Ab initio and Density Functional Calculations on the Ring-Chain Tautomerism of γ-Oxocarboxylic Acids

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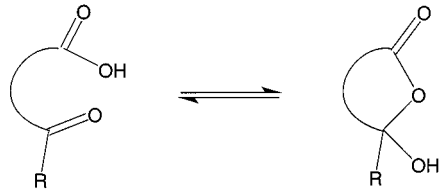
The results of ab initio (HF, MP2) and density functional (B3LYP) calculations on a series of γ-oxocarboxylic acids [(Z)-3-acetyl or benzoylacrylic and 2-acetyl or benzoylbenzoic acids] **A** and their cyclic tautomers **B** are presented. For the open-chain tautomers, different rotamers were considered. Bulk solvent effects were considered by using the polarised continuum model (PCM) and were found to be essential for a proper description of the ring-chain tautomeric equilibrium. Acetyl derivatives generally prefer the cyclic form, whereas for benzoyl derivatives the preference depends on the nature of the link. Introduction of substituents (methyl, phenyl) at C2 and/or C3 for acrylic acid derivatives substantially shifts the equilibrium towards the cyclic form **B**.

Introduction

The phenomenon of ring-chain tautomerism plays an important role in many aspects of chemistry,[1] for example, stability, ring transformation and ease of formation of heterocyclic compounds, intramolecular catalysis by neighbouring-group participation,[2] as well as model reactions for enzymatic transformations.[3] Such tautomerism has been shown to occur in a number of oxocarboxylic acids[1] giving rise to both chain (**A**) and ring (**B**) forms (Scheme 1) with an equilibrium constant K_{eq} defined by $K_{eq} = a_{ring}/a_{chain}$.



A **B**

Scheme 1. Ring-chain tautomeric equilibrium of γ-oxocarboxylic acids

Quantitative determination of K_{eq} can be done by several methods, for example, either directly by UV/Vis, IR, and NMR spectroscopy, or indirectly by pK_a measurements. Each of these methods has its own advantages and shortcomings, restricting their respective application to certain ranges of K_{eq}. Recently, a possible method to overcome some of the problems inherent to the above-mentioned procedures has been described. This method is based on the reactivity differences of ring-chain tautomeric systems.[4] Alternatively, computational chemistry methods could also be used for the determination of K_{eq}. So far, theoretical work largely appears to have been restricted to the ring-chain tautomerism of heterocyclic compounds[5−14] and lactonisation/lactolisation of hydroxycarboxylic acids and aldehydes.[15,16] However, despite its significance, surprisingly little computational work on the ring-chain tautomerism of oxocarboxylic acids has been reported.[17] As an extension of our previous experimental[4,18−26] and theoretical work,[17] we now present the results of a computational study on the ring-chain tautomerism of a series of oxocarboxylic acids (Scheme 2). Special emphasis will be devoted to the effect of the nature of the bridge (olefinic vs. aromatic), the acyl group (formyl or acetyl vs. benzoyl), and of substituents on K_{eq}. The investigated compounds were chosen so as to encompass structural features generally present in oxocarboxylic acids capable of ring-chain tautomerism, as well as to span a reasonably wide range of K_{eq}.

Computational Details

All calculations were done by the Gaussian 98 program suite.[27] Geometries were completely optimised at the ab initio Hartree−Fock and, for compounds **1**−**4** and **9**, also at the second-order Møller−Plesset[28] level of theory. In addition, Becke's three-parameter hybrid HF/density functional method[29] with the Lee−Yang−Parr correlation function[30] was also used. All stationary points were characterised as minima by frequency calculations at the same

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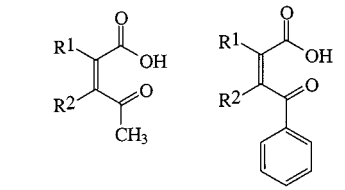
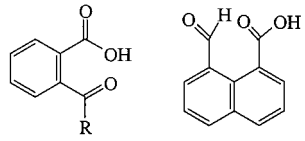


	R1	R2
1	H	H
2	Me	H
3	H	Me
4	Me	Me

	R1	R2
5	H	H
6	Me	H
7	H	Me
8	Ph	Ph



	R
9	H
10	Me
11	Ph

12

Scheme 2. Structures of the investigated compounds

level of theory at which geometry optimisation was done. Zero-point energies are unscaled. For the calculation of thermochemical quantities (ΔH and ΔG correction, 298 K, 1 atm) standard procedures as implemented in Gaussian 98 were employed. Basis sets used were of 6-31G* and 6-311+G** quality. Bulk solvent effects (H_2O, $\varepsilon = 78.5$) were estimated by single-point calculations using the polarised continuum model (PCM).[31,32]

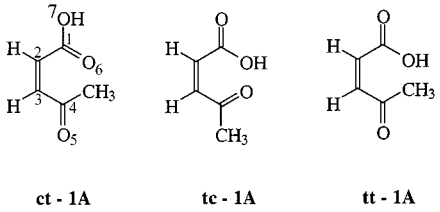
Results and Discussion

Structural features, especially conformational properties and energetics of the open tautomers of compounds **1**−**12**, will be described first. Energies of the ring-chain interconversion in both the gas phase as well as in aqueous solution, with a particular emphasis on the effects of the nature of the acyl group, of the link, and of the substituents, will then be discussed.

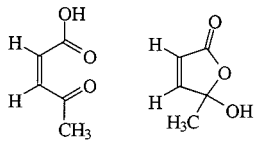
Conformational Properties of the Chain Forms

In principle, all open-chain tautomers of compounds **1**−**12** may exist in four different conformations resulting from rotations around the formal single bonds C1−C2 (carboxyl group) and C3−C4 (acyl group) (Scheme 3; **ct**: *s-cis-s-trans*, **tc**: *s-trans-s-cis*, **tt**: *s-trans-s-trans*, **cc**: *s-cis-s-cis*).

For the prototype (*Z*)-3-formylacrylic acid, the conformations are energetically favoured in the following order: **ct** > **tt** > **tc**.[17] However, for the compounds discussed here, one might expect that replacement of the formyl group by an acetyl or a benzoyl group might rule out an *s-trans* orientation of the acyl moiety. In most cases the acyl group was, in fact, found to be oriented almost perpendicularly [torsion angle $\tau_2 = \tau$(C2−C3−C4−O5) in Table 1; for atom



ct - 1A tc - 1A tt - 1A



cc - 1A 1B

Scheme 3. Structures of the various conformations of open-chain tautomers **A** (including atom numbering) and of the cyclic form **B**

numbering, see Scheme 3] to the olefinic double bond and/or to the aromatic ring of the bridge. Not surprisingly, for the *s-trans* orientation of the acyl functionality of **9** and **12**, both of which contain a formyl group, $\tau_2 \approx 180°$. In several cases a clear distinction between the *s-cis* and *s-trans* conformations of the acyl groups is not possible, especially since the exact value of τ_2 is found to depend on both the computational procedure as well as on the basis set used. It should be pointed out that in the benzoyl derivatives **5**−**8** and **11**, it is generally the benzoyl group that is twisted out of conjugation whereas the carboxyl group is approximately planar to the bridge [$\tau_1 = \tau$(C3−C2−C1−O6) ≈ 0° or ≈ 180°, see Table 1]. The alternative twisted conformation with $\tau_1 \approx 90°$ and $\tau_2 \approx 0°$ collapses on geometry optimisation to the conformation with $\tau_1 \approx 0°$ (or $\tau_1 \approx 180°$) and $\tau_2 \approx 90°$. The effect apparently arises from the greater steric bulk of the phenyl group. For acetyl derivatives **1**−**4**, in addition to the conformations obtained for benzoyl compounds, a structure with a twisted carboxyl group (τ_1 = 100°−110°) and a planar acetyl group ($\tau_2 \approx 10°$, see Table 1) is found. Generally, as already observed for (*Z*)-3-formylacrylic acid,[17] the *s-cis-s-cis* conformation is calculated to be unstable. The only exception among the investigated compounds is the naphthyl derivative **12** (see Table 1). Here, all four principal conformations (Scheme 3) of the open-chain tautomer could be obtained. Torsion angles calculated at different levels of theory are by and large quite similar; however, in a few special cases (e.g. **6**), differences of up to 25° can occur (see Table 1). The other geometrical parameters (see Table 1) were found to be less dependent on the calculation procedure. Generally, for the length of the link [i.e. *r*(C2−C3)], the smallest values are obtained by HF, and the largest by MP2 calculations. B3LYP results are close to the MP2 bond lengths. In contrast, for the distance *r*(C1−C4) between the two carbonyl carbon atoms, the smallest values are obtained at the MP2 level of theory. Substitution at C2 and/or C3 by methyl or phenyl groups leads to a significant decrease of the respective bond angle

Table 1. Selected structural parameters of the various conformations of the open-chain tautomers **1A−12A** (distances in Å; angles in °; for atom numbering, see Scheme 3)

	τ_1[b]	τ_2[c]	*r*(C1−C4)	*r*(C2−C3)	α_1[d]	α_2[e]
ct−1A[a]						
I	−3.8	−103.7	3.054	1.321	122.69	128.07
II	−5.5	−102.1	3.059	1.321	122.78	128.15
III	0.0	−108.5	3.083	1.340	123.10	128.12
IV	−2.0	−105.5	3.080	1.336	123.10	128.18
V	−1.7	−101.5	2.995	1.343	121.33	125.83
tc−1A						
I	110.5	−10.8	3.035	1.320	126.35	123.52
II	106.2	−7.9	3.041	1.319	126.47	123.65
III	108.2	−8.7	3.036	1.339	125.88	123.21
IV	104.0	−6.8	3.041	1.335	126.09	123.39
V	108.7	−12.8	2.983	1.343	124.36	122.26
tt−1A						
I	175.1	−97.4	3.151	1.321	126.43	128.93
II	172.1	−95.0	3.152	1.321	126.37	129.00
III	−179.6	−105.2	3.195	1.340	127.35	129.21
IV	175.6	−99.8	3.183	1.336	127.09	129.17
V	174.5	−95.6	3.119	1.344	125.73	127.25
ct−2A						
I	−6.1	−100.4	2.992	1.324	118.83	128.73
II	−10.4	−97.2	2.992	1.323	118.78	128.72
III	0.2	−105.4	3.007	1.344	118.74	128.59
IV	−2.7	−102.2	3.004	1.340	118.66	128.72
V	−1.0	−102.0	2.948	1.347	118.05	126.64
tc−2A						
I	104.7	−4.8	2.975	1.324	123.16	123.74
II	101.2	−2.0	2.981	1.323	123.08	124.02
III	105.2	−5.4	2.975	1.343	122.57	123.44
IV	100.9	−3.0	2.979	1.340	122.52	123.82
V	107.4	−10.1	2.942	1.346	121.97	122.68
tt−2A						
I	169.2	−91.3	3.096	1.324	122.81	129.56
II	165.6	−88.9	3.091	1.323	122.56	129.57
III	−179.1	−103.6	3.141	1.344	123.51	130.05
IV	168.0	−90.7	3.114	1.340	122.81	129.66
V	−[f]					
ct−3A						
I	−2.8	−105.0	3.001	1.326	123.23	124.82
II	−4.4	−103.1	3.003	1.325	123.37	124.70
III	0.0	−108.0	3.016	1.344	123.39	124.45
IV	−2.1	−104.6	3.013	1.341	123.56	124.32
V	0.8	−106.2	2.957	1.346	121.88	123.47
tt−3A						
I	177.9	−102.4	3.109	1.326	127.32	125.79
II	174.6	−99.7	3.108	1.325	127.33	125.70
III	−179.1	−106.9	3.144	1.345	128.16	125.69
IV	176.0	−101.2	3.133	1.341	128.05	125.52
V	−178.0	−105.1	3.094	1.347	126.67	125.04
tt−4A						
I	173.4	−99.9	3.011	1.332	122.36	125.37
II	167.0	−95.1	2.999	1.331	122.11	125.09
III	−172.4	−111.8	3.038	1.352	122.77	125.20
IV	170.0	−96.7	3.029	1.349	122.60	125.17
V	−160.4	−121.1	2.990	1.355	121.68	124.32
ct−4A						
I	−4.8	−103.3	2.880	1.332	117.80	124.09
II	−8.5	−100.1	2.879	1.331	117.84	123.98
III	0.4	−106.9	2.882	1.352	117.48	123.58
IV	−3.2	−102.3	2.881	1.349	117.57	123.57
V	1.7	−107.2	2.882	1.354	117.48	123.58
tt−5A						
I	176.4	−92.9	3.151	1.321	126.41	128.90
II	173.2	−88.8	3.149	1.320	126.42	128.80
III	−176.3	−102.9	3.188	1.340	127.13	129.04
IV	−179.6	−97.2	3.180	1.336	127.06	128.97
ct−5A						
I	−4.0	−95.6	3.042	1.321	122.44	127.70
II	−5.9	−93.1	3.045	1.319	122.61	127.67
III	0.4	−101.6	3.051	1.339	122.34	127.32
IV	−1.0	−98.9	3.055	1.335	122.61	127.46
tt−6A						
I	165.7	−83.2	3.086	1.323	122.72	129.13
II	162.4	−79.9	3.081	1.322	122.56	129.04
III	−172.0	−105.1	3.144	1.344	123.51	130.10
IV	−[g]					
ct−6A						
I	−8.6	−91.8	2.986	1.323	118.77	128.42
II	−15.2	−86.5	2.981	1.322	118.79	128.19
III	0.4	−100.0	2.998	1.343	118.57	128.25
IV	−1.5	−97.3	2.996	1.340	118.59	128.35
tt−7A						
I	179.2	−97.6	3.109	1.325	127.22	125.86
II	177.8	−96.0	3.108	1.324	127.34	125.70
III	−[g]					
IV	−178.3	−99.2	3.128	1.341	127.95	125.36
ct−7A						
I	−2.5	−98.8	2.992	1.325	122.98	124.63
II	−3.5	−97.4	2.993	1.324	123.20	124.44
III	0.4	−102.2	2.992	1.344	122.77	123.94
IV	−0.7	−100.0	2.995	1.340	123.19	123.87
cc−8A						
I	−21.7	−84.5	2.872	1.333	117.95	123.15
tc−8A						
I	154.7	−79.7	2.964	1.334	121.50	123.68
tt−9A						
I	159.6	165.9	3.130	1.402	125.42	124.83
II	160.3	161.4	3.123	1.401	125.20	124.69
III	161.3	173.9	3.167	1.416	126.28	125.17
IV	158.0	169.1	3.141	1.413	125.71	124.61
V	154.8	169.4	3.116	1.411	125.06	124.43
tc−9A						
I	128.2	−15.1	3.043	1.399	123.68	122.78
II	125.5	−14.3	3.043	1.398	123.56	122.93
III	127.6	−12.0	3.054	1.411	123.70	122.84
IV	120.5	−10.3	3.039	1.408	123.26	122.81
V	126.5	−14.8	3.008	1.407	122.92	121.88
ct−9A						
I	−16.6	169.0	3.049	1.403	121.83	124.67
II	−16.4	162.3	3.035	1.401	121.44	124.41
III	−12.9	177.2	3.076	1.417	122.28	124.93
IV	−18.6	168.5	3.043	1.413	121.55	124.20
V	−23.3	171.8	3.027	1.411	121.23	124.10
ct−10A						
I	−0.4	112.3	3.000	1.397	119.63	124.82
II	3.3	105.9	2.997	1.396	119.71	124.64
III	−5.3	120.2	3.012	1.410	119.46	124.90
IV	−1.4	111.9	3.002	1.408	119.50	124.60
tt−10A						
I	172.1	117.3	3.118	1.398	124.04	125.62
II	−166.9	88.3	3.095	1.395	123.86	124.86
III	166.3	128.9	3.145	1.412	124.37	125.81
IV	−158.6	68.9	3.075	1.406	123.65	123.43
ct−11A						
I	2.0	−103.6	2.999	1.397	119.75	124.69
tc−11A						
I	158.9	−67.9	3.061	1.396	123.58	123.32
tt−12A						
I	−149.7	−163.7	3.035	2.554	125.16	123.55
ct−12A						
I	22.3	−164.2	3.033	2.562	122.33	124.42
tc−12A						
I	−148.6	15.6	3.104	2.556	124.78	125.45
cc−12A						
I	39.2	21.1	3.018	2.545	122.09	124.47

[a] I: HF/6-31G*; II: HF/6-311+G**; III: B3LYP/6-31G*; IV: B3LYP/6-311+G**; V: MP2/6-31G*. − [b] τ_1 = τ(C3−C2−C1−O6). − [c] τ_2 = τ(C2−C3−C4−O5). − [d] α_1 = (C1−C2−C3). − [e] α_2 = (C2−C3−C4). − [f] Collapses to **tc−2A**. − [g] Not converged.

α_1 = (C1−C2−C3) or α_2 = (C2−C3−C4) at the substituted atom (see, e.g. **ct−1A** vs. **ct−2A**, **ct−1A** vs. **ct−3A**, **ct−5A** vs. **ct−6A**, **ct−5A** vs. **ct−7A**, Table 1) with a concomitant decrease of *r*(C1−C4). Thus, substituents at the bridge exert a buttressing effect on the two carbonyl groups.

Energy differences or, more precisely, ΔG differences between the various conformations of the open-chain tautomers (Table 2) are frequently quite small and are to some extent dependent on the computational procedure and on the basis set used. Generally, for the 2-acylbenzoic acids **9−11** as well as acrylic acids either unsubstituted at C2 (**1**, **3**, **5**, and **7**) or substituted both at C2 and at C3 (**4**, **8**), the *s-cis* orientation of the carboxyl group has the lowest energy. For acrylic acids substituted only at C2 (**2** and **6**), the reverse is true. Inclusion of bulk solvent effects by the polarised continuum model has only minor effects on the calculated stability order of the various conformations. Only in a few instances in aqueous solution is a reversal of this order obtained, for example **6** (gas phase: **tc−6A** > **ct−6A**, H_2O: **ct−6A** > **tc−6A**) and **9** (gas phase: **ct−9A** > **tt−9A** > **tc−9A**, H_2O: **ct−9A** > **tc−9A** > **tt−9A**). Apparently, relative energies obtained by B3LYP/6-311+G** calculations are sometimes inconsistent with those resulting from other methods. The same is also true for tautomerisation energies (see below).

Table 2. Calculated conformational free enthalpies (in kJ mol^{-1}) of the chain tautomers **1A−12A** in the gas phase and in aqueous solution [relative to the *s-cis-s-trans* (**ct**) conformer]

Compd.	Method[a]	Gas	H_2O	Compd.	Gas	H_2O
tc−1A	I	6.6	2.5	**tt−1A**	5.1	4.0
	II	7.0	0.5		4.1	1.7
	III	5.3	0.7		5.8	3.3
	IV	5.6	−0.9		4.9	3.0
	V	4.2	0.6		4.6	4.2
tc−2A	I	−3.3	−3.2	**tt−2A**	0.8	0.4
	II	−2.9	−6.3		0.3	3.9
	III	−4.0	−4.5		2.2	2.6
	IV	−4.2	−8.9		0.3	1.9
	V	−3.1	−3.4		—[b]	
tt−3A	I	7.1	5.2	**tt−4A**	2.7	3.2
	II	5.7	2.8		1.2	5.3
	III	6.9	5.3		3.5	3.8
	IV	5.6	3.8		1.0	6.3
	V	6.1	4.3		2.0	2.2
tt−5A	I	1.7	3.9	**tc−6A**	−2.7	0.2
	II	0.8	3.2		−2.7	2.1
	III	2.6	5.5		−1.3	2.9
	IV	1.3	−2.9		—[c]	—[c]
tt−7A	I	3.4	3.4	**tc−8A**	3.5	4.0
	II	2.3	3.0			
	III	—[c]	—[c]			
	IV	3.1	2.9			
tc−9A	I	13.6	6.3	**tt−9A**	5.0	3.4
	II	11.2	0.8		4.2	5.3
	III	13.8	2.0		4.2	7.7
	IV	9.4	−7.8		3.0	2.5
	V	9.0	−5.6		2.5	1.6
tt−10A	I	4.0	5.7			
	II	2.6	9.2			
	III	3.5	5.9			
	IV	2.5	12.6			
tc−11A	I	0.8	2.8			
tt−12A	I	−1.3	0.4	**tc−12A**	0.4	−2.3
cc−12A	I	−0.7	−1.0			

[a] I: HF/6-31G*; II: HF/6-311+G**; III: B3LYP/6-31G*; IV: B3LYP/6-311+G**; V: MP2/6-31G*. − [b] Collapses to **tc−2A**. − [c] Not converged.

Tautomerisation Energies

Calculated tautomerisation free enthalpies [$\Delta\Delta G$ = ΔG(chain) − ΔG(ring)] in the gas phase as well as in aqueous solution are collected in Table 3. (Total energies, ΔG corrections and solvation free enthalpies of all structures discussed in this paper are provided in Table S1 of the Supporting Information.) Experimental equilibrium constants $K_{eq} = a_{ring}/a_{chain}$ are also listed in Table 3. Generally, B3LYP/6-311+G** calculations appear to overestimate the stability of the open-chain tautomers.[17] It is therefore worth mentioning that problems associated with the B3LYP procedure in the proper handling of tautomerisation energies have already been noted.[33,34] Thus, tautomerisation energies obtained by this computational procedure are considered as less reliable for the following discussion. The effects of structural modifications on the intrinsic (i.e. gas phase) stability differences between cyclic and open tautomers will be presented first. The influence of solvation on tautomeric equilibria will then be discussed.

Concentrating on cyclisations involving the most stable of the open-chain forms **A**, the following conclusions with respect to the influence of structural features on the ring-chain tautomerism of γ-oxocarboxylic acids can be drawn: (i) Replacing acetyl (or formyl in case of **9**) by benzoyl [**1** vs. **5**, **9** (**10**) vs. **11**, **2** vs. **6**, and **3** vs. **7**, see Table 3] shifts the equilibrium towards the open tautomer **A**; (ii) introduction of methyl groups at positions 2 or 3 increases the stability of the cyclic tautomer irrespective of the acyl group (compare **1** vs. **2** vs. **3** and **5** vs. **6** vs. **7**); (iii) substitution of both C2 and C3 by methyl (**4**) or phenyl (**8**) has an even more pronounced effect on stabilising the hydroxy lactone structure **B**; (iv) in benzoic acids **10** and **11**, that is, in compounds with an aromatic rather than an olefinic link (compare with **1** and **5**), a shift of the equilibrium towards the carboxylic acid can be seen; (v) in the gas phase, the unsubstituted (*Z*)-3-acetylacrylic acid **1**, the monosubstituted 3-benzoylacrylic acids **5−7** as well as 2-acylbenzoic acids **9−11** are calculated to exist predominantly as such rather than as the cyclic form; and (vi) for 8-formylnaphthalene-1-carboxylic acid **12**, the six-membered cyclic tautomer is calculated to predominate.

Solvent Effects on Tautomerisation Energies

Inclusion of bulk solvent effects (H_2O) by the polarised continuum model of solvation[31,32] leads to a shift of the tautomeric equilibrium towards the cyclic form in case of acetyl (or formyl) derivatives **1−4**, **9**, **10**, and **12**. In contrast, for benzoyl derivatives **5−8** and **11**, a preferred stabilisation by solvation of the chain form **A** is calculated. By and large, this result is independent of the respective conformation of the open-chain tautomer **A**. The calculated solvent shift on tautomerisation free enthalpies is generally in the range of a few kJ mol^{-1}. An unusually large effect (10−45 kJ mol^{-1}) is obtained for 2-formylbenzoic acid **9**,

Table 3. Calculated tautomerisation free enthalpies $\Delta\Delta G$ (in kJ mol^{-1}) in the gas phase and in aqueous solution, and experimental equilibrium constants K_{eq}

Compd.	Method[a]	Conformation								K_{eq}(exp)[b]
		s-cis-s-trans		*s-trans-s-cis*		*s-trans-s-trans*		weighted		
		Gas	H_2O	Gas	H_2O	Gas	H_2O	Gas	H_2O[c]	
1	I	−3.8	−0.2	2.8	2.3	1.3	3.7	−0.5	1.7	12 (±2)[d]
	II	−6.0	2.0	1.0	2.5	−1.8	3.7	−2.9	2.7	
	III	−4.2	1.7	1.1	2.4	1.7	5.0	−1.0	2.9	
	IV	−11.7	−2.9	−6.0	−3.8	−6.8	0.1	−8.6	−2.4	
	V	5.8	8.3	10.0	8.9	10.4	12.5	8.4	9.7	
2	I	12.0	13.8	8.7	10.6	12.8	14.1	10.9	12.6	39 (±5)[d]
	II	10.1	10.3	7.2	3.9	10.5	14.1	9.1	8.1	34 (±4)[21]
	III	10.2	14.1	6.3	9.5	12.4	16.6	9.1	12.8	
	IV	3.8	6.1	−0.4	−2.8	4.1	8.0	2.2	2.0	
	V	16.6	17.7	13.6	14.3	–[e]	–[e]	14.4	15.3	
3	I	2.8	9.0			9.9	14.2	5.5	11.2	1000 (±120)[d]
	II	0.8	15.2			6.5	18.0	3.1	16.4	
	III	2.2	10.2			9.1	15.5	4.8	12.3	
	IV	−5.2	6.8			0.4	10.7	−3.0	8.5	
	V	10.6	16.8			16.7	21.2	13.0	18.7	
4	I	28.8	30.8			31.4	33.9	30.0	32.2	20000 (±2400)[d]
	II	26.5	26.4			27.7	31.8	27.1	28.6	
	III	24.4	28.5			27.9	32.3	25.9	30.1	
	IV	17.6	19.4			18.6	25.7	18.1	21.8	
	V	29.9	32.0			31.9	34.2	30.9	33.0	
5	I	−11.9	−19.5			−10.2	−15.6	−11.1	−17.8 (−11.8)	0.3 (±0.2)[21]
	II	−13.0	−25.2			−12.3	−22.0	−12.7	−23.8	
	III	−12.7	−14.8			−10.2	−9.2	−11.6	−12.5	
	IV	−20.0	−29.1			−18.7	−32.1	−19.4	−30.8	
6	I	3.2	−3.5	0.5	−3.3			1.7	−3.4 (1.4)	7 (±2)[20,37]
	II	2.3	−4.8	−0.4	−2.8			0.8	−3.9	
	III	0.4	−0.4	−1.0	2.5			−0.3	0.9	
	IV	−5.7	−3.6	–[f]	–[f]					
7	I	−5.3	−6.4			−1.9	−3.0	−3.8	−4.9 (−2.2)	11 (±4), 8 (±3)[20]
	II	−6.4	−14.5			−4.2	−11.5	−5.4	−13.1	
	III	−6.7	−2.1			–[f]	–[f]			
	IV	−14.0	−17.9			−10.9	−15.0	−12.6	−16.6	
8	I	18.7[g]	12.6[g]	22.2	16.6			20.2	14.3 (21.0)	1600 (±400)[19]
9	I	−6.8	9.7	6.8	16.0	−1.8	13.1	−2.7	12.4 (4.3)	6.7 (±1.4)[25]
	II	−6.2	24.1	5.0	24.9	−2.0	29.4	−2.5	25.7	
	III	−6.8	10.8	7.0	12.8	−2.7	18.4	−3.0	13.3	
	IV	−7.9	37.1	1.6	29.4	−4.8	39.6	−4.8	33.9	
	V	−6.9	11.1	2.1	5.5	−4.4	12.7	−4.1	9.1	
10	I	−4.4	−4.4			−0.4	1.3	−2.6	−2.1 (−0.7)	2.4 (±0.3)
	II	−6.9	−6.9			−4.4	2.3	−5.8	−3.8	3.0 (±0.5)
	III	−2.0	3.2			1.5	9.0	−0.5	5.5	4.3 (±0.8)
	IV	−8.4	−6.4			−5.9	6.2	−7.2	−2.8	4.7 (±0.7)[25]
11	I	−15.7	−20.4	−14.8	−17.4			−15.3	−18.8	0.07 (±0.02)[25] 0.033[38]
12	I	24.2	30.6	24.6	28.3	23.0 (23.5)[h]	31.0 (29.6)[h]	23.8	29.8	1200 (±100)[39]
	I									

[a] I: HF/6-31G*; II: HF/6-311+G**; III: B3LYP/6-31G*; IV: B3LYP/6-311+G**; V: MP2/6-31G*. – [b] Experimental equilibrium constants were determined in 2-methoxyethanol/water (80%, w/w) for **1**−**8** and **12** by the pK method; those of **9**−**11** in dioxane by the IR method. – [c] Values in parentheses are calculated with ε = 2.21 (corresponding to dioxane). – [d] Calculated using observed pK_a values from ref.[36] and true pK_a values estimated from correlations shown in refs.[20,37] – [e] Collapses to **tc**−**2A**. – [f] Not converged. – [g] *s-cis-s-cis* conformation. – [h] Values in parentheses are for the *s-cis-s-cis* conformation.

which in the gas phase should exist as such. However, in polar solution the equilibrium is predicted to be shifted completely towards the cyclic form. Finally, it should be pointed out that in general the largest solvent shift calculated by the PCM approximation results from the use of the 6-311+G** basis set. However, in some cases (e.g. **9**), solvation free enthalpies obtained with this basis set (both HF or B3LYP) appear to be unrealistic (for problems with basis sets containing diffuse functions in solvation energy calculations, see ref.[35]

Comparison with Experiment

Experimental tautomerisation constants $K_e = a_{ring}/a_{chain}$ are also collected in Table 3. Since conformational energies of the various open structures are quite low (< 10 kJ mol^{-1}, see Table 2), an equilibrium between these rotamers in solu-

tion can be expected. Therefore, comparison with experimental tautomerisation constants will be made with calculated free enthalpies weighted by the corresponding Boltzmann factors. These weighted tautomerisation energies are also included in Table 3. Most of the experimental values were obtained in polar solvents, for example 80% (w/w) 2-methoxyethanol/water (**1**−**5**, **8**−**10**, **12**). Furthermore, in cases where the experiments were performed by different methods as well as in different solvents, the solvent effect was comparable to the effect resulting from different experimental techniques. For instance, K_{eq} values of 2-formylbenzoic acid **9** were found to be 6.7 (IR, dioxane), 4.6 (NMR, dioxane), 5.6 (NMR, MeOH), 4.6 [NMR, 80% (w/w) 2-methoxyethanol/water],[25] and 5.8 by esterification with diazodiphenylmethane (ethanol).[4] Similarly, for compound **10**, K_{eq} = 4.7 (IR, dioxane), 4.3 (NMR, dioxane), 3.0 (NMR, MeOH), 2.4 [NMR, 80% (w/w) 2-methoxyethanol/water],[25] and 4.0 by esterification with diazodiphenylmethane (ethanol).[4] Given these results, using H_2O as a solvent in the calculations appears to be a reasonable choice for the simulation of solvent effects on these tautomeric equilibria. As was the case for the calculated tautomerisation free enthalpies involving the most stable conformation of the respective open structure, for acetyl (formyl) derivatives **1**−**4**, **9**, **10**, and **12** a shift of the equilibrium towards the cyclic form in polar solvents is predicted, whereas for benzoyl derivatives **5**−**8** and **11**, the open tautomer should be preferentially stabilised. In several cases this different response of the individual tautomers towards solvent effects, e.g. **1**, **6**, or **9**, even leads to a reversal of the sign of $\Delta\Delta G$ relative to the gas phase value. Experimentally, for all the formyl and acetyl derivatives, $K_{eq} > 1$ is found (see Table 3). In line with these experimental findings, $\Delta\Delta G = \Delta G_{chain} - \Delta G_{ring}$, at the Hartree−Fock level of theory is calculated to be >0, except for **10**, thus indicating greater stability of the cyclic tautomer in solution (see Table 3). Using the B3LYP/6-31G* procedure for compound **10**, a predominance of the furanone structure is also predicted. Experimentally, a slight decrease in K_{eq} with increasing solvent polarity was found (see above).[25] Indeed, when using dioxane (ε = 2.21) as a model for the solvent, $\Delta\Delta G$ (HF/6-31G*) is reduced from −2.1 to −0.7 kJ mol^{-1}. According to the calculations and to experimental findings, (*Z*)-3-benzoylacrylic acid **5** and 2-benzoylbenzoic acid **11** clearly exist preferentially in the chain form (K_{eq} = 0.3 and 0.07, $\Delta\Delta G$ = −12.5 to −30.8 and −18.8 kJ mol^{-1}, respectively, see Table 3). Although using ε = 2.21 in the PCM calculations (corresponding to dioxane as solvent) slightly reduces the HF/6-31G* $\Delta\Delta G$ values (from −17.8 to −11.8 kJ mol^{-1} for **5**, and from −18.8 to −15.3 kJ mol^{-1}for **11**), there is still a clear preference for the chain forms of these compounds. Substitution of methyl groups at C2 or especially at C3 of the alkene bridge significantly increases K_{eq} (**1** vs. **2** vs. **3**) and double substitution at both C2 and C3 (**4**) leads to a shift of the equilibrium towards the lactone structure by 4 orders of magnitude.[36] In agreement with these experimental findings, the calculations also predict a substantial increase in $\Delta\Delta G$ in the substituted derivatives (see Table 3). A similar but less pronounced substitution effect is also found for the benzoyl derivatives **5**−**8**. This effect is nicely reproduced by the calculations for (*Z*)-3-benzoyl-2,3-diphenylacrylic acid **8**. However, for the mono-methyl-substituted derivatives **6** and **7**, the stability of the chain form is obviously overestimated, except with the B3LYP/6-31G* method. It should be pointed out that both **6** and **7** were measured in dioxane, whereas the calculations refer to H_2O as the solvent. As already described above, using ε = 2.21 in the PCM calculations (corresponding to dioxane as the solvent) for these two molecules at the HF/6-31G* level of theory, a shift towards a less negative (**7**: −2.2 as compared to −4.9 kJ mol^{-1}) or even a positive $\Delta\Delta G$ value (**6**: +1.4 kJ mol^{-1}) is also obtained. Thus, at least in the case of the 2-methyl derivative **6**, a slight preference of the cyclic tautomer is calculated. Finally, as already mentioned above, PCM calculations (both at the HF as well as at the B3LYP level of theory) using basis sets containing diffuse functions sometimes yield unrealistic solvation free enthalpies. Results obtained with the HF/6-31G* procedure are generally quite similar to those using B3LYP/6-31G*. In a few cases, e.g. **6** and **10**, the B3LYP results more closely match the experimental K_{eq} values. Generally, however, B3LYP calculations result in the poorest agreement with experimental ln*K* values. For the various methods used, the following squared correlation coefficients r^2 between $\Delta G_{calcd.}$ and ln*K* were found: r^2 = 0.83 (HF/6-31G*, *n* = 12), 0.570 (HF/6-311+G**, *n* = 9), 0.790 (B3LYP/6-31G*, *n* = 8), 0.338 (B3LYP/6-311+G**, *n* = 8), 0.939 (MP2/6-31G*, *n* = 5).

Conclusions

In this paper we have presented a theoretical study using different levels of ab initio (HF, MP2) and density functional theory (B3LYP) and different basis sets (6-31G*, 6-311+G**) concerning the ring-chain tautomerism of a range of γ-oxocarboxylic acids. For the open-chain tautomers, various conformations resulting from the rotation of the acyl and/or carboxyl functional groups, were considered. Unless there is a substituent at C2 (and none at C3) of 3-acylacrylic acids (**2** and **6**), the *s-cis* orientation of the carboxyl group is the lowest energy conformation. (*Z*)-3-Acetylacrylic acids as well as 2-acetyl (formyl) benzoic acids exist in solution predominantly as the cyclic tautomer. In contrast, for 3-benzoylacrylic derivatives that are not substituted at C2 and/or C3, as well as for 2-benzoylbenzoic acid, the open-chain tautomer is found to be both theoretically and experimentally more stable. Substitution at C2 and/or C3 of the alkene bridge substantially increases the stability of the respective cyclic tautomers. Inclusion of solvent effects are crucial for a proper description of these tautomeric equilibria. Interestingly, with the B3LYP/6-311+G** procedure, inconsistent results are obtained in a few cases. Solvation free enthalpies calculated by basis sets including diffuse functions are frequently unrealistic.

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