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About the conformations of α,β-diunsaturated ketones

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Received July 28, 2003, accepted August 7, 2003

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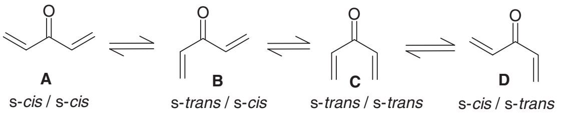
Pharmazie 58: 847–853 (2003)

Substituted 1-(cyclohexenyl)-3-phenylpropen-1-ones, 1-(2-furyl)-3-phenylpropen-1-ones, and 1-(2-thienyl)-3-phenylpropen-1-ones, ketones with 1,4-pentadien-3-one structure, prefer in solution, and at room temperature, according to ^{1}H NMR and IR investigations the s-*trans*/s-*cis* conformation. For some compounds the participation of other conformers in the equilibrium could be demonstrated. These results were obtained by a qualitative study of 25 derivatives in different solvents, and comparison with results from MM+, PM3, AM1 or MMX calculations.

1. Introduction

Rotation around a single bond of two parts of one molecule results in a continuos change of the torsion angle, whereby each torsion angle represents a conformation with a defined energy. The energy curve usually shows a global minimum (lowest energy) and some other minima (local minima), representing defined conformations. For understanding the interactions between two molecules, e.g. drug and receptor, the knowledge of possible conformations and their energy is especially important [1]. The structure of numerous drugs contains α,β-unsaturated carbonyl systems. We report here about our studies with a set of α,β-diunsaturated ketones as model compounds, for which we tried to find the local minima and the favored conformation(s) in solution, to study the influence of substituents, and to find minor conformations by spectroscopic methods, and finally to compare the results with those from calculations.

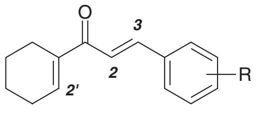
In solution, at least 4 conformers **A**–**D** of the α,β-diunsaturated carbonyl system, type 1,4-pentadien-3-one, may exist in an equilibrium with possibly one preferred form. This equilibrium should be influenced by the substitution pattern at the double bond, by the solvent, and by the temperature. Until today only few knowledge exists concerning such diunsaturated systems [2–5].



2. Invertigatiens and results

Structures, containing one double bond as part of a cyclohexene (**1**), furan (**2**), thiophene (**3**) or a 3-halogeno substituted thiophene ring (**4**), and whose second double bond with (*E*)-configuration was substituted by a substituted phenyl ring [6–8] (Table 1) were chosen as model compounds.

Table 1: Model compounds



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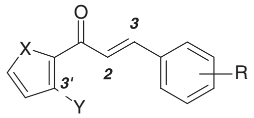


2, 3, 4

Compd.	R	X	Y
1a	H	–	–
1b	4-CH_3	–	–
1c	4-$N(CH_3)_2$	–	–
1d	4-Cl	–	–
1e	4-NO_2	–	–
1f	2-Br	–	–
2a	H	O	H
2b	4-Cl	O	H
2c	4-CH_3O	O	H
2d	4-$N(CH_3)_2$	O	H
2e	4-NO_2	O	H
3a	H	S	H
3b	4-Cl	S	H
3c	4-CH_3O	S	H
3d	4-$N(CH_3)_2$	S	H
3e	4-NO_2	S	H
4a	H	S	Br
4b	4-Cl	S	Br
4c	4-CH_3O	S	Br
4d	4-$N(CH_3)_2$	S	Br
4e	4-NO_2	S	Br
4f	H	S	Cl
4g	4-Cl	S	Cl
4h	4-CH_3O	S	Cl
4i	4-NO_2	S	Cl

Table 2: Shift values δ (ppm) of 2′-H and 3-H in ^{1}H NMR spectra (200 MHz) of 1

Compd.	$\delta_{2'}$ CDCl$_3$	$\delta_{2'}$ C$_6$D$_6$	$\Delta\delta_L$(2′-H)	δ_3 CDCl$_3$	δ_3 C$_6$D$_6$	$\Delta\delta_L$(3-H)
1a	7.02	6.29	0.73	7.62	7.66	−0.04
1b	7.01	6.30	0.71	7.61	7.64	−0.03
1c	6.95	6.39	0.56	7.61	7.82	−0.21
1d	7.03	6.55	0.48	7.57	7.67	−0.10
1e	7.08	6.53	0.55	7.62	7.53	+0.09
1f	7.03	6.51	0.52	7.93	8.31	−0.38

2.1. ^{1}H NMR spectroscopy, ASIS effect

Aromatic solvents like benzene form collision complexes with dissolved polar molecules preferring overall a defined orientation. This can be detected by ^{1}H NMR spectroscopy. Recording the spectra in CDCl$_3$ and benzene a specific signal shift $\Delta\delta_L = \delta_{CDCl_3} - \delta_{C_6D_6}$ is observed called ASIS effect (Aromatic Solvent Induced Shift). Conolly and McCrindle [9] have demonstrated that in α,β-unsaturated ketones protons situated at the same site of the double bond as the oxygen atom of the carbonyl group (s-*cis*) are less influenced by the complexation with benzene and therefore, usually show a very small negative $\Delta\delta_L$ value, while protons situated at the opposite site (s-*trans*) usually are strongly influenced by the complexation with benzene resulting in a positive $\Delta\delta_L$ value. Similar shift values were found not only for flexible open chain systems but even for fixed systems (rings) as described by Timmons [10]. We used this method to get information about the favored conformation of the α,β-diunsaturated systems **1**–**4**, representing a combination of an open chain flexible part with a rigid ring system. Table 2 summarizes the δ values of the protons at positions 2′ and 3 and the $\Delta\delta_L$ values of the compounds **1**, and the analogue values of compounds **2**, **3**, and **4** are collected in Table 3.

All compounds **1** show positive values for $\Delta\delta_L$(2′-H). We can deduce that the favored orientation of the ring double bond and the carbonyl group is the s-*trans* conformation. The same situation is found for compounds **2** and **3** with positive $\Delta\delta_L$(3′-H) values. Analogue values for compounds **4** were not obtained, as the position 3′ is occupied by a halogen atom. But we assume that the interaction between the big halogen atom and the carbonyl oxygen in a s-*cis* conformation favors the s-*trans* conformation in the equilibrium, which is supported by calculations (see 2.4.).

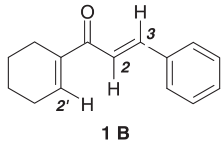
Table 3: Shift values δ (ppm) of 3′-H and 3-H in ^{1}H NMR spectra (200 MHz) of 2–4

Compd.	$\delta_{3'}$ CDCl$_3$	$\delta_{3'}$ C$_6$D$_6$	$\Delta\delta_L$(3′-H)	δ_3 CDCl$_3$	δ_3 C$_6$D$_6$	$\Delta\delta_L$(3-H)
2a	7.34	6.91	0.43	7.88	8.02	−0.14
2b	7.34	7.04	0.30	7.82	7.79	+0.03
2c	7.32	6.94	0.38	7.86	8.09	−0.23
2d	7.28	6.95	0.33	7.86	8.27	−0.41
3a	7.69	6.97	0.70	7.86	7.95	−0.09
3b	7.69	6.92	0.79	7.80	7.70	+0.10
3c	7.66	7.43	0.28	7.83	8.02	−0.19
3d	7.62	6.92	0.70	7.83	8.22	−0.39
3e	7.75	6.92	0.83	7.86	7.59	+0.27
4a				7.84	7.91	−0.07
4b				7.82	7.70	+0.12
4c				7.81	7.97	−0.16
4d				7.82	8.15	−0.33
4f				7.86	7.94	−0.08
4g				7.81	7.72	+0.09
4h				7.83	8.02	−0.19
4i				7.80	7.70	+0.10

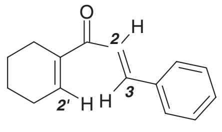
The situation of the $\Delta\delta_L$(3-H) values is more complex. Most compounds exhibit clearly negative values suggesting that the favored conformation of the flexible open chain part prefers the s-*cis* conformation. Compounds **1e**, **3e**, **4i** (R = 4-NO$_2$,) and **2b**, **3b**, **4b**, **4g** (R = 4-Cl) show positive $\Delta\delta_L$ values. Values of compounds **2e** and **4e** were not available as they were not soluble. The positive values are clearly connected with the electron drawing substituents Cl and nitro at the para position of the phenyl ring. This can be interpreted as an effect in the s-*cis* conformation or as a hint that in these compounds the s-*trans*/s-*trans* conformation (**C**) or another one is partially involved in the equilibrium. All other compounds prefer deduced from the ASIS experiments the s-*trans*/s-*cis* conformation (**B**).

2.2. ^{1}H NMR Spectroscopy, nuclear Overhauser effect

Significant qualitative nuclear Overhauser effects (NOE) are observed, if the distance between two hydrogen atoms is smaller than 3 Å [11]. MMX calculations [12] show for all compounds **1** the following distances: Form **B** (s-*trans*/s-*cis*) 2′-H to 2-H d ≈ 2.46 Å, 2′-H to 3-H d ≈ 3.9 Å, out-of-plane rotation of C-2′ ≈ 18°, and for form **C** (s-*trans*/s-*trans*) 2′-H to 3-H d ≈ 2.7–2.9 Å, 2′-H to 2-H d ≈ 3.4–3.9 Å, out-of-plane rotation of C-2′ ≈ 70–80°. Forms **A** and **D** have much larger distances (4–5 Å), and therefore have not to be discussed. The results of the NO experiments with compounds **1** are summarized in Table 4.



1 B



1 C

All compounds **1** show an analoguous behavior with a significant NO effect (++) between 2′-H and 2-H resp. *vice versa* in chloroform except **1e** (R = NO$_2$) with a different behavior by exhibiting an additional NO effect in d$_6$-benzene between 2′-H and 3-H. These results are in

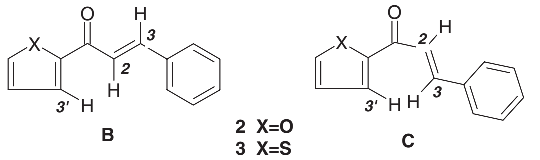
Table 4: NO experiments with 1 (200 MHz, CDCl$_3$, TMS, 288 scans)*

Compd.	Proton	Radiation ↓ δ (ppm)	2′-H	2-H	3-H
1a	2′-H	7,02		++	
	2-H	7,30	++		
	3-H	7,62			
1b	2′-H	7,01		++	
	2-H	7,23	++		
	3-H	7,61			
1c	2′-H	6.95 (6.39)		++	
	2-H	7.10 (6.96)	++		
	3-H	7,61 (7.82)			
1d	2′-H	7.03		++	
	2-H	7.27	++		
	3-H	7.57			
1e	2′-H	7,08 (6.53)		++	(++)
	2-H	7,59 (6.93)	++ (−−)		
	3-H	7,62 (7.53)	(++)		
1f	2′-H	7,03		++	
	2-H	7,19	++		
	3-H	7,93			

* Values in brackets report experiments in d$_6$-benzene

agreement with the ASIS experiments a further indicator for the dominance of conformation **B** (s-*trans*/s-*cis*), and as in the ASIS experiments, for **1e** this might be interpreted as a hint at a larger amount of a second conformer (**C**) in the equilibrium.

Calculations (MMX) of the conformers of compounds **2a** and **3a** give for form **B** a distance between 3′-H and 2-H d ≈ 2.1 Å (**2**) and d ≈ 2.5 Å (**3**) with an out-of-plane rotation of the heterocycle of 0° (furan) and ca. 15° (thiophene), and for the planar form **C** between 3′-H and 3-H d ≈ 0.6–0.8 Å, while form **C** with a out-of-plane rotation of the heterocycle of 41° (furan) and ca. 47° (thiophene) showing a distance between 3-H and 3′-H d ≈ 2.78 Å (furan) and 2.89 Å (thiophene).



B

2 X=O
3 X=S

C

All other distances, and the distances in forms **A** and **D** are much larger (≈ 4–6 Å). Therefore, one should expect NO effects only when a significant amount of form **B** and/or form **C** exists in the equilibrium. The results are collected in Table 5.

Most compounds **2** and **3** behave similar exhibiting a clear NO effect between 3′-H and 2-H without any difference observable between the hetero atom in the ring moiety and, thereby indicating the preference of conformer **B** (s-*trans*/s-*cis*) in the equilibrium. On the other hand, compounds **2b**, **3b** (R = 4-Cl) and **3e** (R = 4-NO_2) do not show a NO effect between 3′-H and 2-H but between 3′-H and 3-H. Even in this serie electron withdrawing substituted compounds behave different. NO experiments with compounds **4** were not done, as position 3′ is occupied by a halogen atom.

Table 5: NO experiments with 2 and 3 (200 MHz, $CDCl_3$, TMS, 288 scans)

Compd.	Proton	Radiation ↓ δ (ppm)	3′-H	2-H	3-H
2a	3′-H	7,33		++	
	2-H	7,46	++		
	3-H	7,88			
2b	3′-H	7.34			++
	2-H	7.42			
	3-H	7.82	++		
2c	3′-H	7,32		++	
	2-H	7,34	++		
	3-H	7,86			
2d	3′-H	7,28		++	
	2-H	7,25	++		
	3-H	7,86			
3a	3′-H	7,69		++	
	2-H	7,29	++		
	3-H	7,86			
3b	3′-H	7.69			++
	2-H	7.39			
	3-H	7.80	++		
3c	3′-H	7,66		++	
	2-H	7,30	++		
	3-H	7,83			
3d	3′-H	7,62		++	
	2-H	7,23	++		
	3-H	7,83			
3e	3′-H	7.70			++
	2-H	7.57			
	3-H	7.86	++		

2.3. *IR Spectroscopy*

ASIS and NO experiments allow suggestions about conformers being dominant in an conformation equilibrium, but usually they cannot give details about conformers participating in low concentrations in the equilibrium. IR spectroscopy on the other hand is a relatively fast and sensitive method enabling the detection even of minor amounts of a conformer, if an unequivocal identification of the bands is possible. Differentiation of bands is usually difficult in KBr-spectra, but very often it is possible when the spectra are recorded in different (nonpolar) solvents.

We have chosen the carbonyl valence bands of compounds **1**–**4**, as these bands were the strongest in the spectra and thereby good detectable. Without detailed considering possible conformers, the carbonyl absorption in spectra of α,β-diunsaturated ketones is reported in the range from 1650 to 1680 cm^{-1}, and for α,β-unsaturated ketones the carbonyl absorption of the s-*trans* form is described at 1660–1690 cm^{-1}, while the absorption of the s-*cis* form is recorded at 1685–1700 cm^{-1} [13]. These values were obtained from fixed structures [14, 15] depending on the substituents. We have found in KBr spectra absorptions of $\nu \approx 1650–1665\ cm^{-1}$ for fixed s-*trans*/s-*trans* 1,4-diarylsubstituted systems [16, 17], and at $\nu \approx 1670\ cm^{-1}$ for analogue s-*cis*/s-*cis* fixed systems [18]. The carbonyl absorption of s-*trans*/s-*trans* fixed testolactone is reported at $\nu = 1650\ cm^{-1}$ [19], and the absorption of the s-*trans*/s-*cis* fixed systems piperitenone and isogermacrone are reported at $\nu = 1665\ cm^{-1}$ [20]. Finally, the IR spectrum (KBr) of the fixed s-*cis*/s-*cis* 2,6-dibenzylidenecyclohexanone shows $\nu = 1667\ cm^{-1}$ including conjugation effects of the aromatics. From these reported results one can deduce for the interpretation of spectra with more than one carbonyl band the following sequence for the wave numbers of the carbonyl absorptions: s-*trans*/s-*trans* (**C**) < s-*cis*/s-*trans* (**D**) or s-*trans*/s-*cis* (**B**) < s-*cis*/s-*cis* (**A**).

For identifying the single C=O bands of the conformers we have studied their hypsochrome shifts and their intensities changing from polar to nonpolar solvents based on the fact that the equilibrium of conformers depends on the polarity of the solvent. Therefore we have recorded IR spectra for each compound in different solvents and in KBr. Table 6 shows the results for compounds **1a** and **1e**.

The IR spectra of **1a** (**1e**) in KBr are characterized only by one intensive band ν_1 at 1650 (1652) cm^{-1}. This band is found in the spectra in polar acetonitrile at 1653 (1656) cm^{-1}, and in spectra in cyclohexane (lowest polarity) at 1662 (1665) cm^{-1}. In solution spectra, a second, less intensive, carbonyl band ν_2 is recorded at higher wave numbers, sometimes as weak shoulder, sometimes as weak band. Using the deconvolution program of FTIR 1650 this band became clearly resolved (Fig. 1, Table 6). As ν_1, the wave numbers of the second band ν_2 are depending on the polarity of the solvent. In acetonitrile, they are registered at 1672 (1673) cm^{-1}, and in the nonpolar cyclohexane, the bands were found at 1678 cm^{-1}. Interestingly, the spectra of **1a** in paraffin fit into the sequence, while the spectra of **1e** in paraffin are comparable to those in KBr. Prob-

Table 6: IR Data of 1a/1e (cm^{-1})

Solvent	ν_1 C=O	ν_2 C=O	
		I	II
Acetonitrile	1653/1656	1672/1673 S	1672/1673 S
Dichloromethane	1653/1656	1672/1674 S	1671/1674 S
Dichloroethane	1653/1657	1672/1673 S	1673/1673 S
Chloroform	1652/1655	–/1672 S	–/1672 S
Diethyl ether	1655/1663	1673/1674 S	1673/1674 S
CS_2	1656/1661	1673/1677 S	1673/1677 B
Benzene	1657/1660	1673/1677 S	1673/1677 B
Toluene	1657/1660	1675/1676 S	1674/1677 B
CCl_4	1658/1662	1674/1674 S	1674/1674 B
Cyclohexane	1662/1665	1678/1678 S	1678/1678 B
Paraffin	1661/1652	1677/1663 S	1677/1663 B
KBr	1650/1652	–	–

S = shoulder, B = band, I = before, II = after deconvolution

ably **1e** is not soluble in paraffin. Finally, all spectra of **1e** show higher wave numbers compared to the spectra of **1a**.

From the above data we conclude that each band is caused by one conformer. The distance between the two bands varies between 13 and 20 cm^{-1}. These small values do not allow any quantitative evaluation, and, furthermore, a band resolved by deconvolution is not allowed to be treated quantitatively. The data of the other compounds **1** in Table 7 show an analoguous behavior except **1c** (R = 4-$N(CH_3)_2$) with significantly lower wave numbers. It has to be noticed that electron withdrawing substituents (**1d**, **1e**) do not show significant shifts.

Correlating the more intensive C=C bands between 1592 and 1610 cm^{-1} with the more intensive C=O bands ν_1 we calculated the ratio $I_{C=O}/I_{C=C}$ [21, 22], being in agreement with the correlation of the more intensive bands to the s-*trans*/s-*cis* form (**B**). Therefore, the minor intensive bands should be caused by another conformer, probably by the s-*cis*/s-*cis* form (**A**). A quantitative result was not deducible as all minor intensive bands were obtained by deconvolution.

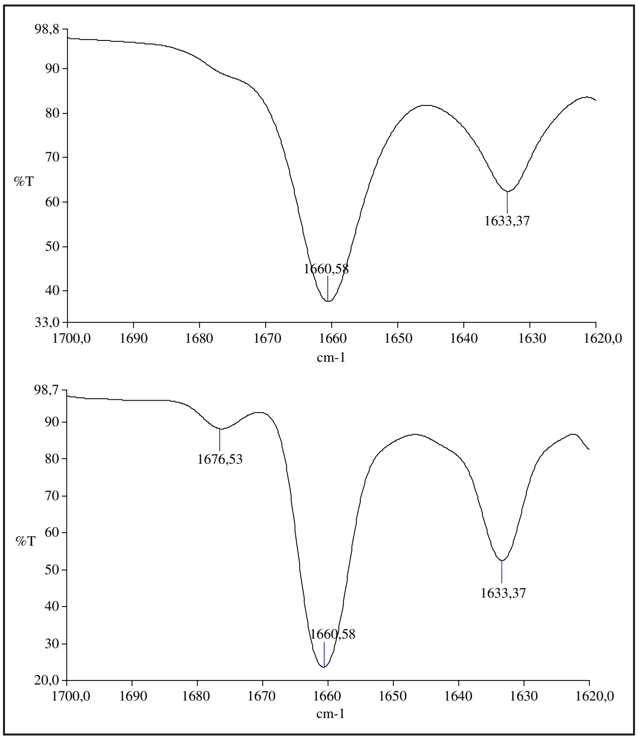


Fig. 1: Deconvolution of the ν C=O shoulder **1e**, IR in CS_2

Table 7: IR Data (carbonyl absorptions) of compounds 1 (cm^{-1})

Compd.	ν_1				ν_2		
	KBr	$CHCl_3$	C_6H_6	Other sol.*	$CHCl_3$	C_6H_6	Other sol.*
1a	1650	1652	1657	1652–1662	1676	1676	1672–1679
1b	1651	1653	1656	1651–1661	–	1678	1670–1677
1c	1643	1645	1650	1645–1653	1655	1669	1655–1669
1d	1652	1652	1658	1653–1663	–	1676	1673–1679
1e	1652	1655	1660	1655–1665	1672	1677	1668–1678
1f	1651	1653	1658	1653–1662	–	1675	1674–1682

* Other solvents: Range of wave numbers found in spectra in: Acetonitrile, dichloroethane, dichloromethane, diethyl ether, CCl_4, toluene, cyclohexane, CS_2, paraffin, ν_1 = strongest band, ν_2 = minor band or shoulder

The analogue data for compounds **2**–**4** are presented in Table 8. As for **1**, we used the deconvolution method for the exact finding of the minor intensive C=O bands ν_2.

The IR spectra of all compounds **2**, **3**, and **4** show ν_1 being the most intensive C=O band. It is found for compounds **2a**–**2c** between 1657 (polar solvent) and 1668 (nonpolar solvent) cm^{-1}, in the spectra of compounds **3a**–**3c**, **3e**, and **4a** between 1649 (polar solvent) and 1659 (nonpolar solvent) cm^{-1}, and for the other compounds **4**, except for **4d**, between 1641 (polar solvent) and 1652 (nonpolar solvent) cm^{-1}. An effect of the p-phenyl substituent is observed in the spectra of **2d**, **3d**, and **4d** (R = 4-$N(CH_3)_2$) with significant lower wave numbers of ν_1. The intensive band ν_1 is always accompanied, resolved by deconvolution, by a minor band or shoulder ν_2. Concerning the wave numbers, we can identify two groups of compounds. The first group, all compounds **2**, all compounds **3**, **4a**, and **4c** show in all solvents in contrast to compounds **1** significantly lower wave numbers for ν_2 than for ν_1. The other compounds **4** show under same conditions a higher wave number for ν_2 than for ν_1. Furthermore, the spectra of **2a**, **2b**, and **2c** exhibit a third C=O band. The C=C in-plane vibrations of 2-monosubstituted thiophenes and furans

Table 8: IR Data (carbonyl absorptions) of compounds 2–4 (cm^{-1})

Compd.	ν_1				ν_2		
	KBr	$CHCl_3$	C_6H_6	Other sol.*	$CHCl_3$	C_6H_6	Other sol.*
2a	1656	1659	1665	1661–1668	1636	1635	1631–1645
					1629	1646	1635–1647
2b	1658	1659	1664	1661–1668	1634	1636	1634–1638
						1650	1642–1653
2c	1657	1656	1661	1657–1665	1633	1633	1633–1639
						1642	1640–1647
2d	1643	1648	1655	1650–1659	–	1650	1645–1653
3a	1652	1652	1656	1653–1661	1630	1634	1630–1640
3b	1648	1651	1656	1653–1659	1630	1637	1628–1640
3c	1647	1649	1653	1650–1656	1626	1629	1625–1637
3d	1634	1641	1647	1642–1649	–	1639	1633–1643
3e	1651	1655	**	1656–1657	1636	**	1636–1649
4a	1649	1649	1654	1650–1659	1636	1635	1632–1640
4b	1642	1644	1647	1644–1651	1661	1665	1661–1668
4c	1644	1645	1650	1646–1652	–	1632	1630–1636
4d	1637	1638	1644	1638–1646	–	1630	1625–1629
4f	1642	1646	1648	1646–1651	1658	1663	1659–1666
4g	1644	1645	1651	1646–1651	1654	1668	1655–1668
4h	1640	1641	1645	1643–1647	1657	1660	1656–1666
4i	1644	1647	1651	1648–1652	1663	1667	1664–1668

* Other solvents: Range of wave numbers found in spectra in: Acetonitrile, dichloroethane, dichloromethane, diethyl ether, CCl_4, toluene, cyclohexane, CS_2, paraffin.
** Not soluble
ν_1 = strongest band, ν_2 = minor band or shoulder

Table 9: Calculated torsion angles of compounds 1

	MM+		AM1 – vacuo		AM1 – H_2O		AM1 – $CHCl_3$	
Torsion angle								
Compd.	Θ_1 [°]	Θ_2 [°]	Θ_1 [°]	Θ_2 [°]	Θ_1 [°]	Θ_2 [°]	Θ_1 [°]	Θ_2 [°]
1a	190	0	216,9	7,7	206,7	17,3	193,7	5,0
1b	190	0	217,8	6,9	212,1	14,4	190,7	4,7
1c	190	0	219,1	6,3	192,5	24,5	197,3	11,1
1d	190	0	217,0	7,7	206,2	8,4	191,6	4,1
1e	190	0	216,0	11,0	184,6	28,6	191,9	3,7
1f	190	0	212,2	18,1	191,8	68,4	188,6	357,2

were found at 1515–1535 cm^{-1}, 1430–1455 cm^{-1}, and 1345–1360 cm^{-1} resp. 1560–1610 cm^{-1}, 1470–1520 cm^{-1}, and 1390–1400 cm^{-1}, and the stretching bands of asymmetric substituted C=C bonds absorbed ~ 1600 cm^{-1}, and thereby do not influence the recording of C=O bands, but as one C=C band of the pentadienone system is part of a heteroaromatic ring, it is not possible to calculate the ratio $I_{C=O}/I_{C=C}$ [21, 22], and therefore, we could not use this method for the elucidation of the conformer equilibrium.

2.4. Calculations

All semi-empirical calculations were done using the appropriate tools (MM+, AM1, PM3) of Hyperchem 4.0 or 5.0 [4, 8, 23]. We have calculated the C=O and C=C bands for all 4 conformers of **1**, **2**, **3**, and **4**. As PM3 calculations were done *in vacuo*, all calculated wave numbers differ from the experimental values by the same amount (ca. 200 cm^{-1}). For compounds **1a**, **1b**, **1c**, and **1e** we found conformer **B** showing the lowest, and conformer **D** having the highest wave number, while for **1d** and **1f** the low wave numbers of **A** and **B** were similar, and the highest number was obtained for **D**.

Furthermore, we calculated the rotation barriers (kcal/mol) for rotation around the bond C-1–C-1′ (Θ_1) and around the bond C-1–C-2 (Θ_2) for all conformers of **1**. Maxima were found between 15.8 and 17.8 kcal/mol. The highest energy of Θ_1 was calculated for **1b** (17.0 kcal/mol), the lowest for **1f** (16.5 kcal/mol). For Θ_2 the highest energy, 17.8 kcal/mol was calculated for **1f**, while the lowest value, 15.8 kcal/mol, was found for compound **1c**. Although the differences are small, one might be tempted to interpretate those as substitution effects.

From energy diagrams and relative population diagrams it was possible to calculate the relative (*in vacuo*) population of the single conformers for each compound **1**. AM1 calculations were done for all conformations of all **1** *in vacuo*, in water and in chloroform, and the results are given in Table 9, which summarizes the torsion angles Θ_1 and Θ_2 with the lowest energy.

While the MM+ method gives insufficient results, and thereby does not seem to be an appropriate method, AM1 calculation show differences for the different substituted compounds **1**. From these values, finally, the relative amount of each conformer in vacuo was calculated, and the results are shown in Table 10.

Table 10: Calculated relative population of the conformers of 1

	A s-*cis*/s-*cis*	**B** s-*trans*/s-*cis*	**C** s-*trans*/s-*trans*	**D** s-*cis*/s-*trans*
1a	39%	61%	0%	0%
1b	37%	63%	0%	0%
1c	23%	77%	0%	0%
1d	38%	62%	0%	0%
1e	38%	62%	0%	0%
1f	35%	65%	0%	0%

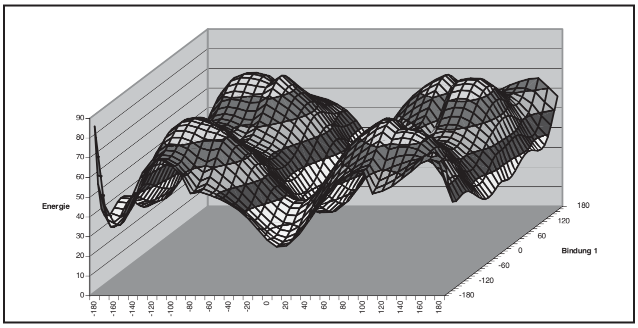


Fig. 2: Calculated energy surface of compound **2a**

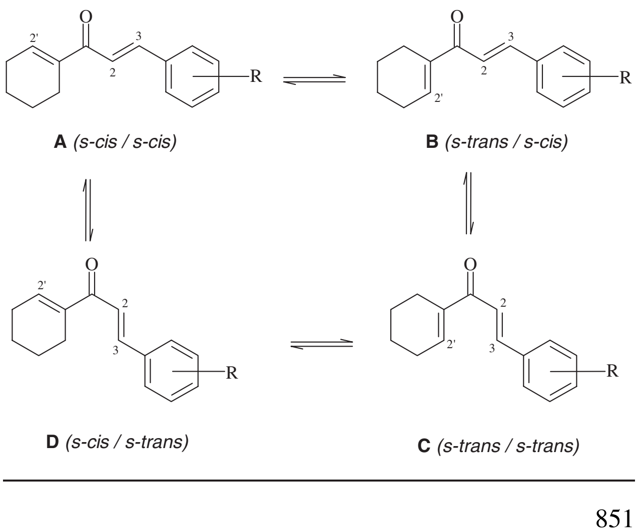
Analoguous calculations were done for all the other compounds. Without giving details [23] we summarize the results here. The lowest wave numbers for ν_1 of compounds **2a**, **2b**, **3a**, and **3b** was calculated for conformer **C**, the highest for conformer **B**, while the sequence for **2d**, and **3d** was **D** < **A** < **B** < **C**, for **4a**, **4b** it was **C** < **B** < **D** < **A**, for **4d** **A** < **D** < **B** < **C**, for **4f**, **4g**, **4i** **C** < **D** < **B** < **A**, and for **4i** calculated in chloroform **A** < **B** < **D** < **C**. All compounds **2** showed a rotation energy for Θ_1 ~ 17 kcal/mol and for Θ_2 of ~ 37 kcal/mol, while the thio compounds **3** had slightly lower values 14.4 and 35.3 kcal/mol. Completely different was the behavior of compounds **4**. For Θ_1 two maxima were found, one with ~ 11–18 kcal/mol, and a second one with >60 kcal/mol (X = S, Y = Br), while the maximum for Θ_2 was with 35–36 kcal/mol in the same range as for **2** and **3** [12].

Furthermore, the energy surfaces of all compounds **2**, **3** and **4** were calculated showing *in vacuo* a global minimum at 0°/0° ± 10° representing the s-*cis*/s-*cis* conformation (**A**), with local minima around 180°/0° (**B**) and −180°/0° (**D**), while around 180°/180° (**C**) a local maximum was found. As an example, Fig. 2 shows the energy diagram of **2a**.

3. Discussion

Substituted 1-(cyclohex-1-en-1-yl)-3-phenylpropenones **1** exist as an equilibrium between at least four conformers (Scheme 1).

Scheme 1



In the ^{1}H NMR spectra, a positive solvent shift $\Delta\delta_L$ for 2′-H in the range between 0.48 and 0.73 ppm (ASIS, Table 2) was found for all studied derivatives of **1**. A $\Delta\delta_L$ shift for 3-H with negative values between −0.03 and −0.38 ppm was recorded for all derivatives except for **1e** ($R = 4\text{-}NO_2$) showing $\Delta\delta_L = +0.09$ ppm. These data suggest that the derivatives of **1** mainly exist in an equilibrium with the s-*trans*/s-*cis* form **B** as the dominant conformer. If the deviation of **1e** is caused by an electronic effect of the substituent in form **B**, or if another conformer is responsible, cannot be decided from ASIS experiments. NO experiments (Table 4) showed short distances between 2′-H and 2-H for compounds **1a**–**1d**, and **1f**, while for **1e** an additional interaction between 2′-H and 3-H was recorded. After geometry optimization the calculated distances between 2′-H and 2-H in form **B** were around 2.5 Å, and for form **C** the distance from 2′-H to 2-H was 3.4 Å, while for 2′-H to 3-H a distance of 2.9 Å was calculated. This might suggest that in the equilibrium of **1e** a visible (dominant ?) amount of conformer **C** (s-*trans*/s-*trans*) is present.

The IR spectra (Tables 6, 7) of all the compounds **1** showed in KBr a strong C=O band at $\nu = 1650\ cm^{-1}$ shifted to $1643\ cm^{-1}$ in the spectrum of **1c** ($R = 4\text{-}N(CH_3)_2$). Spectra in solution exhibited solvent dependent shifts and a less intensive shoulder which could be resolved by deconvolution (Fig. 1) to an absorption band between 1670 and $1680\ cm^{-1}$. Compounds **1** exist in all solvents as an equilibrium of conformers with form **B** as the dominant form and form **A** as the minor conformer. This could not be demonstrated for **1a**, **1d** and **1f** in chloroform, for **1d** and **1f** in dichloromethane and dichloroethane, and for **1d** in acetonitrile.

Although the ^{1}H NMR experiments with the p-nitro substituted **1e** suggested conformer **C** forming a representative amount in the equilibrium the IR data plead for conformer **B**.

Calculations of the carbonyl absorption in IR spectra suggested that in compounds **1a**, **1b**, **1c**, and **1e** the strongest band with the lowest wave number is caused by form **B**. The second band with lower intensity and higher wave number may be caused by form **A**, **C** or **D**. The calculated results for **1d** and **1f** were similar, but showed a slightly higher amount of conformer **A**.

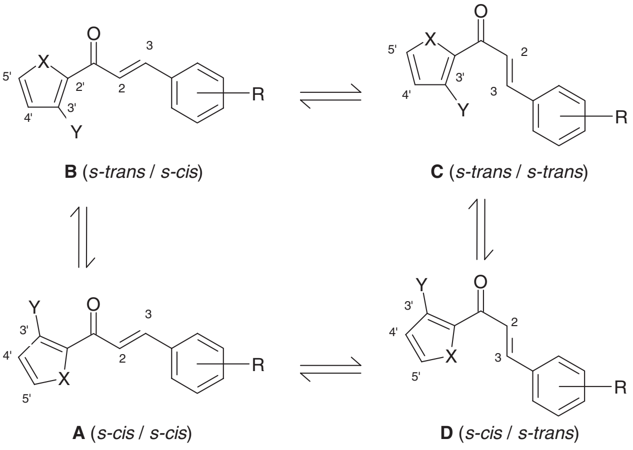
Finally, calculation of the relative population of the conformers in the equilibrium at room temperature (Table 10) showed the dominance of conformer **B** and the presence of smaller amounts of conformer **A**.

The 1-(2-furyl) and 1-(2-thienyl) derivatives of 3-(substituted phenyl)propen-1-ones **2** and **3** may exist in a similar equilibrium as compounds **1** (Scheme 2).

The ASIS effects of the furyl and thienyl derivatives of **2** and **3** are similar to those found at compounds **1** (Table 3). The $\Delta\delta_L$ values for 3′-H were positive in the range of 0.28 to 0.70 ppm, and served as an indicator for the s-*trans* conformation of the left part of the molecules. All $\Delta\delta_L$ values for 3-H were negative (range −0.09 to −0.41 ppm) leading to the conclusion, that even for **2** and **3**, **B** is the favored conformer. This is supported by the NO effects (Table 5), as all derivatives **2** and **3** showed a significant effect for protons 3′-H and 2-H. Calculation of the distances yielded values around 2.5 Å, while the distance 3′-H to 3-H was around 4.0 Å. For conformer **C** (thienyl derivatives) a distance of ~3.0 Å was calculated, but no NO effect was found.

The IR data of **2** and **3** were similary congruent, but **2d**, **3d** and **4d** showed like **1c** a strong shift ($11/10\ cm^{-1}$ in $CHCl_3/C_6H_6$) of the ν_1 C=O band caused by the influence of the substituent p-dimethylamino group. All spectra in KBr showed one intensive C=O band, which was slightly shifted to higher wave numbers when the spectra were recorded as solution spectra. Additional shoulders or bands pointed to the existence of more than one conformer.

Scheme 2



2 X=O Y=H **3** X=S Y=H **4** X=O, S Y=Br, Cl

Intensive bands in the range of $1641–1668\ cm^{-1}$ support the results of ASIS and NO experiments conformer **B** being the preferred conformer. One or two bands/shoulders at $1626–1653\ cm^{-1}$, showing solvent dependent shifts could be interpreted as hints for conformers **D** and **C**. These bands were not found in KBr spectra, and in some cases in the spectra in halogenated solvents. The C=C in-plane vibrations of 2-monosubstituted thiophenes and furans, and the stretching bands of asymmetric substituted C=C bonds do not influence the recording of C=O bands [13]. Calculations of the energy of rotation around Θ_1 and Θ_2 showed for Θ_2 significant higher barriers than for compounds **1** caused probably by the repulsion of two aromatic ring systems during rotation. The lowest energy was found when the complete system was nearly planar supporting the favored conformer **B** in the equilibrium.

Compounds **4** with a halogen substituent at position 3′ of the furan or thiophene moiety exhibited in the ^{1}H NMR spectra a negative ASIS only for 3-H (Table 3), and did not show any NO effects. Furthermore, the high rotation barrier from conformer **B** to conformer **A** excluded conformers **A** and **D**. In addition, MMX calculations [12] suggested that the most favored form is conformer **B**, but with an angle of ~30° between the plane of the heteroaromatic and the other part of the molecule. This form shows the lowest repulsion (longest distance) between carbonyl oxygen and halogen with $\Delta_{Br-O} \sim 4.5$ Å and $\Delta_{S-O} \sim 3.1$ Å for **4a**, while for conformer **A** the analogue calculation yielded $\Delta_{Br-O} \sim 2.9$ Å and $\Delta_{S-O} \sim 3.9$ Å.

The IR spectra in KBr and in solutions showed intensive ν_1 C=O bands, comparable to those of **2** and **3** (Table 8). In the solution spectra of **4a**, **4b** (Fig. 3), and **4g**, the second carbonyl band (ν_2) was better differentiated from ν_1 and more intensive than in the spectra of all other compounds. In addition, this ν_2 is significantly solvent dependent, indicating that this band represents a second conformer with a larger amount in the equilibrium. Considering the above discussion of the results of calculations this conformer should be form **C**. For **4b** we have demonstrated the temperature dependence of the equilibrium in paraffin [8].

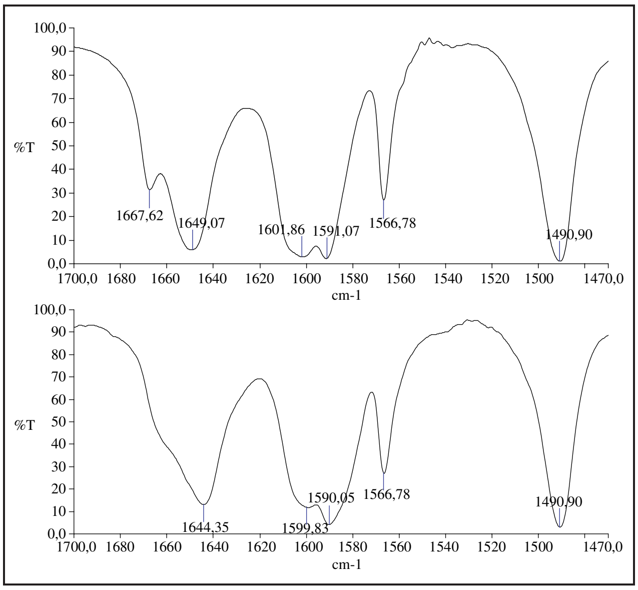


Fig. 3: IR spectra of **4b** in solvents of different polarity, above CCl_4, down $CHCl_3$

We can deduce from the reported ^1H NMR and IR spectroscopic experiments that in the conformation equilibria of the studied compounds **1**–**4** at room temperature in most cases the s-*trans*/s-*cis* conformer **B** is the dominant form. Minor amounts of other conformers are found in many examples and vary within the types. A correlation between the substituents at the phenyl ring and the favored conformation was not found although some substituents showed significant effects in the ^1H NMR and IR spectra. The influence of the solvent on the equilibrium was insignificant for most compounds. MMX calculations suggest that most derivatives of **1**, **2** and **3** are nearly planar, while in the 3-halogen substituted derivatives **4** the heteroaromatic ring seems to be rotated out of plane to reduce the repulsion between the carbonyl oxygen and the halogen. Even this is in agreement with the spectroscopic data, and with the proof of a second conformer.

4. Experimental

^1H NMR spectra: Bruker DPX 200 (200 MHz), inner standard tetramethylsilane (TMS), $\delta_{TMS} = 0.00$ ppm. ASIS experiments in $CDCl_3$ and C_6D_6. NO difference spectra in $CDCl_3$ with TMS, 288 scans.

IR spectra Perkin-Elmer FTIR 1650 in 0.61, 0.25, or 0.1 mm NaCl cuvettes, resolution 2 and 4 cm^{-1}. Spectra in KBr: 300 mg KBr (Uvasol®, Merck) and 0,8–1 mg of the substance. Spectra in solution: 30 mg of the substance was dissolved in 2 ml of the solvent, spectra recorded in NaCl cuvettes as difference spectra with the solvent. Deconvolution software FTIR 1650.

Solvents: Benzene-d_6 (Merck, Darmstadt); $CDCl_3$ (Cambridge Isotope Laboratories CIL, USA); Acetonitrile (Petrolchemisches Kombinat PCK, Schwedt); Benzene, Chloroform, Cyclohexane, Dioxane, Paraffin, Carbondisulfide, Carbontetrachloride, Toluene (each p.a. from Merck, Darmstadt); Diethyl ether, Dichloroethane, Methanol (each p.a. from Riedel-de Haen, Seelze) .

Substances were prepared according literature procedures [2, 3, 4].

Acknowledgement: We thank the Fonds der Chemischen Industrie, Frankfurt/M., for generous financial support, furthermore we are obliged to Prof. Dr. H. Vahrenkamp, Institute of Inorganic and Analytical Chemistry, University of Freiburg i. Br., and to Dr. M. Kindermann, Institute of Chemistry, University of Greifswald, for some special NMR experiments, and F.A.A. thanks the DAAD, Bonn, for a PhD study grant.

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