Thiones as Superdipolarophiles. Rates and Equilibria of Nitrone Cycloadditions to Thioketones

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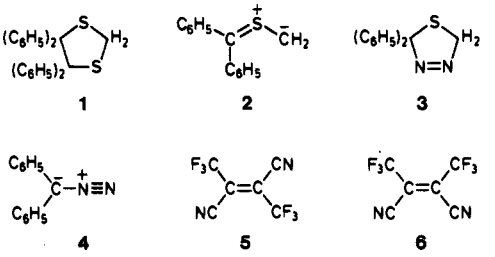
Abstract: 1,3-Dipolar cycloadditions of *N*-methyl-*C,C*-diphenylnitrone (**15**) and *N*-methyl-*C*-phenylnitrone (**16**) with aliphatic thioketones are equilibrium reactions. The 1,4,2-oxathiazolidines were characterized and their dissociation constants measured by ^{1}H NMR analysis and by visible spectrophotometry. K_{diss} of the adduct **28** from **16** and 2,2,6,6-tetramethylcyclohexanethione (**27**) was determined from 20−76 °C, revealing $\Delta H_{add} = -10.8$ kcal mol^{-1} and $\Delta S_{add} = -28$ eu. The inertness of diaryl thioketones vs nitrones has thermodynamic reasons. According to rate measurements with **16**, the activity of the highly hindered thione **27** exceeds 5-fold that of dimethyl acetylenedicarboxylate (DMAD), the top dipolarophile with a CC multiple bond; the cycloaddition to adamantanethione—despite adverse steric effects—is 1500 times faster than that to DMAD. Rate constants for the cycloaddition of **16** to 2,2,4,4-tetramethyl-3-thioxocyclobutanone (**10**) were measured in 12 solvents. The small and slightly inverse relation to solvent polarity rules out a zwitterionic intermediate but is consistent with a *concerted* pathway.

Introduction

The more electron-deficient the dipolarophilic multiple bond, the faster electron-rich 1,3-dipoles undergo cycloadditions. Introduction of electron-attracting substituents into an ethylenic or acetylenic dipolarophile increases the rate constants by many powers of 10. Earlier reasoning with stabilization of partial charges in the transition structure (TS) of the concerted cycloaddition[1] was discarded when Sustmann in 1971 expounded a perturbation MO theoretical model for interpreting reactivity sequences in concerted cycloadditions.[2,3] Both partial charges and rate constants now appear as consequences of the interaction energies of HOMO−LUMO pairs in the early TS.

The clarification of the "Schönberg reaction", e.g., the formation of the 1,3-dithiolane **1** from diazomethane and two molecules of thiobenzophenone,[4] revealed an unusually high dipolarophilic activity of the C=S double bond.[5] Competition of pairs of dipolarophiles for the not isolable *thiobenzophenone S-methylide* (**2**) afforded relative rate constants of 1,3-cycloadditions; e.g., $k_{rel} = 1$ for methyl propiolate, 32 for acrylonitrile, and 33 million for tetracyanoethylene (TCNE).[6] Since thiocarbonyl ylides approximate the high nucleophilicity of the allyl anion, something like an electronic prototype of 1,3-dipoles, the addition of **2** to TCNE is an extreme of the case mentioned above: electron-rich 1,3-dipole plus electron-deficient dipolarophile. The cycloadditions of **2** to dimethyl 2,3-dicyanofumarate, fumaronitrile, and maleonitrile are stereospecific, suggesting concertedness.[7]



1 **2** **3**

4 **5** **6**

Thioketones were highly active versus **2**. The formation of **1** from **2** and thiobenzophenone proceeded with $k_{rel} = 1.2$ million, and thiofluorenone exceeded TCNE 2.4-fold in dipolarophilic activity toward **2**.[6] The reason is not a priori clear. The C=S bond is not electron-deficient since sulfur (2.44) has nearly the same electronegativity as carbon (2.50).[8] According to calculations on $H_2C{=}S$ (B3LYP/6-311+G**) by Schleyer, the CS σ bond is polarized by 11% toward carbon and the π bond toward sulfur to an equal extent.[9]

Thiones were likewise preeminent in the 1,3-cycloadditions of *diazoalkanes*, another class of nucleophilic 1,3-dipoles. Even at −78 °C, thiobenzophenone can be titrated with diazomethane in THF, the colorless thiadiazoline **3** being formed.[5] Kinetic measurements of the additions of diphenyldiazomethane (**4**) at 40 °C gave $10^3 k_2$ (M^{-1} s^{-1}) = 4.7 for acrylonitrile and 3980 for TCNE. However, thiofluorenone was at the top with 450 000; thiobenzophenone showed 4050 and adamantanethione 101.[10] Stereospecificities of >99% observed for the dihydropyrazole formation from diazomethane and the tetraacceptor-substituted ethylenes **5** and **6** suggested concertedness; for

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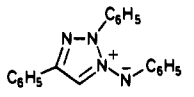
methyl diazoacetate and the same dipolarophiles, retentions of >99.93% and >99.6%, respectively, were measured.[11]

1,3-Cycloadditions to C=S double bonds were described for many 1,3-dipoles, but kinetic data are scarce. Butler et al. measured rate constants for the cycloadditions of the 1,2,3-triazolium imide **7** and found the C=S bond of **8** 1100 times more active than acrylonitrile.[12]



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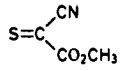
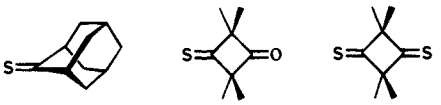


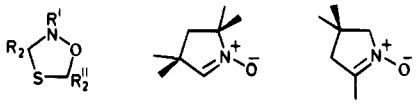
8

We report here on the cycloadditions of nitrones to thioketones. Nitrones (azomethine oxides) are 1,3-dipoles of Sustmann's "type II";[2] Houk and Yamaguchi called them ambiphilic.[13] They react fast with electron-deficient double bonds, slowly with common alkenes, and again fast with the electron-rich enamines. Are thiones superdipolarophiles toward nitrones too?

In 1973, Black and Watson described 1,3-cycloadducts **12** of five nitrones and the sterically hindered thioketones **9**–**11**.[14] In contrast to **14**, the more hindered **13** failed to react.



9 **10** **11**



12 **13** **14**

N-Fluorenylideneaniline *N*-oxide, a ketonitrone, required boiling benzene for the reactions with **9** and **10**, whereas *N*-methyl-*C*-phenylnitrone (**16**) and *C,N*-diphenylnitrone reacted at room temperature. Many of the colorless 1,4,2-oxathiazolidines **12**, originating from **9** and **10**, turned pink or light orange in solution, indicating some dissociation into the reactants. No quantitative data on cycloaddition equilibria were reported.

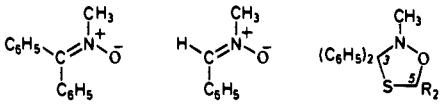
Raasch added **16** to bis(trifluoromethyl) thioketene at 0 °C and isolated the 5-methylene-1,4,2-oxathiazolidine in 90% yield.[15] According to Mazzanti et al.,[16] **16** and thiofluorenone (1 week at 20 °C) gave 17% of a 1:2 product (−SO), $C_{34}H_{25}NS$; the proposed structure needs confirmation.

Thioaldehydes are elusive species. 2,2-Dimethylpropanethial (thiopivaldehyde) can be handled in solution and combined with two nitrones, among other 1,3-dipoles, within minutes at room temperature.[17]

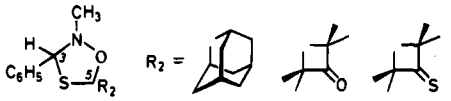
Thioaldehydes and thioketones are highly active *dienophiles*, too. The short-lived cyanothioformaldehyde[18] and thiobenzaldehyde[19] were captured in situ by 1,3-dienes. According to recent rate measurements by Schatz and Sauer, thiofluorenone exceeds maleic anhydride in dienophilic activity 55-fold versus cyclopentadiene and 1300-fold versus 1,3-pentadiene.[20]

Results and Discussion

Cycloaddition Equilibria of Nitrones and Aliphatic Thioketones. *N*-Methyl-*C,C*-diphenylnitrone (**15**) reacted with the easily accessible thioketones **9**–**11** in chloroform at room temperature, establishing cycloaddition/cycloreversion equilibria. Evaporation of the still pink solutions (n → π* transition of **9**–**11**) led to the colorless crystals of **17A,B**; those of **17C** were pink due to the second thione function. The cycloadducts **18A,B** of *N*-methyl-*C*-phenylnitrone (**16**) were described by Black and Watson.[14]



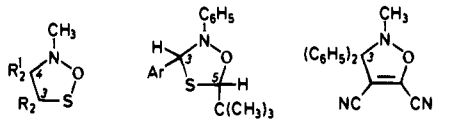
15 **16** **17**



18 **A** **B** **C**

Elemental analyses confirmed 1:1 adducts **17**. The ^{1}H NMR spectra in $CDCl_3$ indicated the signals of the 1,4,2-oxathiazolidines **17** as well as those of nitrone + thione. The NCH_3 singlets of **15** and **16** at δ 3.66 and 3.85, respectively, are shifted to higher field for **17** (δ 2.53–2.61) and for **18**, **24**, and **28** (δ 2.58–2.69). In the ^{13}C NMR spectra ($CDCl_3$), the signals of nitrone **15** and thiones **9**–**11** are likewise superposed on those of the cycloadducts **17A**–**C**; the signals of the latter were obtained by subtraction and found consistent with the structures. The carbonyl C atom of the cyclobutanone ring in **17B** occurred at δ 220.6 (δ 208.3 in the cyclobutanone parent) and the thiocarbonyl of **17C** at δ 285.4 (δ 276.0 in dithione **11**). Values of δ(C-3) and δ(C-5) were in the narrow regions of δ 93.1–95.0 and δ 104.1–107.7, respectively. As expected, the mass spectra of **17A**–**C** were those of nitrone plus thione and their further fragmentation.

Although δ(3-H) = 4.75–5.00 for **18**, **24**, and **28** speaks for the deshielding of the ring proton by *two* heteroatoms, the spectroscopic data do not strictly rule out the regioisomeric 1,2,5-oxathiazolidines **19**. Indirect support comes from cycloadduct **20** obtained by Vedejs and Wilde from *C*-(*p*-



19 **20** **21**

methoxyphenyl)-*N*-phenylnitrone and thiopivaldehyde;[17] two singlets for the ring protons would be inconsistent with the 1,2,5-regioisomer. A stronger argument is based on the heats of formation. The 1,4,2-oxathiazolidines contain *one* weak hetero–hetero σ bond, and the 1,2,5 regioisomers **19**, *two* of them. Calculations (Becke 3LYP/6-31G*) of the parent ring systems (all substituents H) reveal that the 1,4,2-oxathiazolidine is more stable by 9.4 kcal mol^{-1} than the 1,2,5-system.[21] Whereas **17**, **18**, **24**, and **28** exist in mobile equilibria with the reactants, there

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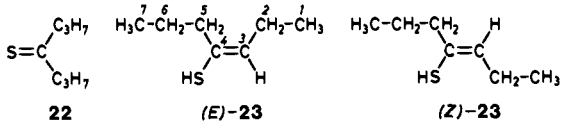
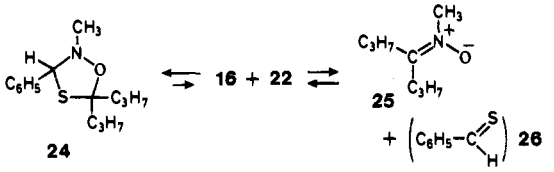
would be no chance of detecting heterocycles **19** which are so much lower in bond energy.

In thermodynamic driving force, nitrone cycloadditions to CC multiple bonds are superior to those with C=S dipolarophiles, but there are limits, too. Isoxazolidines from methyl acrylate and nitrones split into the reactants at 150–170 °C *in vacuo* and triphenylnitrone refused to react with dimethyl fumarate at 100 °C.[22] The greater reaction enthalpy of nitrone cycloadditions to acetylenic dipolarophiles, compared with that of thiones, became obvious when adduct **17B** was treated with dicyanoacetylene in $CDCl_3$ at room temperature; after 45 min, ^1H NMR analysis signaled 100% of dihydroisoxazole **21**.

4-Heptanethione (**22**) occurs in an equilibrium with 23% of *trans,cis*-isomeric enethiols **23** (*E/Z* 67:33). The cycloaddition of nitrone **16** (1.1 equiv) to the thione in $CDCl_3$ was faster than the tautomerization: After 2 h at 5 °C, ^1H NMR analysis (−55 °C) indicated 78% of cycloadduct **24** (NCH_3 at δ 2.60, 3-H



22 *(E)*-**23** *(Z)*-**23**



24 **16 + 22** **25** + **26**

4.79), 1.2% of free thione **22**, and 21% of enethiols **23**. Thus, the ratio of thione to enethiols has changed from 77:23 to 5:95; the tautomerization is lagging behind. After 2 days at room temperature, the ratio 69:31 reveals the approach to equilibrium. The thione–enethiol tautomerism is less mobile[23] than that of keto–enol.

The equilibrium system **16** + **22** ⇌ **24** turned out to be labile. After 2 days, 38% of **24** was accompanied by 59% of a new compound (96% after 9 days); its $\delta(NCH_3)$ at 3.68 in the nitrone region (NCH_3 of **16** at 3.86), the lack of a ring proton, and the two propyl groups in different environments suggested **25**. A metathesis reaction of the kind assumed here has been found in our laboratory; it was catalyzed by hydrogen sulfide.[24] Perhaps the trimerization and polymerization of the postulated thiobenzaldehyde (**26**) drives the conversion to completion.

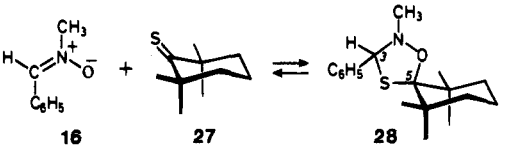
Dissociation Constants. In experiments with defined concentrations of reactants, the dissociation constants of **17** were determined from the ^1H NMR integrals of NCH_3. **15** (0.187 M) and **9** (0.182 M) in $CDCl_3$ at 25 °C equilibrated to a 50:50 ratio of nitrone **15** and cycloadduct **17A**, corresponding to K_{diss} = 0.089 M. The long-wave light absorption of the thioketones allowed a superior spectrophotometric determination of K_{diss}, the knowledge of which was required for the evaluation of rate constants. The extinction of thione **10** (0.0189 M) at λ_{max} 535 nm (ϵ = 13.4) decreased during the reaction with **15** (0.0261 M) to 54% of the initial value, in accord with K_{diss} = 0.020 M for **17B** in chloroform at 25 °C.

Cycloadducts **18** of *N*-methyl-*C*-phenylnitrone (**16**) and thiones have smaller dissociation constants than **17**. A chloroform solution of **16** (0.0167 M) and **10** (0.0103 M) contained 16% of the alicyclic thione **10** after equilibration; K_{diss} = 0.0014 M of **18B** is smaller by a factor of 14 than that of **17B**.

The dissociation constant of **24**, 0.010 M in $CDCl_3$ at 25 °C, is 7 times larger than that of **18B** (0.0014 M). The cycloreversion of **18B** to **15** + **10** is burdened by some increase of angle strain in the cyclobutane ring due to the generation of a second trigonal center.

In benzene or toluene, cycloadducts **18** are less dissociated than in chloroform. The reactions of nitrone **16** (~1.5 equiv) with thiones **9**, **10**, and **22** went virtually to completion, as shown by colorless toluene solutions.

2,2,6,6-Tetramethylcyclohexanethione (**27**) is a sterically very demanding thione. Even in toluene, **27** and **16** (both 0.056 M) equilibrate in 24 h with only 56% of cycloadduct **28**; K_{diss} =



16 **27** **28**

0.019 M at 25 °C is probably the result of van der Waals overlap which is higher in **28** than in **27**. This phenomenon is exacerbated in 1,1,3,3-tetramethylindane-2-thione (**29**); with three trigonal centers in the five-membered ring, its structure is more rigid than the six-membered **27**. After treating **29** with **16** in toluene at room temperature for 4 days, no NCH_3 singlet of a cycloadduct could be seen in the ^1H NMR spectrum.

Thiobenzophenone and its 4,4′-dimethoxy derivative likewise did not combine with nitrone **16** in toluene or $CDCl_3$ at room temperature. The conjugation energy of the aromatic thioketone would have to be sacrificed in the 1,3-cycloaddition, a thermodynamic barrier. The inertness of thiofluorenone or 4,4′-dimethoxythiobenzophenone versus 5,5-dimethyl-1-pyrroline *N*-oxide was mentioned by Black and Watson.[14]

By the way, the isolation of crystalline cycloadducts from the solution is not always feasible even when the equilibrium concentration is high; for example, in the system **16** + **27** ⇌ **28**, nitrone **16** is less soluble than adduct **28** and precipitates. On the other hand, sometimes the yield of a crystalline cycloadduct exceeds the concentration in solution if the cycloaddition/cycloreversion equilibrium is sufficiently mobile.

Temperature Dependence of the Dissociation Constant. We found the equilibrium system of nitrone plus thione with the cycloadduct kinetically stable, i.e., no side reactions occurred (except for **24**). We chose the reactant pair **16** + **27** to study the temperature dependence of the equilibrium constant.

N-Methyl-*C*-phenylnitrone (**16**, 0.0669 M) and 2,2,6,6-tetramethylcyclohexanethione (**27**, 0.0556 M) were equilibrated with **28** in toluene for 26 h. The concentration of the thione was determined by spectrophotometry at 535 nm at seven temperatures from 20 to 76 °C, always allowing time for establishing equilibrium. The portion of the free thione increased from 29% to 81%; the data for K_{diss} are listed in Figure 1. The linear temperature dependence of the free energy changes, ΔG_{diss}, furnished the thermodynamic state functions. After reversal of their signs, the data for the cycloaddition direction were obtained:

$$\Delta H_{add} = -10.8 \text{ kcal mol}^{-1}, \quad \Delta S_{add} = -28 \text{ eu}$$

The magnitude of cycloaddition enthalpy and entropy is not unexpected. ΔG_{add} = −2.5 kcal mol^{-1} at 25 °C and −1.0 kcal mol^{-1} at 76 °C show the near cancellation in the influence of the two terms. When reasons for the high rate constants are discussed in the next section, it is clear that a thermodynamic driving force (high exothermicity) cannot be responsible.

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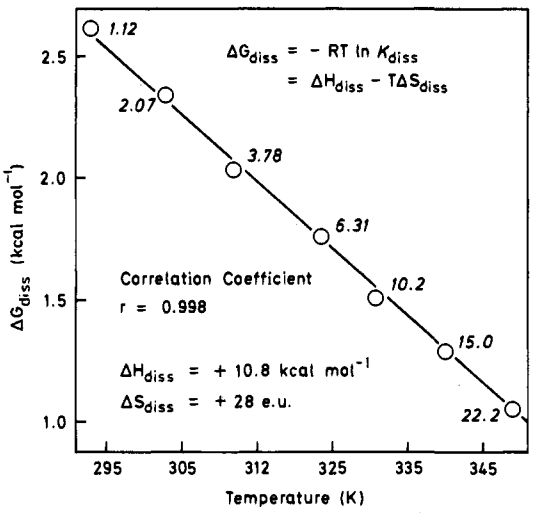

Figure 1. Dissociation of cycloadduct **28** in toluene; dependence of the free energy change on the temperature. Values of $100K_{diss}$ (M) are given in italics.

Reaction enthalpies reflect changes in bond energies. In the chemist's thinking habit, they are dissected into *standard* contributions for bonds to be made or broken; subsequent modifications by steric, conjugation, polarity effects, etc., account for the specific substitution pattern. We ascribed the comparatively high extent of dissociation of **28** to the steric ortho effect by four methyl groups which is more harmful to the cycloadduct than to the free thione. The steric effect will control ΔH_{add} and ΔS_{add}, but the former to a higher extent. The negative entropy term reveals the dominance of the loss of translational freedoms in making one molecule out of two. It may be mentioned that we found the *activation entropies* for the cycloadditions of nitrone **16** to three ethylenic dipolarophiles in toluene to be between −23 and −32 eu.[25]

The inertness of thiobenzophenone toward nitrones appears in new light. On estimating −5 kcal mol^{-1} for the conjugation energy of two phenyls with the CS double bond, we arrive at positive values for ΔG_{add}. With ΔS_{add} kept constant, an increase of the dissociation enthalpy by −5 kcal mol^{-1} would result in a 4600-fold rise of K_{diss} at 25 °C. Supposedly, the small amount of cycloadduct would remain below the analytical limit of ^{1}H NMR analysis.

Rate Constants for the Cycloadditions of *N*-Methyl-*C*-phenylnitrone to Thiones. Our first preparative survey of the (at the time) novel cycloadditions of nitrones to ethylenic and acetylenic dipolarophiles in the 1960s was supplemented by a kinetic study in the Munich laboratory.[25] Rate constants for the cycloadditions of nitrone **16** to 36 dipolarophiles in toluene at 85 °C were measured by dilatometry; no compound with a C=S bond was included. A small selection may reveal the acceleration by electron-withdrawing substituents (10^5k_2, M^{-1} s^{-1}): 1-heptene, 0.33; methyl acrylate, 16; acrylonitrile, 31; fumaronitrile, 166; maleic anhydride, 1010; methyl propiolate, 200; DMAD, 5700.

Thus, dimethyl acetylenedicarboxylate was at the top, 17 000 times faster than 1-heptene. In this kinetic study of 1969, [25] the rate constants were determined *at 85* °C. Less active dipolarophiles required 120 °C for convenient measurement; the value of 1-heptene (above) was extrapolated from the higher temperature. Now it turned out that thiones combined with nitrones rapidly even *at 25* °C.

For reasons of comparison, we chose the same nitrone **16** and toluene as the solvent for the new rate measurements at 25 °C using spectrophotometry of the weak long-wave absorption of aliphatic thiones (Table 1). Methyl propiolate and DMAD served as relays for the rate data at 85 °C; the influence of solvents being small (see the next section), their new rate constants at 25 °C were measured by ^{1}H NMR analysis in $CDCl_3$, based on the NCH_3 singlets of nitrone **16** and the cycloadducts **30**−**32**.

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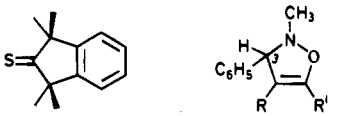
Table 1. Rate Constants for the Cycloadditions of *N*-Methyl-*C*-phenylnitrone (**16**) to Acetylenecarboxylic Esters (^{1}H NMR, $CDCl_3$) and to Thioketones (Visible Spectrophotometry, Toluene) at 25 °C

dipolarophile	$10^4 k_2$ (M^{-1} s^{-1})
methyl propiolate	0.055
dimethyl acetylenedicarboxylate	4.1
2,2,6,6-tetramethylcyclohexanethione (**27**)	22
2,2,4,4-tetramethyl-3-thioxocyclobutanone (**10**)	700
4-heptanethione (**22**)	1520
adamantanethione (**9**)	6200



29

30 R = CO_2CH_3, R' = H
31 R = H, R' = CO_2CH_3
32 R = R' = CO_2CH_3

In the reactions of **9**, **10**, and **22**, the pink toluene solutions became colorless when 1.5−2.5 equiv of **16** was employed; the extinction measurements were evaluated by the second-order rate equation (eq 2). The reaction of **16** with **27** in toluene at 25 °C, both 0.056 M, reached an equilibrium which still contained 44% of the reactants; rate equation (4) (see the Experimental Section) for N + T ⇄ C ($N_o = T_o$) was fulfilled up to 94% approximation to the equilibrium. In the second run with different initial concentrations, the rather unwieldy rate equation (3) for N + T ⇄ C ($N_o \neq T_o$) was obeyed.

The sterically hindered tetramethylcyclohexanethione **27**, the least active thioketone in Table 1, accepts nitrone **16** still 5 times faster than DMAD, the record dipolarophile with multiple CC bond. The back-bending of the methyl groups in the four-membered ring of **10** diminishes the screening of the C=S bond and is rewarded by a 32-fold rate increase. The open-chain thione **22** exceeded **27** 70-fold. The top position of adamantanethione (**9**) is astounding, its rate constant being 1500 times higher than that of DMAD, a dramatic effect. Some rate data with the ketonitrone **15** will follow in the next section.

Thus, thiones are *superdipolarophiles* versus nitrones. The test case is the more convincing, as the cycloaddition/cycloreversion equilibria demonstrate that the low energy of the CS π bond (54 kcal mol^{-1} by MP4/6-31G*)[26] which is sacrificed in the cycloaddition cannot be the reason for the high rate constants.

The LUMO of the thione is used for generating one of the new σ bonds during the cycloaddition. The low activation energy must be the result of a diminished HOMO−LUMO distance. Vedejs and Houk et al. found the $\pi-\pi^*$ energy difference of thioformaldehyde by calculation (ab initio, split valence 3-21G) to be 12.8 eV, i.e., 5.8 eV lower than that of formaldehyde.[27] The $\pi \rightarrow \pi^*$ transition of thiobenzophenone occurs at 314.5 nm, that of benzophenone at 248 nm (both in

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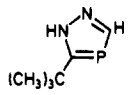
hexane);[28] the substantial bathochromic shift for the thione is in accordance with a lower HOMO−LUMO distance. The high polarizability of the C=S bond, quoted earlier as a rate-increasing factor of the cycloadditions to thiones,[10] may well be a consequence of a low HOMO−LUMO separation too. A deeper understanding of the superdipolarophilic nature of thiones evolves from the high-caliber MO calculations of the subsequent paper.[21]

The C=S bond does not monopolize on low π(HOMO−LUMO) distance which should be widespread among π bonds in which elements of higher long periods participate. Qualitative evidence for high dipolarophilic and dienophilic character of such bonds is abundant. Although no rate data are available, a few examples—an arbitrary choice—may be quoted. In contrast to acetonitrile or its trimethyl derivative, the stable phospha analogue, $(CH_3)_3C-C\equiv P$, readily adds diazomethane at 0 °C, affording the 1*H*-1,2,4-diazaphosphole **33**; [29] the exciting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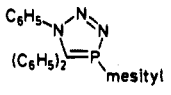
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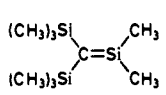
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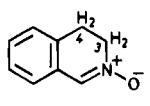
chemistry of "phosphanitriles" was developed by Regitz.[30] The C=P double bond appears to be less reactive, since the addition of phenyl azide to mesityl(diphenylmethylene)phosphane to give **34** requires 80 °C.[31] Wiberg et al. generated the silaethene **35** at −30 °C from a metal−organic precursor; the in situ reaction with 2,3-dimethylbutadiene furnished the [4 + 2] cycloadduct and ene product in a 4:1 ratio.[32] The P=S bond in dithiophosphonic anhydrides is likewise dienophilic.[33]

Solvent Dependence of the Cycloaddition Rate. What can be said about the mechanism of the 1,3-cycloadditions of nitrones? Retention of configuration at the terminal centers of 1,3-dipole and dipolarophile is mandatory for the *concerted* pathway. The cycloadditions of 3,4-dihydroisoquinoline *N*-oxide (**36**) to dimethyl fumarate and maleate gave the pure diastereoisomeric adducts in isolated yields of 100% and 96%, respectively.[22] A superior test of stereospecificity was provided by Gandolfi et al.: the equilibration of **36** and *trans*-β-nitrostyrene with the 1,3-cycloadduct for a certain time—the rate constants of forward and reverse reaction being known—allowed deduction of a retention of >99.89% for the single step.[34]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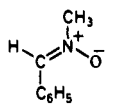
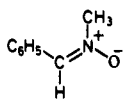
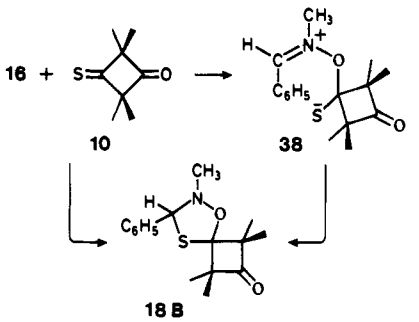

16 *(Z)*


37 *(E)*

The C=S double bond is not amenable to a stereospecificity test. However, the solvent dependence of the rate constant is a significant argument in the mechanistic discussion. We chose the cycloaddition of nitrone **16** to the cyclic thione **10** and determined the rate constants in 12 solvents using visible spectrophotometry again (Table 2). The formation of the zwitterionic intermediate **38** is conceivable as the first step of the cycloaddition, in a two step alternative to the concerted mechanism. The TS of this initial endothermic step should be structurally close to the intermediate, and the solvation is expected to increase with the charge separation in the process **16** + **10** → **38**.

Table 2. Rate Constants for the Cycloadditions of Nitrones **15** and **16** to 2,2,4,4-Tetramethyl-3-thioxocyclobutanone (**10**) and Dissociation Constants of Cycloadducts in Various Solvents at 25 °C (Visible Spectrophotometry)

solvent	$100\,k_2$ ($M^{-1}s^{-1}$)	10^3K_{diss} (M)	E_T (kcal mol^{-1})
a. *N*-Methyl-*C*-phenylnitrone (**16**)			
carbon tetrachloride	8.7	small	32.5
toluene	7.0	small	33.9
anisole	6.3	small	37.2
tetrahydrofuran	7.3	0.79	37.4
chlorobenzene	6.6	small	37.5
ethyl acetate	7.2	small	38.1
chloroform	1.2	1.4	39.1
dichloromethane	1.8	1.3	41.1
benzonitrile	7.1		42.0
acetonitrile	5.9	1.7	45.0
nitromethane	4.2	2.0	46.3
methanol	0.66	5.3	55.5
b. *N*-Methyl-*C*,*C*-diphenylnitrone (**15**)			
chloroform	39.5	20	39.1
dichloromethane	61	12	41.1
methanol	41	26	55.5


10 **38** **18 B**

The solvents are ordered in Table 2 by increasing E_T values, Reichardt's successful empirical parameter of solvent polarity.[35] The largest and the smallest rate constant differ by a factor of only 13. The extremes, $100\,k_2 = 8.7$ and 0.66 $M^{-1}\,s^{-1}$, at the lower and upper ends of the E_T scale, suggest a slightly inverse function of solvent polarity, but the irregularity of the k_2 sequence raises some doubt. Certainly, the rate constants do not confirm a mechanism with an increase of charge separation in the activation process.

In our kinetic study of 1969, the cycloaddition of **16** to ethyl acrylate was measured in 13 solvents. Despite the small range of rate constants (factor of 5.6), the response to solvent polarity had a negative sign, and the relation of log k_2 with E_T was linear.[25] The dipole moments of reactants and cycloadduct—with μ = 3.55 D, nitrone **16** has the highest—gave a clue to the slightly inverse dependence on E_T. There is no motive for postulating different mechanisms for nitrone cycloadditions to ethyl acrylate and to thione **10**.

In the reaction **16** + **10** in THF, some stray shots of higher k_2 values raised the suspicion that a chain reaction initiated by electron transfer might be involved. Rate runs in the presence of 1,4-dinitrobenzene, S_8, or di-*tert*-butylnitroxide did not support this hypothesis. We suppose that, occasionally, trace

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impurities of acid kept the *Z,E* equilibrium of the nitrone **16** with **37** mobile. *N*-Methyl-*C*-phenylnitrone is (*Z*)-**16** in crystal[36] and solution. However, it was shown in our study of 1969 that (*E*)-nitrone **36** was 220 times more active in the 1,3-addition to ethyl crotonate than (*Z*)-**16**.[25] Later, good experimental evidence from several research groups suggested that (*Z*)-aldonitrones like **16** equilibrate in the presence of acid with a small concentration of the *E* form, here **37**, which cannot be seen by NMR but contributes to product formation due to a higher rate constant.[37] By using fresh solutions of **16** in pure solvents, the log k_2 were reproducible, but small deviations from linearity with E_T may originate from a tiny *E* content.

The *equilibrium* **16** + **10** ⇌ **18B** is solvent-dependent, K_{diss} rising with solvent polarity (Table 2). The reason may be the increasing solvation of nitrone **16**, the reactant with the highest dipole moment. The low extinction coefficient of **10**, $\epsilon = 13.4$, makes small values of K_{diss} problematic. Rate runs in solvents, for which a numeral of K_{diss} is given in Table 2, were evaluated with the cumbersome eq 3, the others with the simpler eq 2.

To circumvent the possible interference by *E,Z* structures of open-chain aldonitrones, rate measurements with a ketonitrone, the *N*-methyl-*C,C*-diphenylnitrone (**15**) which is not capable of *E,Z* isomerism, were supplemented (Table 2). The use of the same thione **10** allowed the comparison of nitrone activities. Only three solvents were employed, and the solvent dependence of k_2 is modest. The rate constants of the ketonitrone **15** are higher; k(**15**)/k(**16**) of 33−66 correspond to $\Delta G^{\ddagger} = 2.1-2.5$ kcal mol^{-1}. The interpretation is rendered hard by the fact that the dissociation constants of adduct **17B** likewise exceed those of **18B** by 5−13-fold.

The conjugation energy of two phenyl groups with the C=N double bond in **15** is higher than that of one phenyl in **16**, but not twice as large. One expects propeller-like twisting for the *C,C*-diphenyl compound **15**, whereas nitrones like **16** are planar (X-ray).[36] That explains the difference of **15** and **16** in the K_{diss} of their cycloadducts; but why are the cycloadditions of **15** faster than those of **16**? The reason may well be the stronger lifting of the HOMO energy of **15** compared with **16** as a consequence of orbital compression in conjugated systems.

Conclusions

Rate measurements indicated that nucleophilic 1,3-dipoles like thiobenzophenone *S*-methylide (**2**)[6] and diphenyldiazomethane (**4**)[10] undergo cycloadditions to thioketones much faster than to CC multiple bonds. We now have demonstrated the superiority of thiones, even sterically hindered ones, versus *N*-methyl-*C*-phenylnitrone (**16**), a nucleophilic−electrophilic 1,3-dipole. The equilibrium constants measured for 1,3-additions of nitrones to thiones leave no doubt that the weakness of the CS π bond is not responsible for the high reaction rates; a low HOMO−LUMO energy distance of the CS π bond is suggested as the decisive factor.

The rate constants for the cycloadditions of nitrones **15** and **16** to thione **10** reveal little influence of solvent polarity. That militates against zwitterionic intermediates, but is in accordance with a *concerted* cycloaddition.

There is qualitative evidence that other double bonds involving elements of higher long periods are likewise *superdipolarophiles* and *superdienophiles*, respectively, in cycloaddition reactions.

Experimental Section

General Procedure. ^{1}H NMR spectra were recorded on a Bruker model WP80CW or a Varian VXR400S (400 MHz) and ^{13}C NMR spectra on a Bruker WP80DS instrument at 20 MHz. All NMR spectra were taken in $CDCl_3$ with tetramethylsilane as the internal standard; the $CDCl_3$ was kept acid-free by storing over dry potassium carbonate. In the quantitative ^{1}H NMR analysis (±5% relative) 1,1,2,2-tetrachloroethane was used as a weight standard. Infrared spectra were obtained with a Bruker FT model IFS 45. A Lambda 3 UV/vis from Perkin-Elmer served the spectrophotometric measurements of rates and equilibria; the cuvette was thermostated, and the temperature was measured by thermocouple in the cuvette before the experiment. Mass spectra were taken with an AEI Manchester instrument FINIGAN MAT90. Melting points are uncorrected.

Thiones. Adamantanethione (**9**);[38] 1,1,3,3-tetramethylindane-2-thione (**29**).[39]

2,2,4,4-Tetramethyl-3-thioxocyclobutanone (**10**) and 2,2,4,4-tetramethylcyclobutane-1,3-dithione (**11**):[40,14] The 1,3-dione (21 g, 150 mmol) and P_4S_{10} (18 g, 40.5 mmol) were refluxed in 60 mL of pyridine for 90 min. After workup, separation was achieved by chromatography on 200 g of silica gel; the elution with hexane gave **11** (22%), and with hexane/ether (7:3), **10** (46%) was eluted. With a reaction time of only 40 min in pyridine, 58% of **10** and 15% of **11** were obtained.[41]

4-Heptanethione (**22**): The procedure with benzoic anhydride and H_2S[42] was applied to 4-heptanone anil, yield 54% of **22** as a red oil.[41] ^{1}H NMR: δ 0.96 (t, 2 CH_3), 1.77 (sextet, $J = 7.5$ Hz, 2-H_2 and 6-H_2), 2.84 (t, 3-H_2 and 5-H_2). The specimen used for the kinetic experiments contained 68% of **22**, 21% of enethiols **23**, and 11% of 4-heptanone. Thus, thione/enethiols = 77:23 is in tautomeric equilibrium (80:20).[43]

Enethiols **23**: (*E/Z*) = 67/33. (*E*): ^{1}H NMR δ 5.37 (tt, $J_{2,3} = 6.9$ Hz, $J_{3,5} \sim 0.95$ Hz, 3-H); (*Z*): ^{1}H NMR δ 5.55 (t, $J_{2,3} = 7.3$ Hz, allylic coupling not resolved, 3-H). *E* + *Z*: ^{1}H NMR 0.92, 0.99 (2 t, others overlapping, 4 CH_3), 1.56 (m, 6-H_2), 2.02−2.13, 2.17−2.25 (2 m, 2-H_2, 5-H_2). According to deshielding increments of substituents,[44] δ(vinyl-H) of the (*Z*) form should be higher by 0.2 ppm than that of (*E*).

2,2,6,6-Tetramethylcyclohexanethione (**27**).[45] The conversion of ketones to thiones with trimethyl orthoformate, gaseous HCl, and H_2S in methanol at 0 °C [39] was applied to 2,2,6,6-tetramethylcyclohexanone;[46] spinning-band column distillation gave **27** in 21−31% yield as a red oil, bp 84−85 °C/15 (106 °C/40).[47] ^{1}H NMR: δ 1.31 (s, 4 CH_3), 1.80 (s br, 3 CH_2). ^{13}C NMR δ 18.2 (t, C-4), 33.4 (q, 4 CH_3), 39.5 (t, C-3 and C-5), 52.4 (s, C-2 and C-6), 280.2 (s, C=S).

Nitrones. *N*-Methyl-*C,C*-diphenylnitrone (**15**). ^{1}H NMR: δ 3.66 (s, NCH_3), 7.1−7.5, 7.78−8.03 (2 m, 2 C_6H_5). ^{13}C NMR: δ 52.4 (q, NCH_3), 127.6, 128.9, 129.2, 129.4, 129.8 (5 d, 10 aromat. H), 133.6, 135.8 (2 s, 2 aromat. C_q).

N-Methyl-*C*-phenylnitrone (**16**). ^{1}H NMR: δ 3.85 (s, NCH_3), 7.36 (s, HC=N), 7.38−7.44 (m, 3 aromat. *m*-H, *p*-H), 8.18−8.24 (m, 2 aromat. *o*-H); at −55 °C (experiment with **22**), the aromatic *m*-H, *p*-H, and HC= form a narrow pseudo-t at 7.46, the 2 *o*-H a slim m at 8.26.

2′-Methyl-3′,3′-diphenylspiro[adamantane-2,5′-(1,4,2)-oxathiazolidine] (17A). Nitrone **15** (1.06 g, 5.02 mmol) and thione **9** (0.830 g, 4.99 mmol) in 20 mL of chloroform reacted for several hours at room temperature. The still light orange-red solution was evaporated; colorless **17A** (1.49 g, 79%) crystallized from methanol, mp 128−129 °C (red melt). On dissolving, the reddish color reappeared. IR

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(KBr): 2929, 2912 st; 1492, 1487 (C_6H_5 vibr), 1447 st; 1099, 990, 980, 939, 894 m (C—O, C—N); 768, 763, 702, 694 st (C_6H_5 wagg.). ^{1}H NMR (separated signals of the reactants subtracted, adamantyl signals overlapping): δ 2.61 (s, NCH_3), 3.33–3.50 (m, 2 H), 7.06–7.55 (m, 2 C_6H_5). ^{13}C NMR: δ 43.1 (q, NCH_3), 93.1, 107.3 (2 s, C-3′ and C-5′), 127.1, 127.8, 128.3 (3 d, 10 aromat. CH), 143.4 (s, 2 aromat. C_q). MS (EI, 70 eV): *m/z* (proposed ion, percent intensity) 211 (**15**$^+$, 41), 210 (**15**$^+$− H, 100), 194 (210 − O, 28), 166 (**9**$^+$, 91), 165 (fluorenyl$^+$, 38), 133 (**9**$^+$- SH, 20). Anal. Calcd for $C_{24}H_{27}NOS$: C, 76.35; H, 7.21; N, 3.71; S, 8.49. Found: C, 76,27; H, 7.17; N, 3.69; S, 8.48.

2,2′,2′,4′,4′-Pentamethyl-3,3-diphenylspiro[(1,4,2)-oxathiazolidine-5,3′-cyclobutane]-1′-one (17B). **17B** was prepared analogously from **15** (1.01 mmol) and **10** (1.21 mmol) in 2 mL of $CDCl_3$ at room temperature; the $\delta_H(NCH_3)$ values show **15/17B** = 19:81. From methanol at −78 °C were obtained colorless crystals (90% yield), mp 143–144 °C (red on melting). IR (KBr): 1784 st (C=O). ^{1}H NMR: δ 1.04 (s br, 4 CH_3), 2.53 (s, NCH_3), 7.10–7.56 (m, 2 C_6H_5); thione **10** occurs at 1.34 (s, 4 CH_3). ^{13}C NMR δ 19.7, 23.2 (2 q, 4 CH_3), 41.9 (q, NCH_3), 66.1 (s, C-2′ and C-4′), 95.1, 104.1 (2 s, C-3 and C-5), 127.6, 128.0, 128.2 (3 d, 10 aromat. CH), 145.0 (s, 2 aromat. C_q), 220.6 (s, C=O). MS (EI, 70 eV): *m/z* 211 (**15**$^+$, 19), 210 (**15**$^+$− H, 39), 195 (211 − O, 55), 194 (210 − O, 72), 118 ($C_6H_5C{\equiv}N^+CH_3$, 100), 105 ($C_6H_5CO^+$, 69). Anal. Calcd for $C_{22}H_{25}NO_2S$: C, 71.90; H, 6.86; N, 3.81; S, 8.73. Found: C, 72.10; H, 6.90; N, 3.93; S, 8.74.

2,2′,2′,4′,4′-Pentamethyl-3,3-diphenylspiro[(1,4,2)-oxathiazolidine-5,3′-cyclobutane]-3-thione (17C). The reaction of **15** (5.02 mmol) and dithione **11** (4.99 mmol) in 20 mL of $CDCl_3$ gave pink crystals (1.65 g, 86%, from methanol), mp 156–158 °C. ^{1}H NMR: δ 1.11 (s br, 4 CH_3), 2.54 (s, NCH_3), 7.08–7.53 (m, 2 C_6H_5); dithione **11** at 1.40 (s, 4 CH_3). ^{13}C NMR: δ 23.9, 27.3 (2 q, 4 CH_3), 41.9 (q, NCH_3), 69.9 (s, C-2′ and C-4′), 95.0, 107.7 (2 s, C-3 and C-5), 127.6, 127.9, 128.2 (3 d, 10 aromat. CH), 142.5 (s, 2 aromat. C_q), 285.4 (s, C=S); dithione **11** gives rise to 25.8 (q, 4 CH_3), 276.0 (s, C=S). MS (EI, 70 eV): *m/z* 211 (**15**$^+$, 40), 210 (**15**$^+$− 1, 100), 195 (211 − O, 15), 194 (210 − O, 23), 172 (**11**$^+$, 11), 165 (fluorenyl$^+$, 31), 118 ($C_6H_5C{\equiv}N^+$-CH_3, 30), 86 ($[CH_3]_2C{=}C{=}S^+$, 34). Anal. Calcd. for $C_{22}H_{25}NOS_2$: C, 68.89; H, 6.57; N, 3.65; S, 16.72. Found: C, 69.24; H, 6.64; N, 3.76; S, 16.75.

2,2′,2′,4′,4′-Pentamethyl-3-phenylspiro[(1,4,2)-oxathiazolidine-5,3′-cyclobutane]-1′-thione (18C). **16** (0.962 mmol) and **11** (0.992 mmol) reacted for 1 d in $CDCl_3$. ^{1}H NMR: δ 1.31 (s br, 2 CH_3), 1.34, 1.35 (2 s, 2 CH_3), 2.67 (s, NCH_3), 5.01 (s, 3-H), 7.13–7.50 (m, C_6H_5). The dithione **11** in the equilibrium absorbs at δ 1.39 (s, 4 CH_3). Two s at δ 2.58 and 2.60 were assigned to two bisadducts [14] (82 μmol, 16% yield, along with 852 μmol of **18C**, 84%).

2-Methyl-3-phenyl-5,5-dipropyl-1,4,2-oxathiazolidine (24). Nitrone **16** (137 mg, 1.01 mmol) was combined with thione **22** (130.0 mg of the mentioned specimen, i.e., 679 μmol of **22**, 207 μmol of enethiols, and 129 μmol of 4-heptanone) in 2 mL of $CDCl_3$ at 0 °C; the solution was kept for 2 h at +5 °C. The ^{1}H NMR spectrum (at −55 °C, for slowing down a subsequent reaction) indicated **24** (78% relative yield) with δ 2.60 (s, NCH_3), thione **22** (1.2%) at δ 2.86 (t, 3-H_2 and 5-H_2), and enethiols **23** (21%). ^{1}H NMR of **24** (−55 °C): δ 0.98, 1.00 (pseudo-q of two overlapping t, J_{vic} = 7.3 Hz, 2 CH_3), 1.3–1.6 (br m, β-H_2 and β'-H_2), 1.7–2.4 (complex pattern, two ddt resolved, diastereotopic α-H_2 and α'-H_2), 2.60 (s, NCH_3), 4.79 (s, 3-H), 7.34–7.42, 7.51–7.57 (2 m, C_6H_5).

In 2 d at room temperature the ^{1}H NMR spectrum changed grossly due to a subsequent reaction of **24** or **16** + **22**; besides 36% of cycloadduct **24**, a new and still not isolated product with δ 3.68 (s, NCH_3), probably **25**, appeared in 59% yield; further δ_H of **25**: 0.981 (t, J_{vic} = 7.4 Hz, CH_3), 0.986 (t, J_{vic} = 7.2 Hz, CH_3), 1.50–1.64 (m, two β-H_2), 2.31, 2.51 (two pseudo-t, AA′ of AA′BB′, two α-H_2). In the equilibrium with **24** were 2.1% of **22** and 1.0% enethiols; K_{diss} = 0.010 M at 25 °C resulted for the cycloreversion equilibrium **24** $\rightleftarrows$ **22** + **16**. After 9 d at 25 °C, 96% of nitrone **25** was observed besides 4% of **24**.

The cycloaddition **16** + **22** is much faster than the isomerization of enethiols to **22**; therefore, the evaluation of the rate measurement (Table 1) was based on the thione content only.

2,2,2′,6,6-Pentamethyl-3′-phenylspiro[cyclohexane-1,5′-(1,4,2)-oxathiazolidine] (28). **16** and **27**, equimolar in $CDCl_3$, equilibrated for 5 d with **28**. ^{1}H NMR: δ 1.08, 1.19, 1.21, 1.40 (4 s, 4 CH_3), 2.50 (s, NCH_3), 4.65 (s, 3-H); at δ 1.31, the four CH_3 groups of thione **27** occurred as a singlet. Attempts of isolating **28** failed because nitrone **16** had a lower solubility in methanol or diisopropyl ether.

Dissociation Constants of 1,4,2-Oxathiazolidines. The two methods of determination are illustrated by 2,2′,2′,4′,4′-pentamethyl-3-phenylspiro[(1,4,2)-oxathiazolidine-5,3′-cyclobutane]-1′-one (**18B**).[14]

(a) ^{1}H NMR. Nitrone **16** (0.984 mmol), thione **10** (0.736 mmol), and 1,1,2,2-tetrachloroethane (0.768 mmol, TCE, weight standard) in 2 mL of $CDCl_3$ solution reached equilibrium with **18B** in 24 h. The integrals compared with that of TCE (s, 5.96) added up to 104% and were corrected. **16**: 0.210 mmol by the signal at δ 3.84 (s, NCH_3), 0.208 mmol at δ 8.2 (m, 2 aromat. *o*-H). **10**: 0.0086 mmol by δ 1.34 (s, 4 CH_3). **18B**: 0.728 mmol by the sum of four s at δ 1.23, 1.26, 1.27, 1.28 (4 s, 4 CH_3) and 0.726 mmol at δ 2.65 (s, NCH_3). K_{diss} = 0.0012 M at 25 °C.

(b) Spectrophotometry of **10** at 520 nm, ϵ = 13.4. Thermostated solutions (25 °C) of **16** and **10** in $CDCl_3$ were combined in the 5 cm cuvette, the initial concentrations being N_o = 16.69 mM and T_o = 10.25 mM. The extinction fell from E_o = 0.687 to the equilibrium value of 0.110 in 24 h, corresponding to T_e = 1.64 mM (16% of free **10**). K_{diss} = 0.0015 M was evaluated with eq 1. T_e was the end concentration in a kinetic measurement; the straight line (r = 0.999), obtained with eq 3 up to 94% approach to T_e, made this value trustworthy.

$$K_{diss} = k_1/k_2 = \frac{T_e(T_e + N_o - T_o)}{(T_o - T_e)} \qquad (1)$$

Temperature Dependence of the Equilibrium of 2,2,6,6-Tetramethylcyclohexanethione and *N*-Methyl-*C*-phenylnitrone with the Cycloadduct. Spectrophotometry of the pink solution in toluene (535 nm, ϵ = 13.9, 1 cm cuvette). **16** (N_o = 66.86 mM) and **27** (T_o = 55.66 mM) in degassed toluene in the closed cuvette were kept for 24 h in the dark. After several h in the cuvette chamber of the spectrophotometer at 20.1 °C, the extinction was constant, indicating the established equilibrium. Then the temperature was raised stepwise, and the intervals to attain constant values of E became shorter. The following equilibrium concentrations of **27** were determined from E_{obs} and E_o = 0.774: 100 T_e(°C) = 1.62 (20.1), 2.16 (30.0), 2.77 (39.0), 3.32 (48.3), 3.80 (57.9), 4.16 (67.3), 4.48 M (76.0). Due to the volume expansion with rising temperature, the concentrations decrease. The values of K_{diss} (eq 1) were corrected by the cubic expansion coefficient of toluene[48] and are listed in Figure 1.

Measurement of Rate Constants of 1,3-Cycloadditions. Procedures and methods of evaluation for the reactions of N(itrone) with T(hiones) to give C(ycloadducts) are illustrated by one example each.

N + T → C ($N_o \neq T_o$). The simple integrated rate eq 2 for the second order was applied when the pink or light orange-red solution of the thione became colorless during the reaction, i.e., when the cycloreversion is negligible. T_o and T are the thione concentrations at the beginning and at time t; $N_o - T_o = D$.

$$k_2 t = \frac{1}{D} \ln \frac{T_o(T + D)}{TN_o} \qquad (2)$$

16 + 10 → 18B in Toluene. **16** (369.8 mg, 2.736 mmol) and freshly sublimed **10** (301.0 mg, 1.927 mmol) were dissolved in degassed toluene in two 10 mL volumetric flasks. One milliliter each was pipetted into a 1 cm cuvette; the temperature of the thermostat was adjusted before to 25.0 ± 0.2 °C, measured in the cuvette. N_o = 0.1368 M, T_o = 0.0964 M, 525 nm, ϵ = 13.9, E_o = 1.339. Ten E readings were taken in 6 min (86% conversion), and the solution was colorless after 30 min. The graphic plot according to eq 2 showed no systematic

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deviation, and the linear regression gave $k_2 = 0.0725$ M^{-1} s^{-1} with a fit of $r = 0.999$. In the second run (always two were done), the higher nitrone concentration ($N_o = 0.1824$ M, $T_o = 0.0642$ M, $E_o = 0.893$) led to 83% conversion in 3 min. Nine E_{obs} values furnished $k_2 = 0.0681$ M^{-1} s^{-1}.

N + T $\rightleftarrows$ C ($N_o \neq T_o$). In the cumbersome integrated rate eq 3,[49] T_e is the equilibrium concentration and K the dissociation constant of C. More than one-half of the rate measurements required eq 3 for evaluation.

$$k_2 t = \frac{1}{A}\left[\ln \frac{2T + D + K + A}{2T + D + K - A} - \ln \frac{D + K + A}{D + K - A}\right] \quad (3)$$

$$A = \sqrt{(D + K)^2 + 4KT_o}; \quad K = T_e(T_e + D)/(T_o - T_e)$$

15 + 10 $\rightleftarrows$ 17B in Chloroform. Measurement of the fast cycloadditions of *N*-methyl-*C*,*C*-diphenylnitrone required dilute solutions in a 5 cm cuvette. $N_o = 0.02614$ M, $T_o = 0.01890$ M, 520 nm, $\epsilon = 13.4$. After 12 min the equilibrium with 54% of **17B** was established; $T_e = 0.01025$ M, $K_{diss} = 0.0207$ M. Ten E_{obs} values in 120 s (90% approximation to T_e), treated with eq 3, provided $k_2 = 0.408$ M^{-1} s^{-1} with correlation coefficient $r = 0.999$. In the second run with $N_o = 0.02844$ M and $T_o = 0.01907$ M, the equilibrium contained 50% of **17B**; $T_e = 0.0954$ M, $K_{diss} = 0.0190$ M, $k_2 = 0.400$ M^{-1} s^{-1}.

N + T $\rightleftarrows$ C ($N_o = T_o$). Equality of initial concentrations avoids the punishment of using eq 3. The treatment of the data by eq 4[50] is easier, but achieving $N_o = T_o$ by weighing is tough.

$$k_2 t = \frac{T_o - T_e}{2T_o T_e - T_e^2} \ln \frac{(T_o - T_e)(TT_o - TT_e + T_o T_e)}{T_o^2 (T - T_e)} \quad (4)$$

16 + 27 $\rightleftarrows$ 28 in Toluene. $N_o = T_o = 0.0560$ M in degassed toluene, 535 nm, $\epsilon = 13.8$, 1 cm light path; $T_e = 0.0246$ M was reached after 24 h at 25 °C, i.e., 56% of adduct **26** was in the equilibrium, $K_{diss} = 0.0194$ M. After 300 min the approach to T_e was 95%; 14 E_{obs} data up to 300 min were evaluated with eq 4, and linear regression gave $k_2 = 0.002\,10$ M^{-1} s^{-1} with $r = 0.999$. The second run used unequal initial concentrations, and 12 E_{obs} values were treated with eq 3, $k_2 = 0.002\,32$ M^{-1} s^{-1}.

Cycloaddition Rates of Acetylenecarboxylic Esters were measured by ^{1}H NMR analysis. In a test run carried out with **16** plus DMAD in a *glass* NMR tube, we learned about the sensitivity of the 4-isoxazoline **32**; beyond 50% conversion, the sum of the NCH_3 integrals of **16** and **32** fell below 100%, when compared with the weight standard. The solution in $CDCl_3$, 0.3051 M **16**, and 0.2069 M DMAD, was filled into a clean *quartz* NMR tube. 400 MHz spectra were taken at preprogrammed reaction times. The sum of the NCH_3 integrals of **16** (s, δ 3.86) and cycloadduct **32** (δ 2.98) was set equal to 100 and split up. The absence of side reactions was confirmed by comparison with the integral of 1,1,2,2-tetrachloroethane (δ 5.96). The simple integrated rate equation of second order (N_o + $DMAD_o$) was applied. After 292 min at 25 °C, 76% conversion was reached. Linear regression based on 15 concentration/time readings provided $10^4 k_2 = 4.08$ M^{-1} s^{-1} with $r = 0.999$. The second run, followed until 83% conversion, gave $10^4 k_2 = 4.05$ M^{-1} s^{-1} ($r = 0.997$).

An excess of methyl propiolate (2.99 M, 9.7 equiv) reacted with **16** (0.309 M) in $CDCl_3$ at 25 °C in the quartz tube. The sum of the NCH_3 singlets of **30** and **31** at δ 2.96 and 2.97 was used in addition to that of **16** (δ 3.85); $10^6 k_2 = 5.49$ M^{-1} s^{-1} was based on 18 concentration measurements up to 61% conversion within 16.6 h ($r = 0.999$).

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