The kinetics and mechanism of cyclodimerization of alkylthiopropenals

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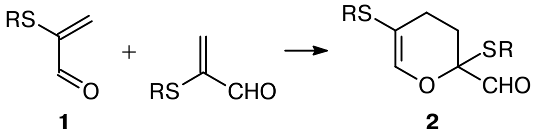
The kinetics of 2-alkylthiopropenals cyclodimerization was studied in the temperature range from −7 to +42 °C in heptane and at 20 °C in various solvents. The rate constants for cyclodimerization of 2-alkylthiopropenals are four orders of magnitude higher than those for dimerization of the oxygen-containing analogs, 2-alkoxypropenals, and are independent of the solvent polarity and substituent steric constant. The activation parameters for 2-butylthiopropenal cyclodimerization were estimated. The distribution of electron density in the 2-methoxy- and 2-methylthiopropenals molecules was calculated by the *ab initio* method. From comparison of the HOMO and LUMO energies for these aldehydes it was concluded that the ratio between the cyclodimerization rates for 2-alkylthio-, 2-ethoxypropenals, and propenal is determined by the HOMO—LUMO gap.

Key words: 2-alkylthiopropenals, Diels—Alder reaction, kinetics, reaction mechanism, 2,5-dialkylthio-3,4-dihydro-2*H*-pyran-2-carbaldehyde, IR spectroscopy, *ab initio* calculations.

Many naturally occurring molecules contain the pyran ring and its hydrogenated forms.[1,2] The Diels—Alder reaction, in which 1-oxa-1,3-butadienes are the diene components, is widely used for the synthesis of these heterocyclic compounds.[1] The interaction between α,β-unsaturated aldehydes or ketones and electron-enriched alkenes such as enol ethers or thioethers is a convenient method for the synthesis of substituted 3,4-dihydro-2*H*-pyrans,[3,4] and some of them are bio-active compounds and medicines.[5—7]

Earlier[8] we have shown that 2-alkylthiopropenals dimerize easily according to the Diels—Alder scheme, transforming into 2,5-dialkylthio-3,4-dihydro-2*H*-pyran-2-carbaldehydes. In our study of the kinetics of cyclodimerization of acrolein and its α-substituted derivatives, we have found that the dimerization of 2-alkylthiopropenals is too fast and inaccessible for kinetic measurements.[9] However, when the retrodiene decay of 2,5-dialkylthio-3,4-dihydro-2*H*-pyran-2-carbaldehydes was used, binary mixtures of a monomer and cyclic dimer containing from 25 to 80% 2-alkylthiopropenal were obtained.[10] The rate constants for cyclodimerization of 2-alkylthiopropenals in $CDCl_3$ have been determined in a ^{1}H NMR study of the composition of these mixtures.[11]

This work continues our studies of the kinetics and mechanism of reaction (1) and also presents the results of quantum-mechanical calculations of the structures of the starting reagents.



(1)

R = Et, Pr, Bu, C_6H_{13}

Results and Discussion

The rate constant of reaction (1) was monitored by IR spectroscopy either by a decrease in the absorbance of the C=O or C=C absorption bands of a monomer or by an increase in the absorbance of these bands in the dimer molecule. The solvents used exclude specific interactions. The frequencies of the absorption bands in the solvents are presented in Table 1. It is seen that the nature of alkyl substituents and solvents have no effect on conjugation in the molecules of the monomer or dimer.

The kinetics of cyclodimerization obeys a second order equation. The rate constant was calculated by the formula

$$k = x/[ta(a - x)],$$

where *a* is the initial molar concentration of monomer **1**, and *x* is the molar concentration of the monomer transformed to dimer **2** at time *t*.

Table 1. Absorption frequencies (ν/cm^{-1}) for monomers **1** and dimers **2** in various solvents

R	Solvent	ν(C=C)		ν(C=O)	
		1	**2**	**1**	**2**
Et	Heptane	1585	1626	1687	1728
Pr	Heptane	1580	1628	1690	1728
Bu	MeCN	1582	1624	1685	1728
	Acetone-d$_6$	1583	1628	1687	1730
	THF	1582	1626	1683	1728
	$CDCl_3$	1584	1626	1685	1730
	Heptane	1584	1628	1687	1732
	Microlayer	1582	1626	1682	1730
C_6H_{13}	Heptane	1580	1626	1692	1725

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Table 2. Rate constants of 2-butylthiopropenal cyclodimerization in various solvents at different temperatures

Solvent	ε (20 °C)	T/°C	$k \cdot 10^4$ /L mol^{-1} s^{-1}
Heptane	1.92	42	3.81±1.2
		32	2.57±1.39
		20	1.21±0.31
		−7	0.21±0.02
THF	7.5	20	0.99±0.81
1,2-Dichloroethane	10.1	20	1.09±1.14
Acetone-d$_6$	20.7	20	0.49±0.15
MeCN	36.0	20	0.35±0.05

The rate constants of cyclodimerization of 2-butylthiopropenals at various temperatures and in different solvents are shown in Table 2.

The temperature dependence of the rate constant for 2-butylthiopropenal cyclodimerization obeys the Arrhenius equation (Fig. 1). On this basis we found the effective activation energy E_a = 39.7±7.5 kJ mol^{-1} and Arrhenius preexponential factor A, log$A$ = 3.2. For cyclodimerization of the oxygen analog of 2-butylthiopropenal (2-ethoxypropenal) E_a = 86.0 kJ mol^{-1} and log$A$ = 7.1 in cyclohexane.[9] Then, the rate constant for cyclodimerization of 2-ethoxypropenal at 20 °C is $6.3 \cdot 10^{-9}$ L mol^{-1} s^{-1}. Thus, 2-alkylthioacroleins cyclodimerize more than four orders of magnitude faster than their oxygen analogs.

The enthalpy of activation $\Delta H^{\neq}$ = 37.2±7.5 kJ mol^{-1} and the entropy of activation $\Delta S^{\neq}$ = −203.9±59.0 J K^{-1} mol^{-1} for 2-butylthiopropenal cyclodimerization at 20 °C were calculated from the values of E_a and log$A$.

The high negative effective entropy of activation found is typical of the reactions of diene synthesis proceeding through a cyclic transition state.[12,13]

To verify the possibility of the participation of free radicals in the reaction, 2-butylthiopropenal cyclodimerization was carried out in the dark in the presence of hydroquinone and in the light in the absense of hydroquinone. In both cases, the reaction rates turned out the same.

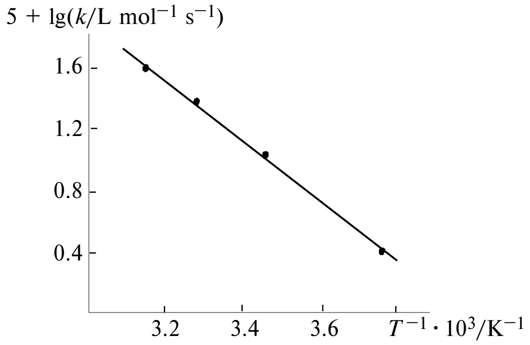

Fig. 1. Temperature dependence of the rate constant of 2-butylthiopropenal cyclodimerization (k) (heptane is the solvent).

It is typical of reactions proceeding through a polar transition state to be accelerated with an increase in the dielectric constant of the medium.[14] Variation in the solvent polarity did not change significantly the cyclodimerization rate for 2-butylthioacrolein (see Table 2). Hence, the transition state of reaction (1) is nonpolar.

Examination of the data of Table 3 on the distribution of the electron density in the aldehydes studied indicates that the highest negative charge occurs, as a rule, at the C$_\beta$ atom of 2-methoxy- and 2-methylthiopropenals in their ground state. The gradient along the C=C bond in the *trans*-form is considerably greater than that in the *cis*-form. The charge on the C$_\beta$ atom in 2-methoxypropenal is nearly two times higher than that in 2-methylthiopropenal.

This does not contradict the ^{1}H and ^{13}C NMR spectral data for 2-ethoxypropenal and 2-butylthiopropenal.[15] The spectra showed that the C$_\beta$ atom in both molecules is more screened than the C$_\alpha$ atom and the β-atom in the oxygen analog is more screened than that in the sulfur analog (see Experimental). It is highly improbable that similarly charged fragments (for example, the C$_\beta$ atoms) of two molecules approached each other in the polar transition state.

It is known[1,13,16] that the reaction rate depends not only on the electron nature of substituents in a diene molecule but also on their effect on the conformational equilibrium, and the reaction rates for open-chain dienes depends on the content of the *cis*-conformer. As the calculation of the overall energy of the conformers of aldehydes showed (see Table 3), the *S-trans*-form is more favorable for the ground states of oxygen- and sulfur-substituted propenals.* The difference between the energies of the *trans*- and *cis*-conformers is 2.5 kcal mol^{-1} (ΔE = 0.00394 Hartree) in the first case (compounds **3a** and **3b**, respectively) and 1.9 kcal mol^{-1} (ΔE = 0.003008 Hartree) in the second case (compounds **4a** and **4b**, respectively). This means that the *trans*-form of the molecules of both oxygen- and sulfur-substituted dienes has to isomerize into the *cis*-form prior to participation in diene synthesis. The barrier for transition from the *S-trans*- to *S-cis*-form was estimated from the potential energy of internal rotation of the aldehyde group about the σ-bond. The energy barrier for this transition is 9.0 kcal mol^{-1} for 2-alkoxypropenal and 7.5 kcal mol^{-1} for its thio-analog. Hence, the relative easiness of the *trans*- to *cis*-isomerization of 2-alkylthio-2-propenals may account for the higher rates of their dimerization as compared to the oxygen analogs.

As is known, bulky substituents in position 3 often favor the formation of the *cis*-like diene conformation and thereby such dienes are more reactive. However, a comparison of the rate constants for cyclodimerization of various 2-alkylthiopropenals shows that the bulk of a

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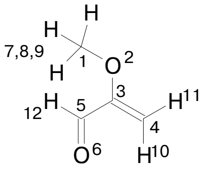
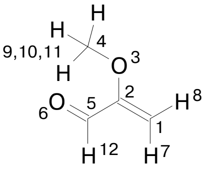
* The orthogonal form of 2-methoxypropenal, in which the MeO group is in the plane of the C=C bond and the carbonyl group comes out of the plane, is less favorable (the overall energy is −306.485469 Hartree) than the *cis*-form (*cf.* Table 3).

Table 3. Energies of molecules and electron density distribution (according to Mulliken) in conformers of 2-methoxy- (**3a,b**), 2-methylthiopropenals (**4a,b**), and propenal (**5a,b**) calculated by the B3LYP/D95++(d,p) method


3a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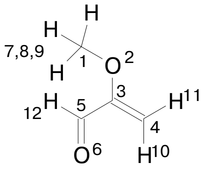
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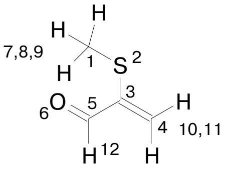
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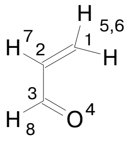
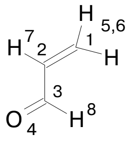

5a


5b

Molecule	E^{1*}	*q*/a.u.							
		C(1)	O(2), C(2), S(2)	C(3), O(3)	C(4), O(4)	C(5), H(5)	O(6), H(6)	H(7) (H(8)) [H(9)]	H(10) (H(11)) [H(12)]
3a	−306.4997769**	−0.433399	−0.328905	0.657223	−0.503881	−0.101188	−0.386915	0.173779 (0.184830) [0.194862]	0.208954 (0.196819) [0.137822]
3b	−306.5037163***	−0.831332	0.755334	−0.337837	−0.399536	0.052586	−0.374084	0.194318 (0.207196) [0.208798]	0.194551 (0.182923) [0.147284]
4a	−629.4618867	−0.573199	−0.292121	0.293971	−0.232724	−0.037616	−0.351819	0.203144 (0.202586) [0.197524]	0.195858 (0.224637) [0.169759]
4b	−629.464895	−0.582509	−0.181778	0.377308	−0.442599	0.036532	−0.364077	0.242825 (0.190417) [0.193234]	0.177478 (0.228783) [0.124385]
5a	−191.95216	−0.456254	0.160073	−0.059190	−0.356560	0.210169	0.183572	0.186281 (0.131907)	—
5b	−191.955390	−0.530280	0.245692	−0.050737	−0.370319	0.185806	0.191272	0.200807 (0.127760)	—

* Total energies in Hartree units.

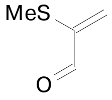
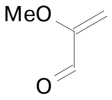
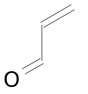
** The energy is presented for a molecule in which the Me group is out of the plane of the double bonds and the O atom of the ether group, and the dihedral angle is 71°.

*** The energy is presented for a molecule in which the Me group is out the plane of the double bonds and the O atom of the ether group, and the dihedral angle is −44.7°.

substituent R does not affect the reaction rate. Average values of the rate constants for dimerization ($k \cdot 10^4$/L mol^{-1} s^{-1}) of α-alkylthioacroleins in heptane at 20 °C and their standard deviations at R = Pr, Bu, and C_6H_{13} are 0.65±0.19, 1.21±0.31, and 0.33±0.049, respectively.

These findings allow us, by analogy with the data[1,3,17,18] on the Diels—Alder reaction, to classify reaction (1) as a pericyclic process, which is controlled by orbital interaction. The stabilization energy for two molecular orbitals of approaching molecules is inversely proportional to the difference in the energies of their levels[1], *i.e.*, the narrower the energy gap, the stronger the interaction[17] and the corresponding contribution to the stabilization of filled orbitals.[19] The HOMO and LUMO mostly contribute to the stabilization energy.[20] The orbital energies of the aldehydes under study were calculated by the B3LYP/D95++(d,p) method[21] (Table 4). As can be seen in Table 4, the substitution of the H atom in position 3 for the O atom and then for the S atom enhances the HOMO energy. A comparison of the energy difference between the HOMO and LUMO for 2-methylthio- and 2-methoxypropenals and unsubstituted propenal shows that the stabilization energy gradually lowers. This likely explains the retardation of aldehyde dimerization in the series of heteroatoms

Table 4. The LUMO and HOMO energies for oxabutadienes (eV) calculated by the B3LYP/D95++(d,p) method

Oxabutadiene	$\Delta E^*_{trans\text{-}trans}$	E_{LUMO}	E_{HOMO}
	0.15160	0.01339 0.00826 −0.00733 −0.01181 −0.08542	−0.23702 −0.27680 −0.31008 −0.34795 −0.38984
	0.178441	0.02157 0.01688 0.00315 −0.00866 −0.08041	−0.25882 −0.27494 −0.33595 −0.36926 −0.40831
	0.18890	0.02076 0.01454 0.00569 −0.00842 −0.08286	−0.27152 −0.30493 −0.40413 −0.40919 −0.43099

Note. $\Delta E^* = E_{\text{LUMO}} - E_{\text{HOMO}}$.

S > O > H. This conclusion is in agreement with the sequence of the experimental rate constants.[9]

Experimental

^{13}C NMR spectra were obtained on a Jeol FX-90 spectrometer (89.95 MHz) in $CDCl_3$ with HMDS internal standard.

A Specord IR-75 spectrometer with a Carl Zeiss Jena temperature cuvette and calibrated thermocouple was used for kinetic measurements. Monomeric 2-alkylthiopropenals prepared by retrodiene synthesis[10] were contaminated by the dimers immediately after distillation. Therefore, the initial concentration of the monomer was determined by ^1H NMR from the ratio of the integral intensities of the singlets from protons in the CHO groups of the monomer and dimer molecules, taking into account the weighted portion of aldehyde and the volume of the solvent. It was found in preliminary experiments that the integral intensities of these signals correlate exactly with those of the protons at the double bond ($H_2C=$ of a monomer and HC= of a dimer) and therefore associates (for example, trimers formed through the carbonyl group of the monomer or dimer) do not form under the experimental conditions. The ^1H NMR spectra were recorded on a Bruker DPX-400 (400 Hz) spectrometer.

Kinetic measurements were performed in a stationary cuvette of the IR spectrometer with the use of as-distilled mixtures of the monomer and dimer of 2-alkylthiopropenal. The kinetic data were calculated from changes in the absorbance of the absorption bands of the C=C or C=O groups of the monomer or dimer. The scale of measurement was 15/100 cm^{-1}, the time of measurement was 11 min, and the resolution in the range of 1550—1700 cm^{-1} was 1 cm^{-1}. The correctness of the analytical procedure is based on the fact that measurements were conducted simultaneously for several absorption bands (ν(C=C), ν(C=O)). The dimerization constant was calculated as an average of 5—9 values obtained for the same absorption band. The second reaction order was observed at an initial concentration of α-alkylthioacroleins from 0.04 to 0.87 mol L^{-1}.

To study the photochemical or radical effects on the cyclodimerization process, the synthesis of 2-formyl-2,5-dibutylthio-3,4-dihydro-2*H*-pyran was carried out according to a procedure described previously[8] in the light without hydroquinone and in the dark in the presence of hydroquinone (0.3 mol.%). In both cases, the same amount of cyclodimer was found by ^1H NMR.

The ^{13}C NMR spectrum of 2-butylthiopropenal (δ): 21.85 (CH_3); 29.34 and 29.79 (CH_2CH_2); 38.51 (SCH_2); 126.10 ($H_2C=$); 147.63 (=CSBu); 190.16 (CH=O).

The ^{13}C NMR spectrum of 2-ethoxypropenal (δ): 13.07 (CH_3); 62.90 (OCH_2); 102.02 ($=CH_2$); 157.82 (=C—O); 187.24 (CHO).

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