical structures, increasing the CS and shortening the CO separations (see **3** and **5** for distances). The dip in the energy profile for the OC is retained but decreases from -3.7 to $-1.6 \text{ kcal mol}^{-1}$ including ZPVE. The energy of the TS is raised from -2.5 to $-0.8 \text{ kcal mol}^{-1}$. The important result is, thus, that the conclusion from the isolated molecules approach is not changed qualitatively when solvent effects are taken into account.

Regioselectivity of the Cycloaddition of the Parent Nitrene to Thioformaldehyde

The experimental evidence for the 1,4,2-oxathiazolidine structure of the cycloadducts was weak.⁶ The possibility of forming the 1,2,5-regioisomer instead was investigated by RHF/6-31G*, MP2/6-31G*, and Becke3LYP/6-31G* calculations. The energies are given in Tables 1 and 2; the Becke3LYP/6-31G* results are displayed in Figure 3. A weak OC (**7**) is indicated by Becke3LYP/6-31G* and MP2/6-31G* but not by the RHF/6-31G* calculation. Transition structure **8** leading to 1,2,5-oxathiazolidine can be located; its energy is $+3.2 \text{ kcal}$

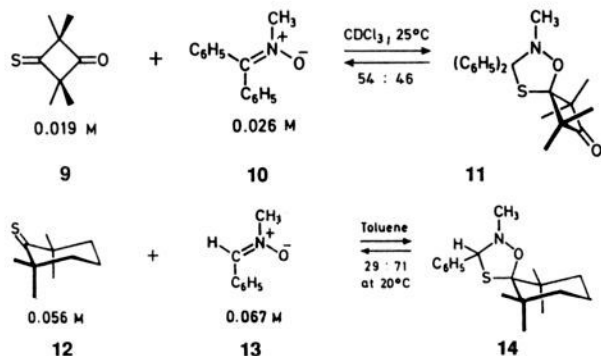
(20) Wong, M. W.; Frisch, M. J.; Wiberg, K. B. *J. Am. Chem. Soc.* **1991**, *113*, 4776.



mol^{-1} above the isolated reactants in the Becke3LYP procedure. Although small, this activation energy is by $5.7 \text{ kcal mol}^{-1}$ higher than that for the 1,4,2-oxathiazolidine TS. In the latter case a negative activation energy had been obtained. It is, therefore, not expected that the cycloaddition of the parent nitron to thioformaldehyde produces a mixture of regioisomers in a kinetically controlled reaction. A value of $9.4 \text{ kcal mol}^{-1}$ in favor of 1,4,2-oxathiazolidine does furthermore exclude detectable amounts of the 1,2,5-regioisomer, if the cycloaddition is reversible and thermodynamically controlled.

Equilibrium between Reactants and Products in Nitron Cycloadditions of Thiones

At 25°C in CDCl_3 the cycloaddition of 2,2,4,4-tetramethyl-3-thioxocyclobutanone (**9**) to *N*-methyl-*C,C*-diphenylnitron (**10**) leads to a 54:46 mixture of thione **9** and product **11**. A similar situation is found for the cycloaddition of 2,2,6,6-tetramethylcyclohexanethione (**12**) to *N*-methyl-*C*-phenylnitron (**13**) leading to **14**. In toluene at 20°C the mixture is 29:71 in favor of



the cycloadduct. A temperature-dependent measurement of the equilibrium constant from 20 to 76°C yielded $\Delta G_{80^\circ\text{C}} = -0.87 \text{ kcal mol}^{-1}$, $\Delta H = -11.0 \text{ kcal mol}^{-1}$, and $\Delta S = -29 \text{ cal K}^{-1} \text{ mol}^{-1}$. The qualitative confirmation of these values by theoretical calculations constitutes a challenge, keeping in mind, however, that they are solution values.

Table 3 lists the heats of reaction which were calculated from the heats of formation of the reactants and products (Table 4) for the cycloaddition of nitrones to thiones. As the experimental examples are prohibitive for ab-initio calculations, a calibration of ab-initio and PM3 calculations for the unsubstituted reactants might provide a good basis for the reliability of the PM3 values. Interestingly, the heats of reaction including ZPVE, calculated by MP2/6-31G* ($-31.5 \text{ kcal mol}^{-1}$) and Becke3LYP ($-28.5 \text{ kcal mol}^{-1}$), are close to the PM3 and AM1 values. This result gives some confidence in the heats of reaction for the other cases. The figures in Table 3 indicate a trend. Increasing substitution of the thiones (compare entry 1 with entries 3 and 4) dramatically decreases the exothermicity of the cycloaddition. The calculated heat of reaction sinks to $-12.0 \text{ kcal mol}^{-1}$ (PM3) and $-9.0 \text{ kcal mol}^{-1}$ (AM1) for the addition of **9** to **10**.

Table 3. Heats of Reaction for Cycloadditions of Nitrones to CS Double Bonds (kcal mol^{-1})

entry	reaction	PM3	AM1
1	1 + 2 ^a	-35.2	-36.7
2	1 + 2 ^b	-45.1	-39.2
3	1 + 15 ^c	-27.7	-26.9
4	1 + 9	-21.7	-23.5
5	13a + 9	-18.7	-15.2
6	10 + 9	-12.0	-9.0
7	13a + 12c	-17.8	-12.0
8	13a + 12a	-15.1	-10.6
9	13b + 12a	-14.5	-12.1
10	13b + 12b	-15.5	-13.1

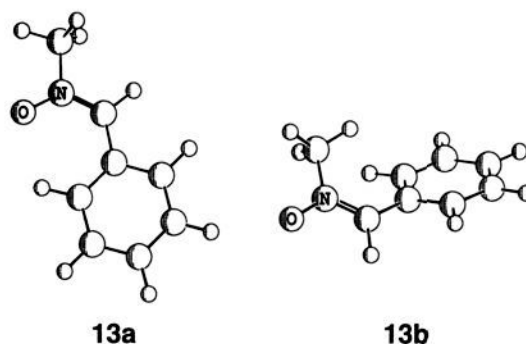
^a 1,4,2-Oxathiazolidine. ^b 1,2,5-Oxathiazolidine. ^c **15** = 3-thioxocyclobutanone.

Table 4. Heats of Formation (ΔH_f°) (kcal mol^{-1}) for Reactants and Cycloadducts in Additions of Thiones to Nitrones from PM3 and AM1 Calculations

compd	PM3	AM1
1	11.4	16.9
2	37.6	29.9
9	-10.3	-4.0
10	66.9	76.1
11 (CA ^a 10 + 9)	44.6	63.1
12a	2.5	-7.3
12b	3.5	-6.3
12c	5.2	-5.9
13a	37.5	45.0
13b	36.9	46.5
14 (CA 12 + 13)	24.9	27.1
15 ^b	11.8	13.0
CA (1 + 2 ^c)	13.8	10.1
CA (1 + 2 ^d)	3.9	7.6
CA (1 + 15 ^b)	-4.5	3.0
CA (1 + 9)	-20.6	-10.7
CA (13 + 9)	8.5	26.0

^a CA = cycloadduct. ^b **15** = 3-thioxocyclobutanone. ^c 1,4,2-Oxathiazolidine. ^d 1,2,5-Oxathiazolidine.

As for the cycloaddition of *N*-methyl-*C*-phenylnitron (**13**) to thiones, the *E,Z* isomerism of nitrones has to be considered. The ^1H NMR spectrum of **13** did not reveal any *E*-isomer alongside the *Z*-configuration (**13a**, C_6H_5 and CH_3 trans at the $\text{C}=\text{N}$ double bond).^{21,22} A minute equilibrium concentration of the *E*-form **13b** may increase the cycloaddition rate but



certainly does not influence the cycloaddition/cycloreversion equilibrium. Assuming that $\leq 2\%$ of **13b** could have escaped detection, the free energy change **13a** \rightarrow **13b**, would amount to $\geq 2.3 \text{ kcal mol}^{-1}$.

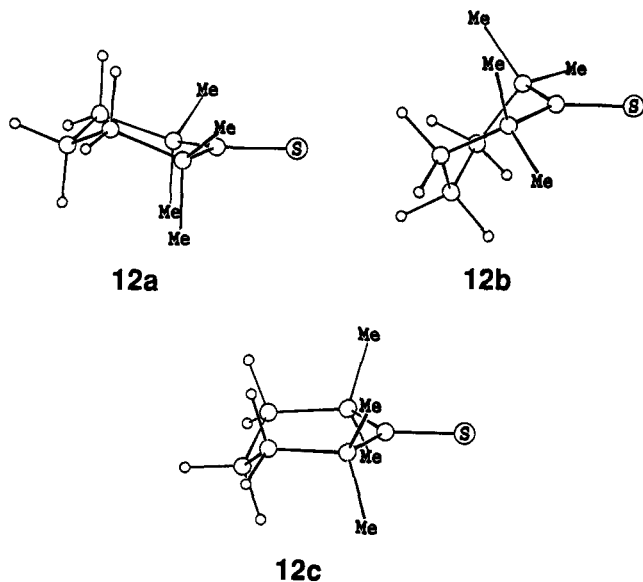
The minimum energy structure **13a** (*Z*) found in the optimization process shows coplanarity of phenyl and nitron systems;

(21) Buehler, E. *J. Org. Chem.* **1967**, *32*, 261.

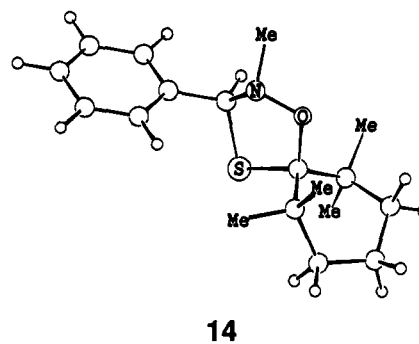
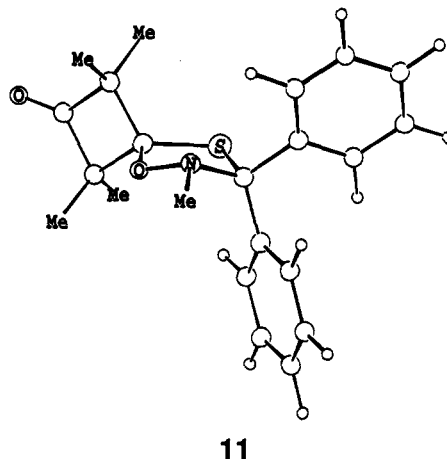
(22) Boyle, L. W.; Peagram, M. J.; Witham, G. H. *J. Chem. Soc. (B)* **1971**, 1728.

in the *E*-form, twist angles of 43° (AM1) and 69° (PM3) resulted. Whereas the AM1 calculation provided heats of formation in the correct order, *Z* better than *E* by $1.5 \text{ kcal mol}^{-1}$, PM3 came forth with a difference of $0.6 \text{ kcal mol}^{-1}$ in the opposite direction (Table 4).

Similarly, conformations of slightly different energy were obtained for **12**. The energy optimization of 2,2,6,6-tetramethylcyclohexanethione (**12**) afforded three minima. According to both calculation procedures, the chair conformation (**12a**) is better than the boat form **12b** by 1 kcal mol^{-1} (Table 4),



whereas the absolute values of ΔH_f° in PM3 and AM1 vary by as much as 10 kcal mol^{-1} . The conformation **12c**, in which only C-4 deviates from the plane of the ring carbon atoms, is $2.7 \text{ kcal mol}^{-1}$ (PM3) or $1.4 \text{ kcal mol}^{-1}$ (AM1) above the energy level of **12a**. In the cycloadduct **14** the former thione assumes a twist conformation of the six-membered ring. Values for the heat of reaction (entries 7–9 in Table 3) are calculated by taking different conformations of **12** and **13** as reference points. For PM3 they are found in the range -14 to $-18 \text{ kcal mol}^{-1}$, for AM1 they lie between -10 and $-13 \text{ kcal mol}^{-1}$. The



experimental ΔH value in toluene is $-11 \text{ kcal mol}^{-1}$.⁶ It is not an exaggeration to state that calculated and experimental values are in satisfactory agreement; the comparison of a gas phase calculation with an experimental result in solution limits the precision anyway.

Acknowledgment. The generous allocation of computer time by the HLRZ of the KFA Jülich and support by the Fonds der Chemischen Industrie is gratefully acknowledged.

JA951668U