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ARTICLE *in* JOURNAL OF MOLECULAR STRUCTURE · JANUARY 1994

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Hydrogen-bonded complexes of α , β -unsaturated carboxylic esters with phenols: a molecular mechanics study

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(Received 27 May 1993)

Abstract

The hydrogen-bonded complexes between phenol derivatives and methyl acrylate, methyl *trans*-crotonate and methyl *trans*-cinnamate were studied using the interactive molecular modelling program PCMODEL which uses the features of Allinger's MMX force field, including pi-valence electron self-consistent field (Pi-VESCF) calculations. The results successfully reproduce experimental ΔH values associated with the formation of the hydrogen-bonded complexes and account for the experimentally observed dependences of ΔH on the electron releasing/withdrawing abilities of the substituents in the phenol aromatic ring or in the ester. In addition, the conformational change in the ester moiety of the hydrogen-bonded complexes gives rise to energetically similar hydrogen bonds, in agreement with previous infrared spectroscopic results. In general, the results obtained confirm or expand the previous spectroscopic or quantum mechanical results of M. Dulce G. Faria et al. (J. Mol. Struct., 263 (1991) 87; Vib. Spectrosc., 2 (1991) 43, 107), and lead to the possibility of successfully applying the MMX/Pi-VESCF method to the study of hydrogen-bonded complexes involving other biochemically important molecules.

Introduction

α , β -Unsaturated carboxylic esters have been used as model compounds of substrates in enzyme–substrate complexes formed within the enzyme active site during the catalytic action of serine proteases (e.g. chymotrypsin) [1–4]. In particular, it has been shown [3,4] that the reaction intermediates which are covalently bonded to the enzyme exist as two different species associated with distinct carbonyl environments: in one, the carbonyl group remains in an almost hydrophobic environment; in the other, an active form of the intermediate is hydrogen bonded in the active site, the hydrogen bond

being a decisive factor in the catalytic deacylation process as it stabilizes the C–O[−] bond of the tetrahedral intermediate formed by deacylation.

In order to understand this process in detail, the hydrogen bond between an α , β -unsaturated carboxylic ester (methyl acrylate (MA), methyl *trans*-crotonate (MCro) and methyl *trans*-cinnamate (MCin)) and a proton donor molecule (phenol (Ph), 4-methylphenol (MPh) and 3,5-dichlorophenol (2CPh)) was studied by infrared spectroscopy [5], the enthalpies (ΔH) of complex formation in CCl₄ dilute solutions being evaluated from formation constants at four different temperatures. The ΔH values were shown to correlate with the electron releasing/withdrawing abilities of the substituents in both the phenol ring and the ester [5]. In

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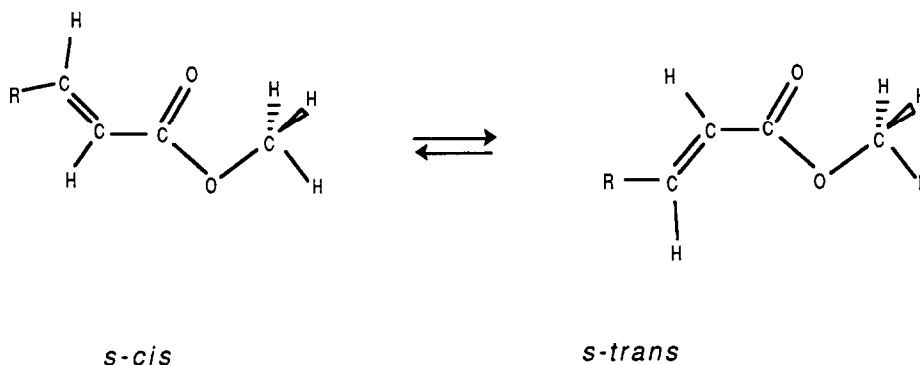


Fig. 1. *s*-Cis and *s*-trans conformers of an α,β -unsaturated carboxylic ester. In the studied compounds, R = H, CH₃ or C₆H₅.

addition, the changes of the stretching carbonyl frequencies of the two stable forms of the ester (*s*-cis and *s*-trans, Fig. 1) associated with the hydrogen bond were found to be of similar magnitude, in consonance with similar ΔH values for the two complexes of the ester conformers [5].

The main objectives of the present study are: (i) to estimate the effect on ΔH of changing the conformation of the ester molecule within each complex; (ii) to obtain information on the structures of the hydrogen-bonded complexes; (iii) to assess the relative importance of the geometrical changes of the ester molecules in the complexes, as their conformation changes from *s*-cis to *s*-trans. If attained, these objectives enable us to gain further insight into the importance of the hydrogen bond in the above-mentioned catalytic deacylation processes.

Owing to the large dimension of the systems of the present study — complexes of MA, MCro and MCin with Ph, MPh and 2CPh — a suitable method of calculation had to be found, enabling us to deal with complexes as large as MCin...2CPh. The MMX/Pi-VESCF method was adopted, but not before its suitability was judged appropriate by comparison of the geometrical variations caused by the *s*-cis \rightarrow *s*-trans transition in the smaller ester molecules (MA and MCro), with the results obtained at the *ab initio* 4-31G level for the same molecules.

Computational methods

The MMX/Pi-VESCF calculations were carried

out using the PCMODEL-PI program (version 3.0) [6], running on a UNISYS 386 computer with 640 K RAM memory. The force field used in this program is derived from Allinger's MM2 force field [7], with the Pi-VESCF routines taken from MMP1 developed by Allinger and Sprague [8]. The PCMODEL-PI built-in potential energy parameters as well as the standard geometry optimization routines were used in all the calculations for the monomeric and dimeric structures. In particular, dipole/dipole interaction terms and the default parameters for the hydrogen bond were adopted.

Results and discussion

Structures and energies of the ester conformers: an assessment of the MMX/Pi-VESCF results

The molecular geometries and relative energies of the three studied esters, in the *s*-cis and *s*-trans forms, as calculated by the MMX/Pi-VESCF method, are presented in Tables 1 and 2. Table 1 also presents previously calculated *ab initio* 4-31G molecular geometries for MA and MCro, for comparison [9,10]. The equilibrium geometries of the two forms of MCin are now described for the first time. Owing to the large dimension of this molecule, an *ab initio* calculation could not be performed in this case.

While the comparison between the *ab initio* 4-31G results and the MMX/Pi-VESCF values for MA and MCro is not a theoretically sound

Table 1

Calculated molecular geometries for methyl acrylate (MA), methyl *trans*-crotonate (MCro) and methyl *trans*-cinnamate (MCin)^a

Coordinate	MA (R = H)		MCro (R = CH ₃)		MCin (R = C ₆ H ₅) ^b	
	s-cis	s-trans	s-cis	s-trans	s-cis	s-trans
	4-31G [9]	MMX/Pi-VESCF	4-31G [9]	MMX/Pi-VESCF	4-31G [10]	MMX/Pi-VESCF
C=O	121.2	122.1	121.1	122.1	121.2	122.2
C–O	134.2	135.1	134.3	135.1	134.6	135.1
O–C	144.3	141.4	144.4	141.4	144.3	141.4
C _α –C	146.8	147.1	146.7	147.4	146.2	147.4
C=C	131.8	135.2	131.8	135.0	132.2	135.4
C–H ₍₁₎	106.9	110.3	107.0	110.3	107.1	110.2
C–H ₍₂₎	107.2	110.2	107.0	110.2	107.3	110.2
OC–H _(1p)	107.4	111.4	107.4	111.4	107.4	111.4
OC–H _(2o.p.)	107.7	111.4	107.7	111.4	107.7	111.4
O=C–O	122.3	120.6	122.1	120.6	122.8	120.4
C–C=O	125.8	121.2	123.8	119.0	124.0	118.8
C–C–O	111.9	118.2	114.1	120.4	113.2	120.8
C=C–C	121.1	123.2	123.9	122.9	124.0	123.0
C–O–C	119.7	123.8	119.6	123.8	119.5	123.8
H ₍₁₎ –C–C	116.0	117.7	113.8	118.0	113.9	116.0
H ₍₂₎ –C=C	121.1	121.9	121.6	121.9	118.7	117.6
H _(1p) –C–O	105.2	108.2	105.2	108.2	105.2	108.2
H _(2o.p.) –C–O	110.1	108.9	110.1	108.9	110.1	108.9
H _(2o.p.) –C–O–C	60.4	60.8	60.4	60.8	60.4	60.8
<i>R group</i>						
C _β –H	107.1	110.2	107.1	110.2		
C _β –C					149.4	147.4
C–H _(1p)			108.1	111.4	108.1	111.4
C–H _(2o.p.)			108.5	111.4	108.5	111.4
H–C=C	121.6	120.1	121.2	120.1		
C–C=C					124.6	125.8
H _(1p) –C–C			124.9	122.0	124.6	122.0
H _(2o.p.) –C–C			111.8	112.8	111.9	112.8
H _(2o.p.) –C–C=C			110.6	109.9	110.6	109.9
H _(2o.p.) –C–C=C			120.9	120.4	120.8	120.4

^a Bond lengths in pm; angles in deg.^b Mean values for the ring coordinates are: C–C, 140.3 pm; C–H, 110.3 pm; C–C–C, 120.2°.

Table 2

Experimental and calculated relative energies (kJ mol^{-1}) of the s-trans and s-cis conformers of methyl acrylate (MA), *trans*-crotonate (MCro) and *trans*-cinnamate (MCin)

Molecule	$\Delta E(\text{s-trans}) - (\text{s-cis})$		
	MMX/Pi-VESCF	Ab initio (4-31G)	Exp. (IR; CCl_4)
MA	0.63	2.38 [9] 2.40 [9] ^a	1.90 ± 0.20 [9]
MCro	2.01	2.99 [10]	2.65 ± 0.27 [10]
MCin	-0.04	—	3.43 ± 0.84 [13]

^a Calculated with a 4-31G* basis set.

comparison as two quite different molecular models are perceived by these methods, a comparison of variations in the geometrical parameters yielded by the two calculations is admissible as both methods are internally consistent. With this perspective, it should be pointed out that the variations due to the conformational changes s-cis \rightarrow s-trans as given by the ab initio calculation are generally well reproduced by the MMX/Pi-VESCF method. In particular, variations in important geometrical coordinates, like C=C, C-C=O, C-C-O, C-O-C and H-C-O (methyl, in-plane), are satisfactorily reproduced by both methods, thus supporting the use of the MMX/Pi-VESCF results for the assessment of the conformationally induced changes in the hydrogen-bonded complexes.

Notwithstanding the above general conclusion, an analysis and discussion of the systematic differences found in the absolute values of various geometrical parameters is now considered, as they may provide guidance for the reliability of the MMX/Pi-VESCF structures. First of all, some of these differences may result from the use of experimental data (e.g. X-ray results) in the force field parameterization [6]. In particular, for C-H bond lengths, the X-ray derived values are usually appreciably different from the C-H equilibrium bond lengths, mainly because of the vibrational contributions which are necessarily present in the experimentally derived values.

The most relevant differences between the MMX/Pi-VESCF structures and the reference

ab initio values occur for the O-C and C=C bond lengths and for the C-C_{sp}²-O, C-O-C and H-C-O (methyl, in-plane) bond angles. In particular, the C=C double bond appears to be systematically longer, consistent with an overestimation of the canonical form III (Fig. 2) and, consequently, with a relative stabilization of the s-trans form [9,10]. This explanation is supported by the fact that the MMX/Pi-VESCF calculations tend to reduce the $\Delta E_{(\text{s-trans}) - (\text{s-cis})}$ energy differences.

When compared with the 4-31G ab initio values, the MMX/Pi-VESCF O-C(H₃) bond lengths are systematically shorter. However, when d orbitals are added to non-hydrogen atoms and p orbitals to hydrogen atoms — the 4-31G* basis set — both methods yield the same bond length (141.4 pm, [9]), which, if not accidental, should result from a reasonable parameterization of the molecular mechanics method.

All the above-mentioned bond angles are overestimated by the MMX/Pi-VESCF calculations, suggesting an overestimation of the repulsive interactions between the vinyl and methyl groups and the

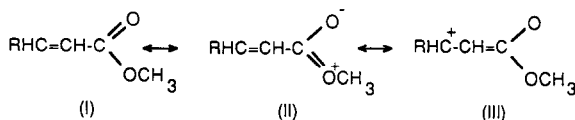


Fig. 2. Relevant canonical forms of an α,β -unsaturated carboxylic ester (I), showing the mesomerisms within the carboxylic group (II) and involving the two double bonds (III).

Table 3

Experimental and calculated enthalpies (kJ mol^{-1}) of formation of the hydrogen-bonded complexes between methyl acrylate(MA), *trans*-crotonate (MCro) and *trans*-cinnamate (MCin), and 4-methylphenol (MPh), phenol (Ph) and 3,5-dichlorophenol (2CPh)

Molecule	$-\Delta H$			
	MPh	Ph	2CPh	
MA	s-cis	12.67	15.48	17.28
	s-trans	11.79	14.94	17.49
	Exp. [5]	10.79	13.39	14.18
MCin	s-cis	15.35	15.98	18.41
	s-trans	14.06	14.35	17.20
	Exp. [5]	12.80	13.10	14.60
MCro	s-cis	15.98	16.48	18.28
	s-trans	16.23	16.44	19.41
	Exp. [5]	12.89	13.81	15.61

oxygen atoms. This comes as no surprise, as the repulsive components of non-bonding interactions involving hydrogen atoms are much too large in the MMX method [11,12].

Hydrogen-bonded complexes

Table 3 shows the $-\Delta H$ values obtained with the MMX/Pi-VESCF method for the studied hydrogen-bonded complexes (a higher $-\Delta H$ value implies a more stable hydrogen-bonded complex). While the calculated values generally overestimate the experimental results by about 25%, the variations associated with changing the phenol or the ester molecules are satisfactorily reproduced by the MMX/Pi-VESCF calculations (see Fig. 3). In addition, slightly lower $-\Delta H$ values are generally obtained for the complexes of s-trans ester molecules, in consonance with the variations obtained for the ab initio charges of the carbonyl oxygen atom,

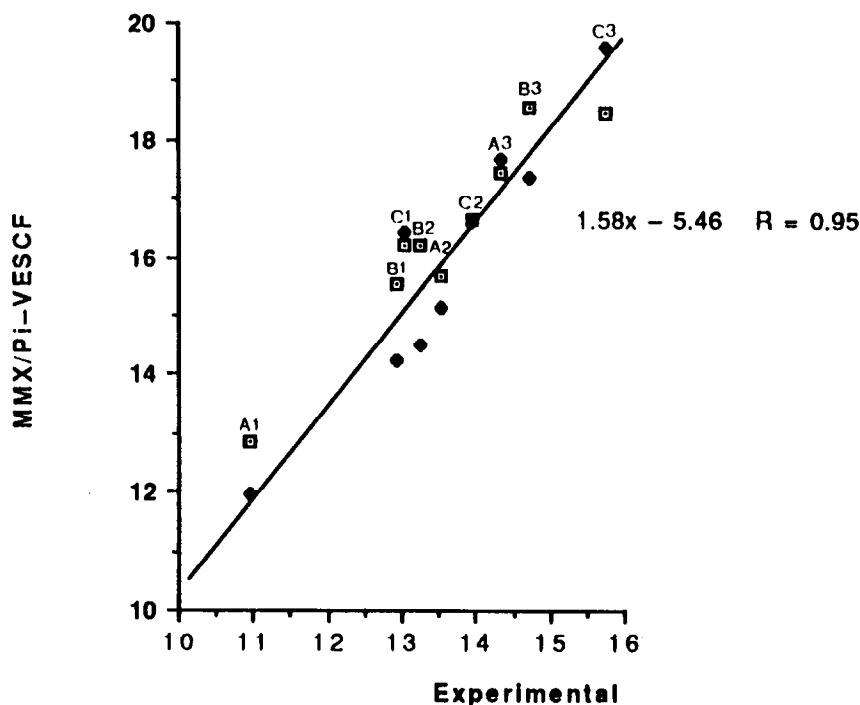


Fig. 3. $-\Delta H$ values (kJ mol^{-1}) — MMX/Pi-VESCF vs. experimental (IR, CCl_4 solution [5]) — associated with the formation of hydrogen-bonded complexes between α, β -unsaturated carboxylic esters and substituted phenols: ◆, complexes where the ester adopts the s-trans conformation; □, complexes where the ester adopts the s-cis conformation; ■, superposition of □ and ◆; A = MA; B = MCin; C = MCro; 1 = MPh; 2 = Ph; 3 = 2CPh.

during an s-trans \rightarrow s-cis transition (MA: $-0.010e$; MCro: $-0.014e$; [13]). In fact, a higher negative charge on the carbonyl oxygen atom correlates with a larger proton acceptor ability and, therefore, with a stronger hydrogen bond.

Looking now at the relative values of $-\Delta H$ for the complexes of a given ester (Table 3), the MMX/Pi-VESCF method reproduces the experimentally observed trend according to which the larger the electron withdrawing power of a phenol substituent, the stronger the hydrogen bond [5]. In fact, $-\Delta H$ values follow the sequence 2CPh > Ph > MPh, in consonance with the relative pK_a values of the various phenol compounds (2CPh = 8.18; Ph = 10.00; MPh = 10.27 [14]). In contrast, for a given phenol, the strength of the hydrogen bond increases with the electron releasing ability of the ester substituent (Table 3).

The MMX/Pi-VESCF calculations yield similar geometries for all the studied hydrogen-bonded complexes (Fig. 4 and Table 4). The phenol ring

occupies a position near the C=C double bond of the ester molecule, but twisted in such a way that the repulsive interactions between the $H'_{(1)}$ atom of the phenol and the $H_{(1)}$ or $H_{(2)}$ atom of the ester (respectively in the s-trans or s-cis forms) are minimized. The $H' \cdots H$ interaction is stronger when the ester adopts the s-cis conformation, as the $H' \cdots H$ distance is then considerably shorter. This fact is also reflected in the calculated values of some relevant angles, which can be correlated with the extension of the twisting in the various studied complexes. For instance, the O=C=O \cdots H' dihedral angle is systematically smaller for the complexes of the s-cis ester molecules, while both the $C_\alpha \cdots O = \cdots O'$ and the $C_\alpha \cdots O = \cdots O' \cdots C'_{(2)}$ angles are larger for these systems (Table 4). Generally speaking, these structural parameters are very similar for the complexes of MA and MCro, while slightly different values are found for the complexes of MCin. At least in part, these differences can be due to the presence of

Table 4

Structural parameters of the hydrogen-bonded complexes between methyl acrylate (MA), *trans*-crotonate (MCro) and *trans*-cinnamate (MCin), and 4-methylphenol (MPh), phenol (Ph) and 3,5-dichlorophenol (2CPh)^a

System	τ_1 O=C=O \cdots H'	τ_2 C $_\alpha \cdots$ O= \cdots O' \cdots C' $_{(2)}$	τ_3 C=C \cdots C' $_{(2)} \cdots$ C' $_{(5)}$	α C $_\alpha \cdots$ O= \cdots O'	O \cdots H'
MA(s-cis) \cdots MPh	158.4	72.0	76.0	114.5	187
MA(s-trans) \cdots MPh	157.2	67.9	5.1	112.3	187
MA(s-cis) \cdots Ph	160.6	72.9	77.0	114.9	185
MA(s-trans) \cdots Ph	166.0	67.7	17.3	104.0	186
MA(s-cis) \cdots 2CPh	165.5	72.7	79.7	114.8	184
MA(s-trans) \cdots 2CPh	168.6	68.7	17.1	103.9	184
MCro(s-cis) \cdots MPh	158.3	72.0	79.4	113.9	185
MCro(s-trans) \cdots MPh	174.6	72.8	26.9	96.2	185
MCro(s-cis) \cdots Ph	159.5	72.9	79.3	114.1	184
MCro(s-trans) \cdots Ph	170.2	66.3	20.7	101.8	184
MCro(s-cis) \cdots 2CPh	159.1	71.9	79.2	114.2	184
MCro(s-trans) \cdots 2CPh	171.2	66.1	20.1	102.5	184
MCin(s-cis) \cdots MPh	153.2	69.7	73.2	119.4	185
MCin(s-trans) \cdots MPh	164.2	71.5	17.8	108.6	186
MCin(s-cis) \cdots Ph	153.3	70.3	74.1	118.3	185
MCin(s-trans) \cdots Ph	162.5	72.4	12.6	114.1	186
MCin(s-cis) \cdots 2CPh	155.5	70.8	73.6	119.4	184
MCin(s-trans) \cdots 2CPh	164.8	72.2	11.9	114.8	184

^a Angles ($\tau_1, \tau_2, \tau_3, \alpha$) in deg; bond distances (O \cdots H') in pm.

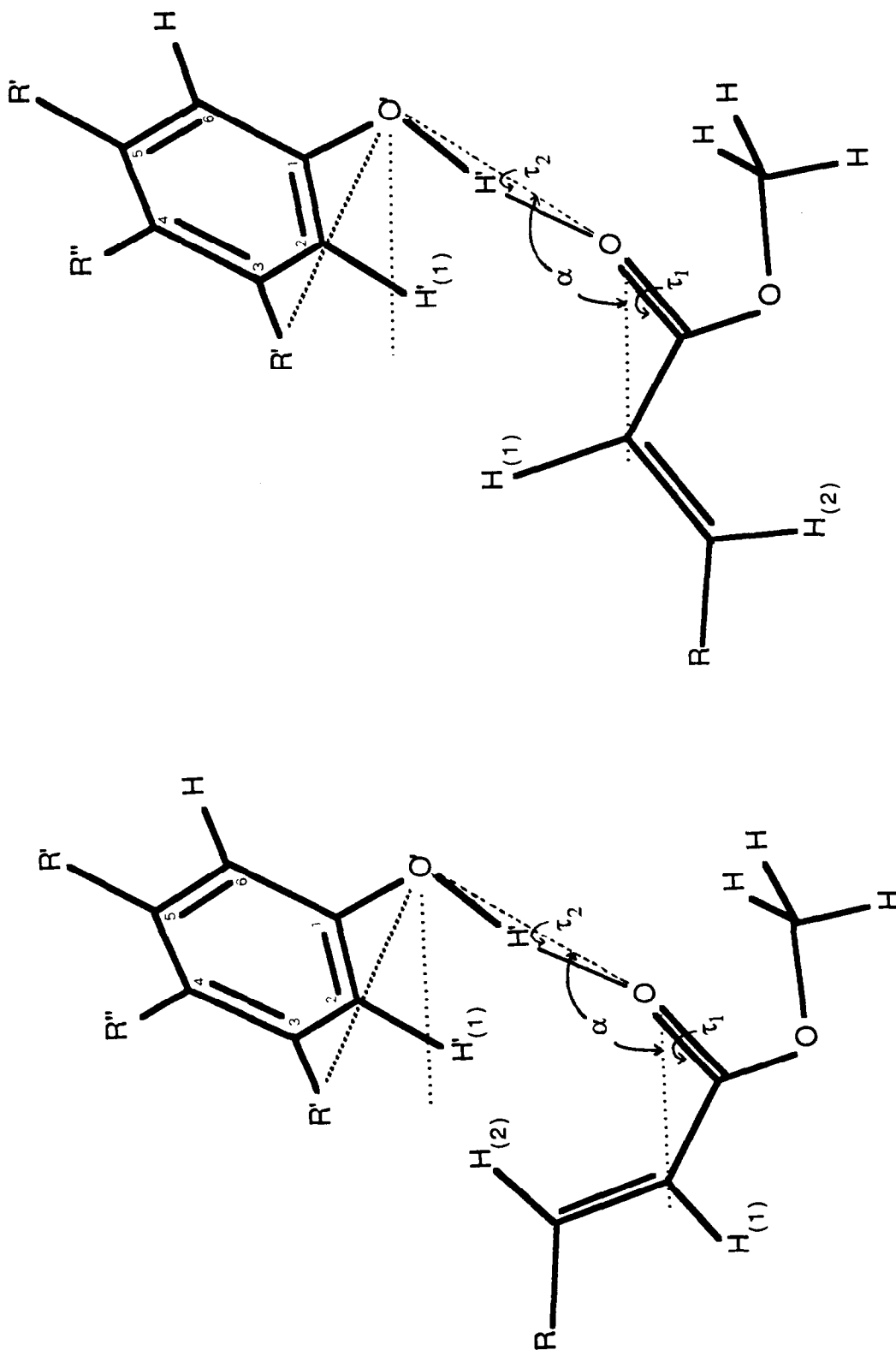


Fig. 4. Schematic representation of the geometry of hydrogen-bonded complexes between the α,β -unsaturated carboxylic esters and phenols. The values of the indicated angles ($\alpha = C_{\alpha} \cdots O = \cdots H'$; $\tau_1 = O-C=O \cdots H'$; $\tau_2 = C_{\alpha} \cdots O = \cdots O'-C'_{(2)}$) for the studied systems are presented in Table 4. $R = H, CH_3$ or C_6H_5 ; $R' = H$ or Cl ; $R'' = H$ or CH_3 .

additional repulsive $H' \cdots H$ interactions involving the phenyl ring of the ester molecule (in particular, those between the ortho-H atoms of the phenyl ring of the ester and $H'_{(1)}$), as the observed changes tend to increase the distance between the two aromatic rings.

The $O = \cdots H'$ distances are predicted to be very similar, ranging from 184 pm in 2CPh hydrogen-bonded complexes to about 187 pm in the weakest $MA \cdots MPh$ complex (Table 4). While the expected correlation between $O = \cdots H'$ distances and the relative strength of the hydrogen bond is reasonably predicted by the calculations, this may be accidental, as the accuracy of molecular mechanics to predict small changes in bond lengths is not remarkable.

Conclusion

It was shown that the MMX/Pi-VESCF method is a convenient method for studying hydrogen-bonded complexes involving carbonyl/hydroxyl interactions. The method yields ΔH values in reasonable agreement with experiment and accounts for conformational and substituent changes in either the proton donor or in the acceptor molecules. The results now obtained confirm or expand previous spectroscopic or quantum mechanical results [5,9,10], and lead to the possibility of successfully applying the MMX/Pi-VESCF method to the study of hydrogen-bonded complexes involving other biochemically important molecules.

Acknowledgements

The Brazilian group thanks the CNPq, PADCT and FINEP for financial help to the Laboratório de Química Computacional e Arquitetura Molecular

of the UFPe. J.J.C.T.D. and R.F. acknowledge financial support from NATO (RG No. 890743) and Junta Nacional de Investigação Científica e Tecnológica (JNICT), Portugal.

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