PERKIN 2

Semi-empirical AM1 and PM3 molecular orbital calculations on the mechanism of the hydrolysis of unsaturated lactones: substituted (*E*)-5,5′-diphenylbifuranylidenediones and 3,7-diphenylpyrano[4,3-*c*]pyran-1,5-diones

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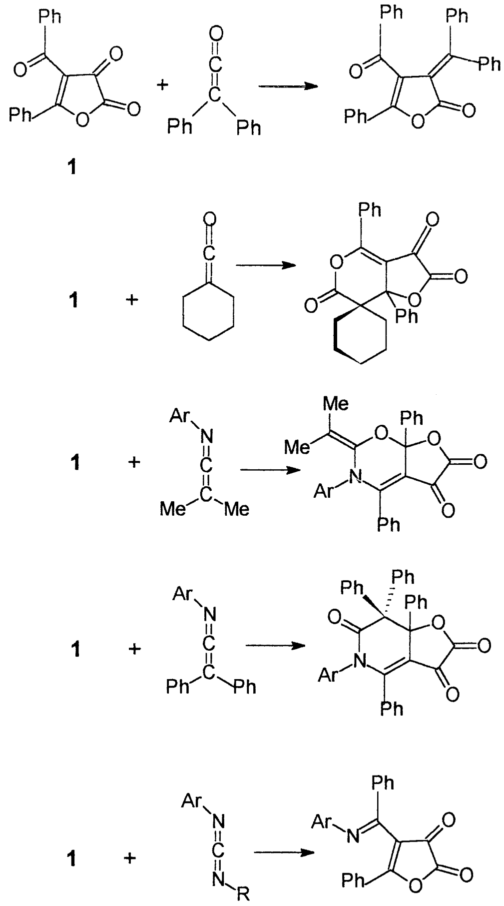
Semi-empirical molecular orbital (AM1 and PM3) calculations including solvent effects by the SCRF model on the mechanism of the addition of nucleophiles to unsaturated five- and six-membered bislactones of the Pechmann dye type indicate a similar mechanism for both systems. The rate-determining step appears to be the addition of a second nucleophile to the enol of the ring-opened monolactone. The five-membered lactones are found to be more reactive than their six-membered analogues. Electron donor substituents (*p*-Me, *p*-MeO) increase and acceptor substituents (*p*-Cl, *m*-NO$_2$) decrease the activation energy.

Introduction

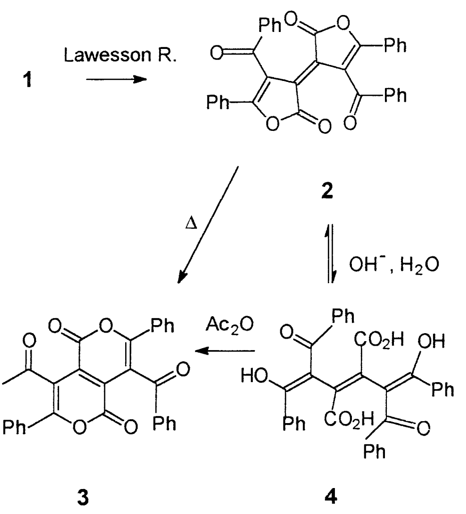
4-Acyl substituted heterocyclic 2,3-diones **1**, *e.g.* furan- or pyrrole-diones, are versatile starting materials for a variety of reactions, *e.g.* generation of α-oxoketenes by thermolysis, cycloaddition of heterocumulenes across the oxa-1,3-diene subunit as well as addition of nucleophiles leading to a number of mono- and bi-cyclic heterocyclic systems.[1] Quite frequently these reactions were accompanied by novel and unexpected rearrangements giving in some cases hitherto unknown ring systems.[2] The outcome of these reactions depends strongly on rather subtle variations of the starting materials (see Scheme 1).

In order to investigate this pronounced structural influence several attempts to modify the functional groups in **1**, *e.g.* transformation of a carbonyl into a thiocarbonyl group using the Lawesson reagent or into a C=C double bond *via* Wittig reaction had been made.[3] Instead of the expected sulfurization, however, reaction with Lawesson reagent gave highly coloured products ($\lambda_{max} = 518$ nm/log $\varepsilon = 4.36$; $\lambda_{max} = 545$ nm/log $\varepsilon = 4.33$). Spectroscopic data and an X-ray structure determination established the bisfuranone structure **2** (see Scheme 2) with an iso-oxindigoide skeleton for these products.[3] On heating compound **2** a colour change to pale red occurred indicating some thermal rearrangement. Spectroscopic evidence as well as molecular orbital calculations[3] rule out *E*/*Z*-isomerization as found in several similar iso-indigoide systems.[4] Instead, all the available evidence indicates that a bicyclic pyrano[4,3-*c*]pyrane system **3** is formed (Scheme 2). Semi-empirical molecular orbital calculations[3] indicate a mechanism analogous to the thermal gas phase isomerization of indigo to dibenzonaphthyridindione.[5] Finally, alkaline hydrolysis of **2** gave the fumaric acid derivative **4** (Scheme 2) which can be cyclized to a mixture of **2** and **3**. Such behaviour is commonly found for so-called Pechmann dyes.[6]

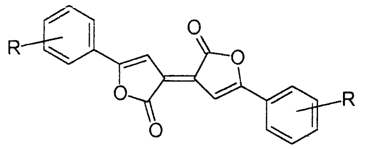


Scheme 1

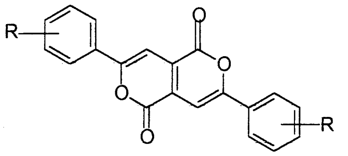
As part of a series of papers on the mechanism of reactions of carbonyl compounds in basic solution[7] a detailed kinetic study of the alkaline hydrolysis[8] of substituted (*E*)-5,5′-diphenylbifuranylidenediones **5** and 3,7-diphenylpyrano[4,3-*c*]pyran-1,5-diones **6**, respectively, as well as their rearrangement reactions in various solvents[9] have been published. Given the close resemblance between the systems treated in ref. 8 and those described by us[3] we found it worthwhile to investigate these reactions in more detail with the aid of computational methods. In view of the very general importance of nucleophilic addition reactions on carbonyl compounds a number of theoretical papers either at the *ab initio*[10] or the semi-empirical[11–13] level have already been published. Of special rele-



Scheme 2



5



6

R = H, *p*-CH3O, *p*-CH3, *p*-Cl, *m*-NO2

vance to the present problem are calculations on lactone ring opening reactions of neutral colourless forms of rhodamine derivatives to their deeply coloured quinoid structures.[12]

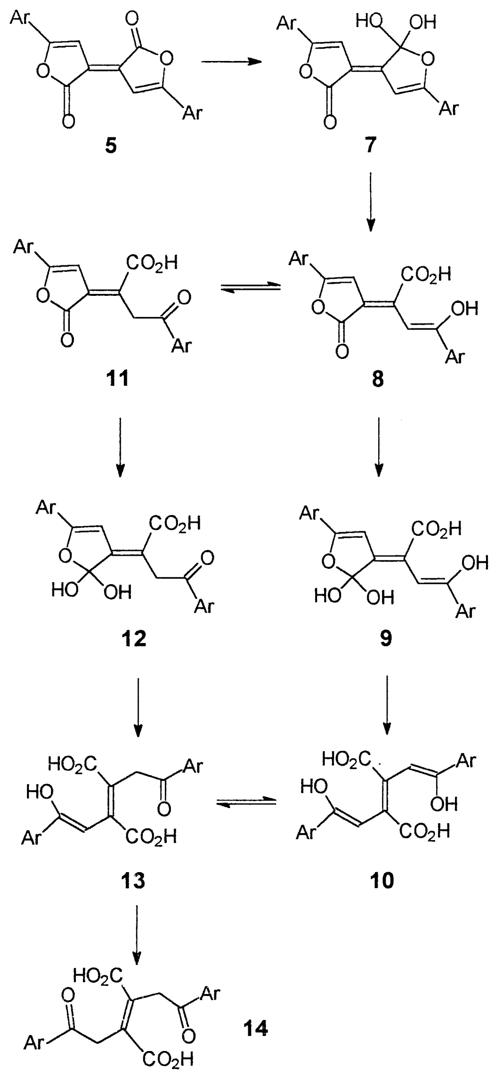
Semi-empirical calculations on the mechanism of the addition of anionic nucleophiles to carbonyl groups face several problems: (*i*) small anions like OH^- are rather poorly described by these procedures (the same also holds for lower level *ab initio* calculations).[14] (*ii*) For isolated molecules, *i.e.* gas phase calculations, addition occurs without any barrier.[10f,11d,f,15] Therefore, activation energies of reactions measured in solution have been attributed to desolvation of the anionic nucleophile rather than its addition.[15] Thus it cannot be expected that reasonable agreement between experimental solution phase activation energies and those calculated for the addition of anionic nucleophiles without explicit consideration of solvation shells will be obtained. (*iii*) Instead of the experimentally observed OH^- addition quite frequently deprotonation is found by semi-empirical calculations.[11e] Similarly, an AM1 transition state for the alkaline hydrolysis of carbamates corresponds to a switch between E1cB and Bac2 mechanisms rather than one for addition of OH^- to the carbonyl group.[11d]

The size of these molecules considered in this paper, however, precludes a treatment by reasonably high level *ab initio* methods. Therefore, we have used semi-empirical (AM1[14] and PM3[16]) molecular orbital calculations. Given the above mentioned limitations the reactions in question will be modelled using H_2O rather than OH^- as a nucleophile. Such an approach has proved to give quite reliable results in related reactions.[17] Using H_2O as reagent implies that besides addition to the carbonyl carbon also proton transfer to the oxygen atom is necessary. The activation energy for such a process, thus, will be considerably higher than for simple addition. Furthermore, the stability of tetrahedral intermediates appears to be overestimated by the AM1 method. For instance, the *ab initio* MP2/6-31G*//HF/6-31G* reaction energy[18] for addition of H_2O to the formyl group of glyoxylic acid is -11.4 kcal mol^{-1} (1 cal = 4.184 J) whereas AM1 calculations yield a value of -22.1 kcal mol^{-1}. The result using the PM3 method is much closer to the *ab initio* one ($\Delta H_f = -13.7$ kcal mol^{-1}). As a consequence, the activation energy—at least with AM1 calculations—of the ring opening reaction of the tetrahedral intermediates (**7**, **9**, **12** in Scheme 3; **15**, **17**, **19** in Scheme 4) will be overestimated. Apart from these drawbacks, however, a reasonable description of mechanistic aspects as well as substituent effects on the kinetics can be expected. As a major advantage of using a neutral instead of a charged nucleophile, solvent effects can be treated by the self-consistent reaction field (SCRF)[19] approximation. To model the experimental conditions [70% (v/v) aqueous dioxane],[8] H_2O has been used as a solvent in the calculations.

Results

(*E*)-5,5′-Diphenylbifuranylidenediones

The mechanism for the nucleophilic addition and ring opening of compounds **5** found by the calculations is depicted in Scheme 3.



Scheme 3

Table 1 Calculated (AM1 and PM3) relative energies[a] for the various structures shown in Scheme 3 and the transition states between them

	AM1					PM3				
	H	*p*-MeO	*p*-Me	*p*-Cl	*m*-NO_2	H	*p*-MeO	*p*-Me	*p*-Cl	*m*-NO_2
5	−18.8	−95.6	−34.4	−31.7	−9.1	−40.8	−117.7	−59.9	−53.5	−57.0
TS (**5–7**)	45.5	45.5	45.4	45.0	44.2	44.9	45.0	45.0	44.7	43.9
7	−11.9	−12.0	−11.9	−12.3	−13.0	−7.8	−7.8	−7.8	−8.0	−8.9
TS (**7–8**)	21.8	22.2	22.0	20.7	18.7	45.9	46.0	45.9	45.8	45.4
8	−12.4	−12.4	−12.4	−12.9	−13.4	−6.4	−6.2	−6.4	−6.5	−6.3
TS (**8–9**)	33.9	34.1	34.0	33.2	31.8	36.6	36.9	36.8	36.2	34.6
9	−23.8	−23.7	−23.8	−24.6	−25.7	−16.5	−16.1	−16.3	−16.8	−18.2
TS (**9–10**)	13.2	13.6	13.5	12.1	9.9	37.4	37.7	37.5	37.2	15.6
10	−25.7	−25.5	−25.6	−26.4	−27.8	−18.0	−17.7	−17.9	−18.4	−20.7
TS (**8–11**)	49.8	49.2	49.6	49.6	50.5	47.1	46.4	46.9	47.1	48.0
11	−16.9	−16.1	−16.0	−16.1	−14.4	−13.9	−14.0	−13.9	−13.9	−13.4
TS (**11–12**)	25.6	25.3	25.6	25.2	24.4	26.4	26.2	26.3	26.4	27.1
12	−31.3	−31.5	−31.4	−31.9	−32.8	−24.0	−24.3	−24.1	−24.1	−24.3
TS (**12–13**)	5.3	5.5	5.9	5.2	4.0	7.2	6.8	7.2	7.0	6.5
13	−28.7	−28.7	−28.6	−29.2	−30.1	−24.7	−24.6	−24.7	−24.6	−25.5
TS (**13–14**)	35.0	34.1	34.8	34.8	35.2	35.6	35.1	35.5	35.8	35.9
14	−32.9	−33.1	−32.9	−33.3	−33.9	−27.4	−27.4	−27.0	−27.1	−28.1
TS (**10–13**)	38.8	37.9	38.6	38.4	38.3	39.7	39.2	39.7	39.7	39.4

[a] Energies (in kcal mol^{-1}) are given relative to the separated reactants **5** + $2H_2O$ [$\Delta H_f(H_2O) = -63.2$ (AM1) and -56.9 (PM3)]; for compounds **5** their respective ΔH_f values are quoted.

Energies for the structures shown there as well as the transition states connecting them relative to the separated reactants, *i.e.* **5** + $2H_2O$, are summarized in Table 1. The activation energies discussed below are generally measured with respect to the minimum immediately preceding the respective transition state.

As indicated by the structure [as an example the AM1 structure for R = H is shown in Fig. 1(*a*); the corresponding PM3 structure is very similar] of TS **(5–7)** as well as the respective imaginary frequencies [ν(AM1) *ca.* 1960 i; ν(PM3) *ca.* 2200 i cm^{-1}] a significant part of the activation energy stems from the proton transfer step. Addition of the water oxygen to the carbonyl carbon is quite advanced [$R = 1.51$ Å (1.39 Å in the adduct **7**)] and the carbonyl C–O bond has already stretched by *ca.* 0.1 Å to a distance midway between the C=O (*ca.* 1.22 Å) and the C–O bond in **7** (*ca.* 1.38 Å). The water oxygen–hydrogen distance is already elongated from *ca.* 0.97 to 1.24 Å. For the second step—ring opening of the adduct **7** to the carboxylic acid **8**—completely different results are obtained with the two semi-empirical methods. Whereas according to AM1 calculations in TS **(7–8)** the lactone ring is almost completely opened [R(C–O) *ca.* 2.96 Å] and stabilised by an intramolecular hydrogen bond to the hydroxy group [see Fig. 1(*b*)] with the PM3 method a four-membered cyclic transition state with a largely intact lactone ring [R(C–O) *ca.* 1.62 Å] and involving mainly proton transfer is obtained [see Fig. 1(*c*)]. This difference in structure also manifests itself in the transition state frequencies [ν(AM1) *ca.* 500–530 i; ν(PM3) *ca.* 2340–2410 i cm^{-1}] as well as in the calculated activation energies; according to AM1 the activation energies for addition of H_2O [TS (**5–7**), see Table 1] are considerably higher (>10 kcal mol^{-1}) than those for the second step [TS (**7–8**)]; ring opening, therefore, should proceed much faster than addition of the nucleophile. In contrast, with the PM3 method ring opening should be disfavoured over addition by *ca.* 9 kcal mol^{-1}. The AM1 results appear to be more in accordance with experiment.[7,8] It should be noted at this point that neither AM1 nor PM3 led to a stable structure for the anionic forms of **7** (corresponding to using OH^- as nucleophile). Rather, only the ring opened forms, *i.e.* anions of **8**, could be obtained, indicating a quite low activation energy. This further demonstrates that the AM1 results should be more reliable for this reaction step. The ring opened enol **8** either can directly add the second nucleophile or prior to this addition isomerize to the corresponding keto tautomer **11**.

The transition states for addition of the second nucleophile to **8**, *i.e.* TS (**8–9**) closely match the structures of TS (**5–7**) as do those for addition to the keto tautomer [TS (**11–12**), see structure (*a*) in Fig. 1]. Also very similar are the transition state frequencies (TS (**8–9**): ν(AM1) *ca.* 1960 i, ν(PM3) *ca.* 2210 i; TS (**11–12**): ν(AM1) *ca.* 1980 i, ν(PM3) *ca.* 2230 i cm^{-1}), indicating an analogous mechanism. In the latter ones a stabilising intramolecular hydrogen bond between one H-atom of the approaching water molecule and the keto carbonyl function is present, leading to a lower activation energy (3–4 kcal mol^{-1}) for TS (**11–12**) as compared to TS (**8–9**). As for the opening of the first lactone ring AM1 calculations also lead to a significantly lower activation energy for opening of the second lactone ring [TS (**9–10**) and TS (**12–13**)] than for addition of the nucleophile, especially for the enol tautomer. The respective transition states [see structure (*b*) in Fig. 1] are also very similar to TS (**7–8**). According to PM3 calculations ring opening of the enol adduct **9** to the dienolic carboxylic acid **10** should require a higher activation energy than addition of H_2O except for the *m*-NO_2 derivative. Here, a two-step process involving an intramolecular hydrogen bonded highly dipolar ring open intermediate [structure (*d*) in Fig. 1] is found (in Table 1 the higher one of the two transition states *i.e.* the one for proton transfer, is listed). For the other derivatives the transition structure closely resembles structure (*c*) in Fig. 1. None of the anions of adducts **9** and **12** are calculated to be stable but instead only those of **10** or **13** are obtained, indicating a very low activation energy for the ring opening step. Thus, AM1 calculations appear to give a better mechanistic description. For the transformation **12** $\longrightarrow$ **13** with PM3 for each substituent a two-step process as described above was found with the first—higher energy—step being ring opening to the dipolar intermediate. With both methods the final product **14** in the reaction sequence depicted in Scheme 3 is the most stable one. Experimentally, addition of the nucleophile to the enol **8** has been proposed as the rate-determining step in the alkaline hydrolysis of the bifuranylidenediones **5**.[8] This is exactly what is found with the AM1 calculations. Moreover, the calculated activation energies for this step give an excellent correlation with the measured[8] rate coefficients (Fig. 2).

3,7-Diphenylpyrano[4,3-*c*]pyran-1,5-diones

The mechanism suggested by the calculations for the alkaline hydrolysis of compounds **6** is shown in Scheme 4. The final reaction products, *i.e.* the doubly ring opened structures (**10**, **13** and **14**) are identical to those obtained in the hydrolysis of the bifuranylidenediones **5**. The energetics for this reaction sequence are collected in Table 2.

Table 2 Calculated (AM1 and PM3) relative energies[a] for the various structures shown in Scheme 4 and the transition states between them

	AM1					PM3				
	H	*p*-MeO	*p*-Me	*p*-Cl	*m*-NO_2	H	*p*-MeO	*p*-Me	*p*-Cl	*m*-NO_2
6	−43.4	−120.0	−59.0	−56.3	−33.3	−60.0	−136.9	−79.1	−72.6	−76.1
TS (**6–15**)	48.1	48.0	48.1	47.7	46.6	48.5	48.6	48.4	48.2	47.4
15	−7.5	−7.6	−7.5	−7.9	−9.0	−3.3	−3.3	−3.4	−3.7	−4.8
TS (**15–16**)	47.3	46.8	47.2	47.1	26.0	48.4	48.5	48.4	48.3	48.0
16	−0.4	−0.5	−0.3	−0.9	−2.2	0.5	0.4	0.3	0.3	−0.5
TS (**16–17**)	46.5	46.5	46.6	45.5	43.3	46.9	47.0	46.8	46.4	45.0
17	−8.5	−8.5	−8.4	−9.3	−11.2	−3.2	−3.1	−3.3	−3.6	−5.1
TS (**17–10**)	46.8	46.3	46.9	46.2	44.9	48.4	48.3	48.5	48.1	47.5
10	−1.1	−1.1	−1.0	−1.8	−3.6	1.2	1.5	1.3	0.7	−1.6
TS (**16–18**)	62.1	61.4	61.9	61.9	61.7	57.8	57.4	57.6	57.7	57.7
18	−5.1	−5.4	−5.1	−5.4	−4.4	−4.2	−4.5	−4.1	−4.2	−3.8
TS (**18–19**)	41.8	41.5	41.8	41.4	40.6	39.3	39.4	39.3	39.3	39.8
19	−14.2	−14.6	−14.3	−14.8	−16.1	−10.5	−10.5	−10.5	−10.6	−11.1
TS (**19**–Int)	14.6	14.0	14.5	14.0	11.5	20.0	19.8	19.9	19.8	19.3
Int	3.8	2.7	3.8	3.2	1.1	−1.7	−1.8	−1.5	−2.0	0.3
TS (Int–**13**)	25.4	25.0	25.4	25.3	25.1	20.7	20.3	20.6	20.7	21.5
13	−4.1	−4.3	−4.0	−4.6	−5.9	−5.5	−5.4	−5.5	−5.5	−5.1
TS (**10–13**)	63.4	62.3	63.2	63.0	62.5	58.9	58.4	58.9	58.8	58.5
TS (**13–14**)	59.6	58.5	60.3	59.4	59.4	54.8	54.3	54.7	54.9	55.0
14	−8.3	−8.7	−7.4	−8.7	−9.7	−8.2	−8.2	−7.8	−8.0	−9.0

[a] Energies (in kcal mol^{-1}) are given relative to the separated reactants **6** + $2H_2O$ [$\Delta H_f(H_2O) = -63.2$ (AM1) and −56.9 (PM3)]; for compounds **6** their respective ΔH_f values are quoted.

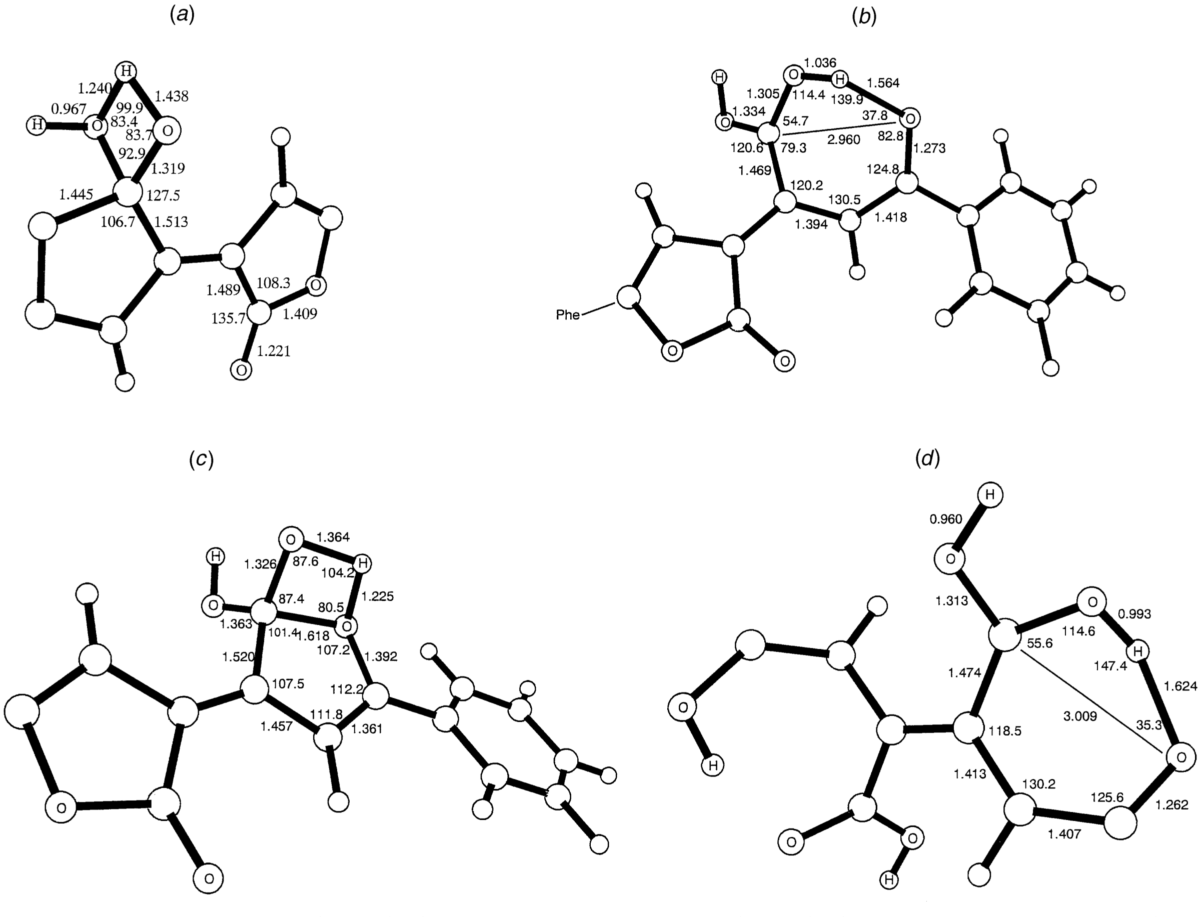


Fig. 1 (*a*) Calculated (AM1) structure for TS (**5–7**); (*b*) calculated (AM1) structure for TS (**7–8**); (*c*) calculated (PM3) structure for TS (**7–8**); (*d*) calculated (PM3) structure of the dipolar intermediate. Bond lengths (Å), bond angles (°). For clarity, only the relevant portion of the structures is shown.

With respect to the structures of the transition states for addition of H_2O to the pyranopyrandiones [TS (**6–15**)] as well as their frequencies [ν(AM1) *ca.* 1980 i, ν(PM3) *ca.* 2260 i cm^{-1}] there is essentially no difference to the corresponding ones for addition to bisfuranylidenediones [TS (**5–7**)]. The calculated activation energies are, however, considerably higher. In fact, $\Delta H^{\ddagger}$ for this step is even higher than the activation energy for the rate-determining step, *i.e.* TS **(8–9)**, of the reaction of the five-membered lactones by *ca.* 1–2 kcal mol^{-1}. For the ring opening of the primary intermediate not only with PM3 but also with AM1 a transition structure with a largely intact six-membered lactone ring and a four-membered cyclic array for proton transfer [see Fig. 3(*a*)] is obtained. The only exception is the AM1 result for the *m*-NO_2 derivative; here a two-step

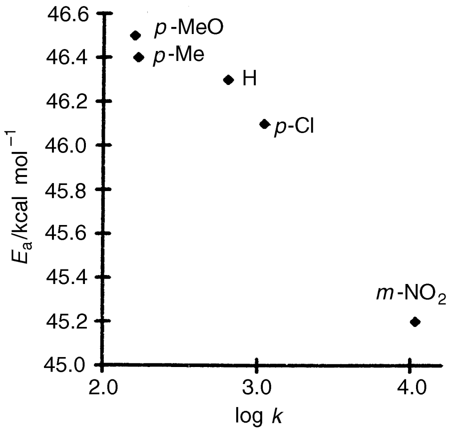
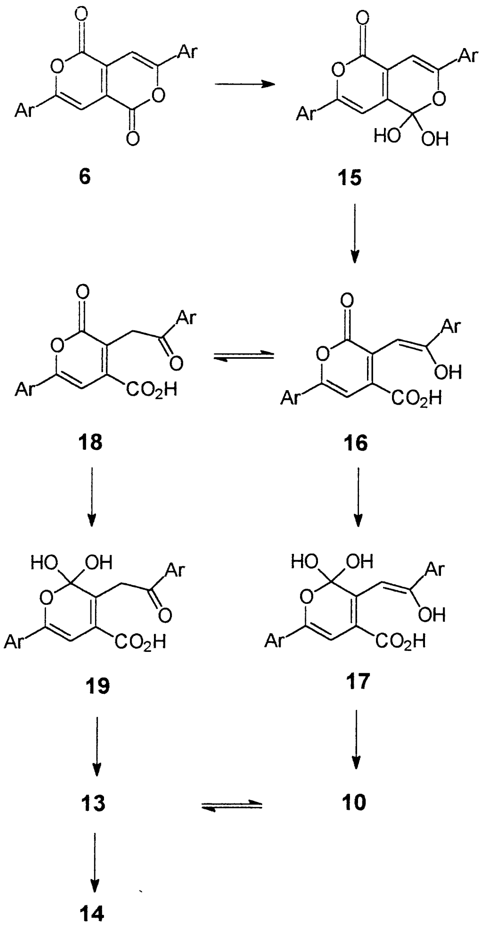


Fig. 2 Plot of experimental log *k* values (H: 2.81, *p*-MeO: 2.20, *p*-Me: 2.22, *p*-Cl: 3.04, *m*-NO_2: 4.03)[8] *vs.* AM1 calculated activation energies for addition of the second nucleophile TS (**7–8**) to compounds **5**



Scheme 4

mechanism–ring opening to a highly dipolar hydrogen bonded intermediate similar to (*d*) in Fig. 1 followed by proton transfer [see structure (*b*) in Fig. 3 for the transition state of this process]. The energy given in Table 2 refers to this step which is higher in energy than the opening to the dipolar intermediate. Consequently, except for the *m*-NO_2 derivative, the activation energies for this step will be overestimated.

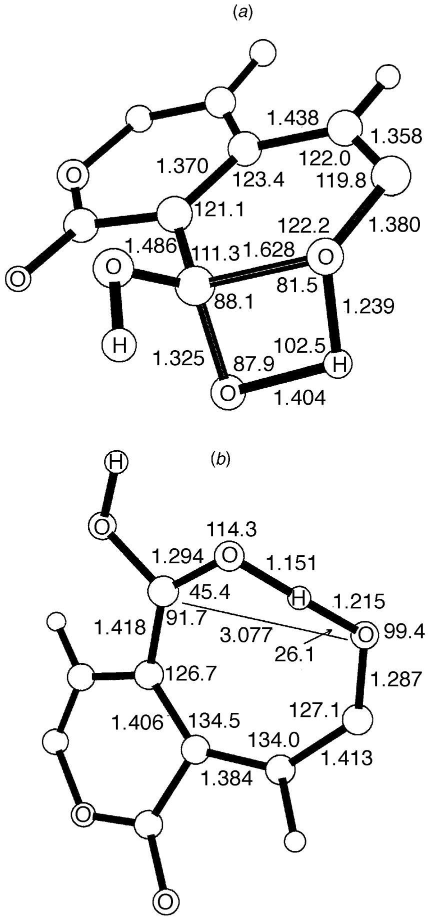


Fig. 3 (*a*) Calculated (AM1) structure of the transition state TS (**15–16**) for ring opening of the first lactone in pyranopyrandiones **6** for R = H, *p*-MeO, *p*-Me and *p*-Cl; (*b*) calculated (AM1) structure of the transition state TS (**15–16**) for ring opening of the first lactone in pyranopyrandiones **6** for R = *m*-NO_2. Bond lengths (Å) and bond angles (°). For clarity, only the relevent portion of the structures is shown.

It should be noted, however, that except for this latter molecule, calculations for addition of the hydroxide anion lead to stable tetrahedral intermediates in striking contrast to the five-membered counterparts. Also in contrast to the reaction of the bifuranylidenediones is the slightly lower calculated activation energy [TS **16–17**] for the addition of the second nucleophile to enol **16** of the monocyclic lactone. By symmetry, however, the rate coefficient for addition to the bicyclic lactones **5** and **6** should be twice that for addition to the monocyclic ones **8** and **16** which translates into a *ca.* 0.5 kcal mol^{-1} lowering of the activation energy for the first addition step. For the bifuranylidenediones this effect only further strengthens the assumption of TS (**8–9**) being rate determining. Concerning the rate-determining step [TS (**6–15**) or TS (**16–17**)] of the alkaline hydrolysis of the pyranopyrandiones the results are less clear-cut. With both transition states a good description of substituent effects on reaction rates can be obtained. As an example, in Fig. 4 a plot of experimental log *k* values *vs.* calculated (PM3) activation energies for addition of the second nucleophile is shown. For the ring opening [TS (**17–10**)] of this second tetrahedral intermediate both methods give for all derivatives a transition structure similar to (*a*) in Fig. 3 and, correspondingly, a rather high activation energy and transition frequencies characteristic for proton transfer [ν(AM1) *ca.* 1960 i cm^{-1}, ν(PM3) *ca.* 2210 i cm^{-1}]. Again, calculations for the addition of OH^- predict a stable reaction product in contrast to the five-membered lactones. For the analogous reaction of the keto tautomer not only the PM3 method—as was the case for the bifuranylidenediones—predict a two-step mechanism [(*d*) in Fig. 1] but also AM1. Again, although thermodynamically feasible, the pathway involving reaction of the enols rather than the keto forms appears to be more consistent with the experimental observations. Finally, the end product **14** of the reaction sequence depicted in Scheme 4, which is identical to that in Scheme 3, is among the most stable ones—at least if the enol pathway is followed. It will be further stabilised in the alkaline conditions by forming the corresponding dianion.

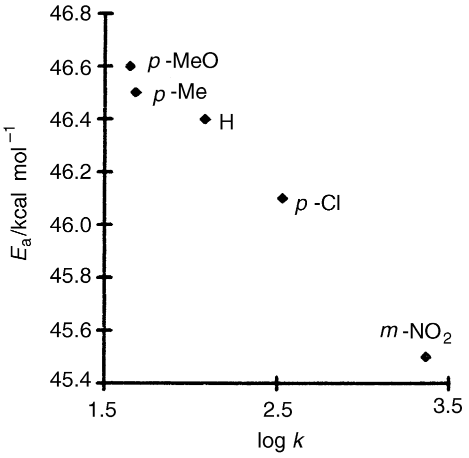


Fig. 4 Plot of experimental log k values (H: 2.08, p-MeO: 1.64, p-Me: 1.68, p-Cl: 2.53, m-NO$_2$: 3.37)[8] *vs.* PM3 calculated activation energies for addition of the second nucleophile [TS (**16**–**17**)] to compounds **6**

Conclusions

The calculations presented in this paper give a detailed picture of the alkaline hydrolysis of Pechmann dye type unsaturated five- and six-membered lactones to diphenacylfumaric acids—a reaction which has been used as structure proof[3] of a recently described analogous compound (**2** and **3** in Scheme 2). Both systems—(E)-5,5′-diphenylbifuranylidenediones **5** and 3,7-diphenylpyrano[4,3-c]pyran-1,5-diones **6**— follow a quite similar mechanism. Consistent with experiment, bifuranylidenediones **5** are predicted to be more reactive than their six-membered isomers. Addition of the nucleophile to the second lactone ring of the monocarboxylic acids **8** (or their keto forms **11**) is the rate-determining step (for the pyranopyrandiones addition of the first nucleophile might be competitive). A pathway involving the enols (**8**–**9**–**10** and **16**–**17**–**10**) is more likely than one involving the respective keto tautomers (**11**, **12**, and **18**, **19**). The effect of substituents on reaction rates, *i.e.* slight retardation by electron donors (p-MeO, p-Me) and moderate (p-Cl) to strong (m-NO$_2$) acceleration by acceptors on both systems is in excellent agreement with calculated activation energies. AM1 calculations seem to fit experimental data better than do the PM3 results.

Calculational details

All semi-empirical AM1[14] and PM3[16] calculations were done by using the VAMP program.[20] Geometries were completely optimized by the eigenvector following routine. Transition states were approximately located by reaction path calculations, refined by gradient norm minimization and characterised as true transition states by force constant calculations. Downhill optimizations (intrinsic reaction coordinate (IRC) calculations) along both directions of the normal mode corresponding to the imaginary frequency established the two minima connected by the transition structure in question. Solvent effects (H_2O) were approximated by the SCRF[19] method. For the ring open compounds prior to the semi-empirical calculations a detailed conformational search by the random search routine of the SYBYL[21] molecular modelling package was carried out. Each one of the structures found thereby was then optimized by semi-empirical methods.

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