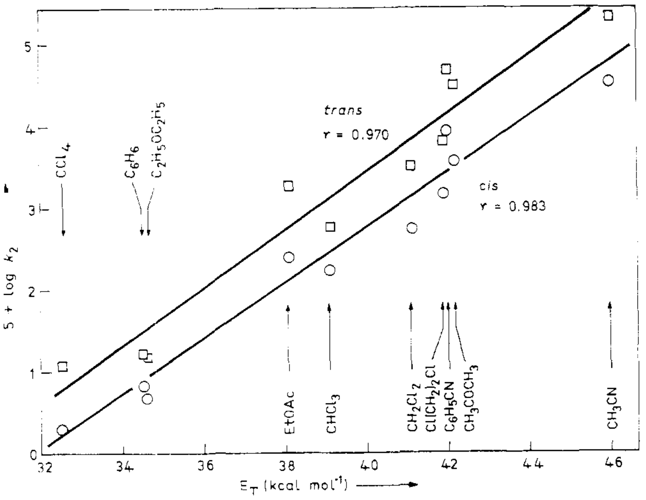

Figure 1. Rate constants k_2 for TCNE cycloadditions to ethyl *cis*- and *trans*-propenyl sulfide in various solvents at 25 °C in a logarithmic plot against E_T.

of **1** and **2** (0.075–0.085 M) kept polarity changes of the medium by the thioenol ether at low levels.[5]

The overall second-order rate constants k_2 display a spectacular increase with solvent polarity (Figure 1). The addition to **1** and **2** is in acetonitrile 17 100 and 16 800 times faster than in CCl$_4$, compared with k_2(acetonitrile)/k_2(CCl$_4$) = 2900 for isobutenyl ethyl ether, 17 000 for 3,4-dihydro-2*H*-pyrane, and 7600 for anethole.[6] The increase of k_2 corresponds to $\Delta\Delta G^{\ddagger}$ = 5.8 kcal mol^{-1}, which is due to the rising dielectric constant of the solvent and the $\Delta\Delta G$ of solvation during the activation process. The data harmonize with the formation of the zwitterion **3**. The experimental k_2 value contains besides k_1 a partition coefficient of the intermediate **3** for cyclization and dissociation,[7] $k_c/(k_{-1} + k_c)$; its solvent dependence is probably small compared with that of k_1, but may well be responsible for variations of the net trans,cis rate ratios (2.4–8.2), which disclose no obvious relation to solvent polarity.

The cycloaddition constants on structural variation of the thioenol ether[3] are compared in Table I with those of corresponding O ethers.[8]

(a) Surprisingly, the k_2 values of S and O ethers are of similar magnitude. The argument that sulfonium zwitterions of type **3** are not as good as oxonium zwitterions is somewhat fallacious, because the ground-state energies likewise influence $\Delta G^{\ddagger}$.

(b) Steric effects of β-alkylation are greater for S than for O ethers. The rate constant of vinyl ethyl *ether* is increased two- to threefold by *trans*- or *cis*-β-methyl, whereas β,β-dimethyl causes a decrease by a factor of 0.7. The same substituents decrease the rate of vinyl ethyl *sulfide* 5-, 19-, and 450-fold. Thus, the acceleration of addition to O ethers due to the electron release by CH$_3$ is superseded in the S ethers by steric hindrance, which is especially evident in the k_2 of *cis*-1-alkenyl ethyl sulfides: vinyl/*cis*-propenyl/*cis*-1-butenyl = 1:0.052:0.0043.

(c) Greater trans,cis rate ratios (3.8–30) of 1-alkenyl sulfides compared with alkenyl ethers (1.1–1.5) are a consequence of this steric effect. The screening of the reacting β-carbon atom may contribute to it as well as steric inhibition of resonance in the sulfonium zwitterion of type **3**.

Table I. Rate Constants for TCNE Cycloadditions to Thioenol Ethers in Ethyl Acetate at 25 °C

RR'C=CHSR"					
R	R'	R"	configuration	10^3k_2, M^{-1} s^{-1}	enol ether, 10^3k_2, M^{-1} s^{-1}
H	H	CH$_3$		24	
H	H	C$_2$H$_5$		63	19
H	H	*n*-C$_4$H$_9$		77	20
H	H	CH(CH$_3$)$_2$		71	112[a]
H	H	C(CH$_3$)$_3$		72	255
H	H	C$_6$H$_5$		0.63	0.0045
CH$_3$	H	CH$_3$	cis	2.74	16
CH$_3$	H	CH$_3$	trans	15	13
CH$_3$	H	C$_2$H$_5$	cis	3.3	40
CH$_3$	H	C$_2$H$_5$	trans	12.6	53
CH$_3$	H	*n*-C$_3$H$_7$	cis	2.7	32
CH$_3$	H	*n*-C$_3$H$_7$	trans	18	48
CH$_3$	H	CH(CH$_3$)$_2$	cis	1.8	
CH$_3$	H	CH(CH$_3$)$_2$	trans	13.4	
C$_2$H$_5$	H	C$_2$H$_5$	cis	0.27	15
C$_2$H$_5$	H	C$_2$H$_5$	trans	8.1	17
CH$_3$	CH$_3$	C$_2$H$_5$		0.14	15

[a] Cyclohexyl vinyl ether.

(d) Branching of the *O*-alkyl increases the k_2 of cycloaddition by increasing electron release; this effect is compensated by the larger steric requirements of *S*-alkyl.

(e) Fueno et al.[1] observed a higher ρ value for the TCNE cycloadditions to aryl vinyl sulfides (−5.5) than for aryl vinyl ethers (−3.1). The a priori expectation of the opposite effect underlines that the diverse substituent effects of OR and SR are not fully understood.

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[5] Increasing concentrations of enol ether (3,4-dihydro-2*H*-pyrane) increased the polarity of dibutyl ether and decreased the polarity of acetonitrile, thereby alluding to a concentration dependence of the rate constants: see R. Huisgen and R. Schug, *J. Chem. Soc., Chem. Commun.*, 59 (1975).

[6] G. Steiner and R. Huisgen, *J. Am. Chem. Soc.*, **95**, 5056 (1973).

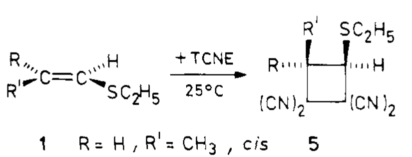
[7] R. Huisgen and H. Graf, *J. Org. Chem.*, following paper in this issue.

[8] R. Huisgen and G. Steiner, *Tetrahedron Lett.*, 3763 (1973).

Stereochemistry of Tetracyanoethylene Cycloadditions to Thioenol Ethers

Summary: In the cyclobutane formation from ethyl *cis*-propenyl sulfide and *cis*-1-butenyl ethyl sulfide with tetracyanoethylene, the nonstereospecific portion of the cycloadduct rises with increasing solvent polarity in accordance with a zwitterionic intermediate, whereas cis → trans isomerization of the excess of thioenol ether signals the reversibility of zwitterion formation.

Sir: Cis and trans isomers of ethyl propenyl sulfide and 1-butenyl ethyl sulfide were separated by preparative VPC; steric purity: **1**, 99.6%; **2**, 99.5%; **3**, 99.2%; **4**, 98.8%. We



1 R = H, R' = CH$_3$, *cis* 5
2 R = H, R' = C$_2$H$_5$, *cis* 6
3 R = CH$_3$, R' = H, *trans* 7
4 R = C$_2$H$_5$, R' = H, *trans* 8

reacted 0.022–0.063 M thioenol ether with 0.025–0.072 M tetracyanoethylene (TCNE), i.e., a ~10% excess of the

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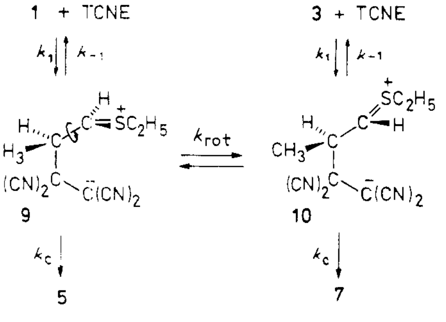
Table I. Nonstereospecific Portion (% in 100 % Adduct) in TCNE Cycloadditions to Thioenol Ethers at 25 °C

	% thioenol ether adducts		% enol ether adducts	
solvent	**7**	**8**	**7**[a]	**8**[a]
(a) Cis Ether **1** or **2**				
benzene	11	12	5	2
ethyl acetate	10	17	6	10
dichloromethane	11	14	5	7
acetone	13	22	8	
acetonitrile	17	27	15	18
	% thioenol ether adducts		% enol ether adducts	
	5	**6**	**5**[a]	**6**[a]
(b) Trans Ether **3** or **4**				
benzene	6	2.9	4	2
ethyl acetate	4	2.8	10	5
dichloromethane	5	4.0	6	3
acetone	6	3.9		
acetonitrile	6	3.6	23	16

[a] Corresponding cycloadducts with OC_2H_5 instead of SC_2H_5 from enol ethers.

latter, until the charge-transfer color disappeared; this required at 25 °C 1 min for **3** in acetonitrile, but 30 days for **2** in benzene due to the high dependence of the rate constant on solvent polarity.[1] The presence of 0.04–0.095 M *p*-benzoquinone suppressed a thermal cis,trans isomerization of the thioenol ethers. The cis,trans ratios of the quantitatively formed cycloadducts were determined by NMR analysis of the 1-H doublets. Reproducibility in duplicate runs was ±1%.

The nonstereospecificity observed is evidence that rotation in the zwitterionic intermediates **9** and **10** competes with their cyclization. The data are compared in Table I with those of TCNE cycloadditions to the corresponding enol ethers.[2] Starting with the *cis*-alkenyl sulfides **1** and **2**, the nonstereospecific portion of the cycloadduct, i.e., the trans adducts **7** and **8**, rose from 11 and 12% in benzene up to 17 and 27% in acetonitrile. The values of percent trans adduct from the cis enol ethers (**1** and **2**, O instead of S) are lower in the nonpolar benzene, but increase faster with rising polarity.[2]



S and O ethers differ more in the *trans*-1-alkenyl series. Whereas **3** and **4**, with O instead of S provide similar nonstereospecific portions (now cis adducts) as the cis enol ethers, the trans thioethers **3** and **4** afforded 4–6% **5** and 3–4% **6**, virtually independent of solvent polarity.

Table II. TCNE and *cis*-1-Propenyl Ethyl Sulfide (1) in Acetonitrile at 25 °C; Cis → Trans Isomerization of Unconsumed 1

		unconsumed sulfide			(2 + 2) cycloadducts
[**1**], mM	[**1**]/[TCNE]	mM calcd	mM found	**1**:**3**	**5**:**7**
719	1.05	33	19	80:20	84:16
608	1.11	60	63	84:16	88:12
723	1.20	118	142	97:3	87:13

The cis,trans isomeric adducts **5**–**8** were configurationally stable even in the most polar solvent, acetonitrile, at 25 °C. However, with 2 M $LiClO_4$ in diethyl ether[3] a cis,trans equilibrium of 7% **6** and 93% **8** was established with $k_{cis} + k_{trans} = 2.9 \times 10^{-4}\ s^{-1}$ at 25 °C. Thus, the larger free-energy difference, $\Delta G = 1.5$ kcal mol^{-1}, vs. $\Delta G = 0.9$ kcal mol^{-1} for the corresponding cycloadducts with C_2H_5O instead C_2H_5S might be responsible for the lower level of percent of **5** and **6** from **3** and **4**.

After reacting 0.608 M *cis*-1-propenyl sulfide **1** (99.6% pure) with 0.548 M TCNE (ratio 1.11:1) in acetonitrile in the presence of 0.06 M benzoquinone, VPC of the excess of thioenol ether indicated 16% **3** besides 84% **1** as a result of cis,trans isomerization. When we ascribe the isomerization to rotation **9** → **10** and subsequent dissociation, **10** → **3**, one must take into account that **3** combines faster than **1** with TCNE.[1]

The still unsatisfactory numerical results of Table II do not warrant the unwieldy calculation of k_c/k_{-1} for the trans zwitterion **10**. This rate ratio is larger here than for the zwitterions **9** and **10**, O instead of S, where it was found to be 1.1 and 0.9, respectively.[4] The premise of double conformational rotation being forbidden[4] leads to $k_c/k_{rot} = 2.7$ for **9** and 27 for **10** in acetonitrile.

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(1) H. Graf and R. Huisgen, *J. Org. Chem.*, preceding paper in this issue.

(2) R. Huisgen and G. Steiner, *J. Am. Chem. Soc.*, **95**, 5054 (1973); R. Huisgen, *Acc. Chem. Res.*, **10**, 117 (1977).

(3) Y. Pocker and D. L. Ellsworth, *J. Am. Chem. Soc.*, **99**, 2284 (1977), and previous papers.

(4) R. Huisgen and G. Steiner, *J. Am. Chem. Soc.*, **95**, 5055 (1973).

Synthetic Studies on Anthracyclines

Summary: Brief, regiospecific syntheses of the functionalized tetracyclic hydronaphthacene analogues **5a**, **5b**, and **5c** of the anthracyclinones of daunomycin, adriamycin, and carminomycin have been accomplished.

Sir: The anthracycline antibiotics adriamycin,[1a] daunomycin,[1b] and carminomycin[2] have attracted much synthetic interest[3] because of their antineoplastic activity. Several

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(1) (a) F. Arcamone, G. Franceschi, P. Orezzi, G. Cassinelli, W. Barbier, and R. Mondelli, *J. Am. Chem. Soc.*, **86**, 5334 (1964); (b) F. Arcamone, G. Franceschi, S. Penco, and A. Selva, *Tetrahedron Lett.*, 1007 (1969).

(2) M. Wani, H. L. Taylor, M. E. Wall, A. T. McPhail, and K. D. Onan, *J. Am. Chem. Soc.*, **97**, 5955 (1975); G. R. Pettit, J. J. Einck, C. L. Herald, R. H. Ode, R. Von Dreele, P. Brown, M. G. Brazhnikova, and G. F. Gause, *ibid.*, **97**, 1387 (1975).

(3) Only the most recent papers are listed here. References 3a and 3b contain extensive current bibliographies. (a) J. R. Wiseman, N. I. French, R. K. Hallmark, and K. G. Chiong, *Tetrahedron Lett.*, 3765 (1978); (b) J. S. Swenton and P. W. Raynolds, *J. Am. Chem. Soc.*, **100**, 6188 (1978); (c) F. A. J. Kerdesky and M. P. Cava, *J. Am. Chem. Soc.*, **100**, 3635 (1978); (d) A. S. Kende, J. Rizzi, and J. Riemer, *Tetrahedron Lett.*, 1201 (1979); (e) K. A. Parker and J. L. Kallmerten, *ibid.*, 1197 (1979).