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Molecular Mechanics/Continuum Reaction Field/Quantum Mechanics Study of the Intramolecular Diels−Alder Reaction of 2-Furfuryl Derivatives

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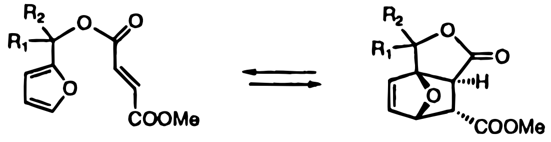
Molecular mechanics (SIBFA)/continuum reaction field computations have been performed on 2-furfuryl fumarates (**1**). The results show that the presence of a methyl or *gem*-dimethyl substituent on the diene−dienophile linker and also polar solvents such as DMSO stabilize the folded conformation precursor of the transition state in the intramolecular Diels−Alder reaction. The calculated variations of the energy difference between the folded and extended conformations are in agreement with experimental and related theoretical data. A detailed analysis of the energy contributions involved in these phenomena has been carried out, taking into account the experimental results. Complementary AM1 computations have also been undertaken on the starting materials, the transition states, and the cycloadducts. Those confirm that the stereochemistry of the lactones obtained is the thermodynamically favored one and that the variation in the activation barrier runs parallel to the SIBFA folding energy values. When the ester linkage is replaced by a ketone (**4**), the SIBFA results underestimate the activation by the spacer substitution while the AM1 transition states data overestimate it. In this case, none of these theoretical approaches is completely satisfactory when compared to experiment.

Introduction

Interest in the intramolecular version of the Diels−Alder reaction (IMDA) has increased considerably over the last 20 years. Because it has found elegant, economical, and stereocontrolled applications in the construction of polycyclic skeletons of special interest in the synthesis of natural products,[1] the IMDA compares very favorably with its intermolecular [4 + 2] counterpart. However, many limitations are reported for this reaction, generally with regard to the regio- and stereoselectivities it affords, which are known to depend mainly on connecting chain length and structure as well as the diene configuration.[2] The physicochemistry underlying the kinetic and thermodynamic parameters of this reaction remains poorly understood even though it is of prime importance in elucidating the key parameters controlling these selectivities.



1a: $R_1 = R_2 = H$
1b: $R_1 = H, R_2 = Me$
1c: $R_1 = R_2 = Me$

2a: $R_1 = R_2 = H$
2b: $R_1 = H, R_2 = Me$
2c: $R_1 = R_2 = Me$

In this context, an extensive study of 2-furfuryl methyl fumarates **1** has recently shown that the rate of intramolecular cyclization into the corresponding bicyclic lactones **2** (eq 1) increases dramatically upon *gem*-dialkyl substitution of the carbons in the chain tethering the two reactive centers (*gem*-dialkyl effect).[3a,b] The rate of this reaction was also found to be strongly solvent dependent, its rate increasing rapidly with the solvent dielectric constant. Furthermore, the same cyclization experiment carried out on similar compounds in which the ester linkage was replaced by a ketone (**4**) showed that the *gem*-dialkyl effect is also present but reduced by 1 or more orders of magnitude.[3c] Experimental data[3a,b] for the cyclobutyl derivative also provided clear evidence of the minor contribution of the angle compression (Thorpe−Ingold effect) to the rate increase, while the values of the kinetic activation parameters link the acceleration almost exclusively to the lowering of the enthalpy of activation with little contribution from entropy.[3b] A recent theoretical investigation of this effect using the WIZARD/MM2[4] procedure has led to the conclusion that, in agreement with the Curtin−Hammett principle, the acceleration is indeed determined mainly by reductions of the overall $\Delta H^{\ddagger}$, presumably related to the stabilization of the folded conformations. On the other hand, the experimental results allowed a convincing assignment of the unexpected strong solvent influence to the passage through more polar transition states stabilized in polar solvents.[3a,b] The selective stabilization of the *E*-isomer of esters by polar solvents was shown convincingly by a new NMR technique for measuring the ground-state populations of formate esters.[3d] This interpretation is supported by the results of Monte Carlo simulations of the solvent effects on *Z* and *E* forms of acetic acid[5] and methyl acetate[6] as

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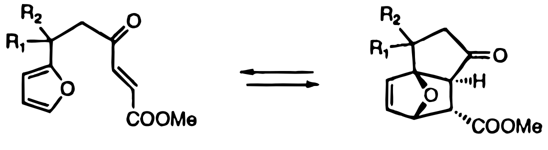
well as from an investigation of methyl formate and methyl acetate solvation using the Onsager reaction field.[7]

This set of experimental and theoretical data suggests that a theoretical study of the relative stabilities, in different solvents, of the extended and folded conformations could account for the observed variation of the intramolecular cyclization rate of some of the 2-furfuryl derivatives studied. To take place, the cyclization reaction indeed requires a folding of the trienic structure to place the diene and the dienophile in an approximate face to face situation. The local energy minima corresponding to folded conformations will provide a zeroth order approximation of the transition state and of the variations they undergo on substitution and changes in the solvent. This approach is similar to Lightstone and Bruice's[8] "near attack conformation" (NAC) search but is based on energy criteria rather than on geometrical ones. The availability of a very homogeneous body of experimental data[3] as well as the strong $\Delta H^{\ddagger}$ component in the *gem*-dialkyl effect (see above) should render such an approach especially meaningful. Using an integrated procedure[9] interfacing SIBFA[10] (sum of interactions between fragments ab initio computed) molecular mechanics systematics and the Langlet−Claverie[11] continuum reaction field method offers the advantage of providing access not only to the forces responsible for the stabilization of the pretransition state but also to those accounting for the solvent contribution to the reaction rate. Furthermore, semiempirical (because of the size of the system considered) quantum mechanical calculations have been performed on the final possible cycloadducts as well as on the transition states. The former results will be used to assess the relative stabilities of the products with respect to the corresponding starting material, a result of interest considering that only one of the two possible epimers is selectively formed experimentally. The latter will provide values to which the variation of the folding energies upon substitution could be compared and indications on the conformational differences between the folded forms and the TS. In addition, because of the important role played by the tethering group on the cyclization rate as evidenced by the slower rate enhancements of the corresponding keto esters **4**[3c] (see above and eq 2), it was worth repeating the same set of computations on **4a**−**c**. The conclusions of the comparison of the reactions of **1** and **4** could eventually help to extend the scope of this study since comparable observations have recently been made for amide intramolecular cyclizations.[12,13]



4a: $R_1 = R_2 = H$
4b: $R_1 = H$, $R_2 = Me$
4c: $R_1 = R_2 = Me$

5a: $R_1 = R_2 = H$
5b: $R_1 = H$, $R_2 = Me$
5c: $R_1 = R_2 = Me$

Computational Details and Input

We chose to use the sum of interactions between fragments ab initio computed (SIBFA) molecular mechanics systematics[10] since a previous study involving sterically demanding folded conformations with strong through-space interactions had shown good agreement with the corresponding experimental results.[14] The precision of the results obtained by the SIBFA procedure relies to a large extent on the quality of the distributed multipoles used for the computation of the electrostatic and polarization contributions.[9,10] These multipoles are obtained from preliminary post Hartree−Fock ab initio calculations on molecular fragments.[9] The fragments used here to build up the molecules under study are a furan ring, methane molecule(s), methyl fumarate, or methyl 4-oxopenten-2-oate. For the first two fragments, the experimental geometries have been used.[15] For the two latter ones, the geometrical and conformational parameters were obtained from a complete geometry optimization that has been carried out within the framework of density functional theory (DFT), using the B3P86 functional,[16] since it has been shown in numerous cases that this method provides bond length and angle values as well as relative conformational energies in good agreement with those obtained from an MP2 treatment but at a lower computational cost.[17] These two unsaturated fragments required further breakdown into more elemental pieces to take into account the existing conjugation while allowing rotations, preliminary to the cyclization process, around otherwise rigid bonds. The methyl fumarate molecule has thus been split into two methane and two water molecules plus one ethylene and two formaldehyde units. Methyl 4-ketopenten-2-oate was similarly divided into two methane molecules, only one water molecule, one ethylene unit, and two formaldehyde units. The multipoles calculated for the original whole fragment were then spread over these subfragments. As done previously,[9] the 6-31++G** basis set has been used for these nonempirical calculations that were carried out with Gaussian 92/DFT.[18] All molecular mechanics and continuum solvent effects parameters are identical to those used in ref 9. Therefore, the reported contributions to the total intramolecular energy (E_{intra}) are electrostatic (Elec), polarization (Pol), dispersion (Disp), repulsion (Rep), and torsion (Tor) (ref 14 provides a precise description of these terms). For the solvation internal energy variations (E_{solv}), the components reported are the sum of electrostatic and polarization (El + Pol), the cavitation (Cav), and the sum of the dispersion and repulsion (Disp + Rep). The computational steps concerning solvent effects have been validated on a number of reference compounds in a previous study.[9]

All semiempirical calculations on the unfolded conformation of compounds **1** and **4**, of cycloadducts **2**, **3**, **5** and **6**, and of

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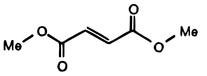
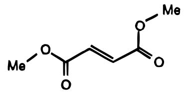
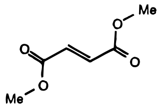
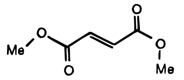
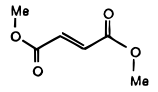
(18) GAUSSIAN 92, Revision B: Frisch, M. B.; Trucks, G. W.; Head-Gordon, M.; Gill, P. M. W.; Wong, M. W.; Foresman, J. B.; Johnson, B. G.; Schlegel, H. B.; Robb, M. A.; Replogle, E. S.; Gonperts, R.; Andres, J. L.; Raghavachari, K.; Binkley, J. S.; Gonzalez, C.; Martin, R. L.; Fox, D. J.; Defrees, D. J.; Baker, J.; Stewart, J. J. P.; Pople, J. A. Gaussian, Inc., Pittsburgh, PA, 1992.

Table 1. Calculated DFT Energies of the Different Possible Conformers of Methyl Fumarate

	Conformer	E_{tot} (a.u.)	E_{rel} (Kcal/Mol)
	tcct	-535.7109	0.0
	tctt[a]	-535.7095	+0.9
	tctt[b]	-535.7089	+1.3
	tttt	-535.7084	+1.6
	tccc	-535.6975	+8.4
	cccc	-535.6843	+16.7

[a] Staggered OCH_3 group. [b] Eclipsed O-CH_3 group.

the corresponding transition states have been carried out using AM1 with Dewar's original parametrization.[19]

Results and Discussion

To determine the most probable conformation of the fumarate part of the 2-furfuryl derivatives under study, we first carried out a complete geometry optimization of dimethyl fumarate under the five different threshold conformers obtained by rotation around its four significant single bonds. The corresponding energies of the optimized structures are reported in Table 1. We have labeled those by a set of c (for cisoid) and t (for transoid) referring to the C–O–C–C bond of the methyl ester in a *Z* or *E* configuration, respectively. The position of the carbonyl groups with respect to the O=C–C=C bond has been described by the same lettering system. Four-letter tags are thus obtained to characterize the conformers (see Table 1). Our computations indicate that the tcct is the most stable ground-state conformer. This result does not reproduce the crystal conformation of fumaric acid[20] or the substituted dimethyl fumarates,[21] but such a conformation has been observed in at least one substituted di *tert*-butyl fumarate.[22] At this point, it is worth mentioning that all possible conformations of the fumarate skeleton can be found in the literature.[23] This result is also supported by previous theoretical results on acrolein and other closely related compounds.[24] The fumarate constitutive fragments used from here on for the SIBFA computations were constructed from the optimized geometrical parameters and correlated wave functions obtained from the particular computation for the tcct conformer. Switching the carbonyl groups from a *Z* to an *E* configuration destabilizes the system by 0.9 kcal/mol for only one CO (tctt) or by 1.6 kcal/mol for both (tttt). We have also checked that the energy difference induced by a 60° methyl rotation around a O–CH_3 bond (that is going from a staggered to an eclipsed situation) is reasonably low (+0.4 kcal/mol). By contrast, a 180° rotation around the O=C–O–C bond induces a sharp energy rise since the tccc conformer lies at +8.4 and the cccc at +16.7 kcal/mol. However, such a rotation has to take place preliminary to the cycloaddition itself since only a tccc-type conformation puts the diene and dienophile moieties in a face to face (reactive) situation. We have thus decided to check the quality of our SIBFA data for the two threshold (tcct and tccc) cases (Table 2). Both the order and the energy gap between conformers are in reasonable agreement with corresponding DFT results, the SIBFA data slightly underestimating the destabilization experienced by the tccc conformer (7.0 vs 8.4 kcal/mol). These values nicely fit the theoretical[25] and experimental[26] data available in the literature for the syn/anti energy difference for methyl acetate (8–9 kcal/mol). The SIBFA energetic contributions in Table 2 indicate that all terms but dispersion are in favor of the tcct conformer.

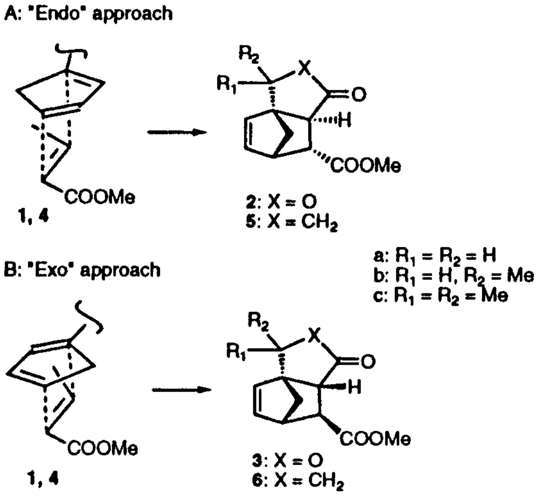


Figure 1. Schematic representation of the endo (A) and exo (B) approaches for **1** and **4**.

Table 2. SIBFA Energetical Contributions (kcal/mol) for the tcct and tccc Conformers of Methyl Fumarate

conf	Rep	Disp	Pol	Elec	Tor	E_{tot}	ΔE
tcct	550.7	−37.9	−76.2	174.3	−33.0	577.9	0.0
tccc	559.7	−44.6	−73.5	176.3	−33.0	584.9	+7.0

Three threshold conformers have been considered. They correspond to the extended (unfolded) situation along with the two possible folded ones. Figure 1 shows that two approaches between the diene and the dienophile are possible, which are named "endo" and "exo" with respect to the relative orientation of the terminal methyl ester group and the diene of the furan. While the endo approach yields the cycloadducts **2** or **5** (Figure 1A), the exo mode would lead to the unobserved diastereomers **3** or **6** (Figure 1B).

Let us now consider the *gem*-dialkyl effect on the cyclization of the fumarates **1**. The first three entries of Table 3 indicate that folding the extended conformation

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(25) (a)Wang, X.; Houk, K. N. *J. Am. Chem. Soc.* **1988**, *110*, 1870. (b) Wiberg, K. B.; Laidig, K. E. *J. Am. Chem. Soc.* **1988**, *110*, 1872.

(26) Blum, C. E.; Gunthard, H. H. *Chem. Phys. Lett.* **1981**, *84*, 267.

Table 3. SIBFA and Solvent Contributions (kcal/mol) to Conformational Energy Minima of Diesters 1a−c Under Their Threshold "Extended" ("Extd"), "Endo", and "Exo" Conformations in Vacuum, Chloroform, and Dimethyl Sulfoxide (ΔE in Parentheses)

solvent	compd	conf	Rep	Disp	Pol	Elec	Tor	E_{intra}	El + Pol	Disp + Rep	Cav	E_{solv}	total
none	**1a**[a]	extd	578.5	−47.1	−77.7	135.9	−42.3	547.2					547.2
		endo	581.0 (+2.5)	−52.3 (−5.2)	−76.9 (+0.8)	141.5 (+5.6)	−35.2 (+7.1)	558.3 (+11.1)					558.3 (+11.1)
	1b[a]	extd	613.8	−54.7	−80.1	105.5	−42.3	542.2					542.2
		endo	618.3 (+4.5)	−61.7 (−7.0)	−79.5 (+0.6)	110.8 (+5.3)	−35.2 (+7.1)	552.8 (+10.6)					552.8 (+10.6)
	1c[a]	extd	652.9	−66.0	−83.0	71.5	−42.5	532.9					532.9
		endo	652.4 (-0.5)	−70.8 (−4.8)	−82.0 (+1.0)	75.6 (+4.1)	−35.1 (+7.4)	540.8 (+7.9)					540.8 (+7.9)
$CHCl_3$	**1a**[a]	extd	578.7	−47.2	−77.7	136.1	−42.5	547.4	−13.5	−24.7	10.1	−28.2	519.2
		endo	580.4 (+1.7)	−51.6 (−4.4)	−76.9 (+0.8)	141.8 (+5.7)	−35.3 (+7.2)	558.4 (+11.0)	−15.4 (−1.9)	−23.6 (+1.1)	9.2 (−0.9)	−29.8 (−1.6)	528.5 (+9.3)
	1b	extd	613.6	−54.6	−80.0	106.2	−42.7	542.5	−13.6	−26.8	10.5	−29.9	512.6
		endo	618.4 (+4.8)	−61.7 (−7.1)	−79.4 (+0.6)	110.9 (+4.7)	−35.2 (+7.5)	552.9 (+10.4)	−15.2 (−1.6)	−25.5 (+1.3)	9.5 (−1.0)	31.2 (−0.3)	521.6 (+9.0)
		exo	616.2 (+2.6)	−59.5 (−4.9)	−79.6 (+0.4)	109.8 (+3.6)	−35.6 (+7.1)	551.3 (+8.8)	−14.9 (−1.3)	25.6 (+1.2)	9.6 (−0.9)	−31.0 (−0.1)	520.3 (+7.7)
	1c	extd	652.6	−65.7	−82.8	72.1	−43.0	533.2	−13.3	−28.3	10.6	−31.0	502.2
		endo	652.3 (-0.3)	−70.0 (−4.3)	−82.0 (+0.8)	75.5 (+3.4)	−35.0 (+5.0)	540.9 (+7.7)	−14.6 (−1.3)	−27.3 (+1.0)	9.7 (−0.9)	−32.2 (−1.2)	508.7 (+6.5)
		exo	649.5 (-3.1)	−66.7 (−1.0)	−82.4 (+0.4)	74.2 (+2.1)	−36.7 (+6.3)	537.9 (+4.7)	−13.9 (−0.6)	−27.6 (+0.7)	9.9 (−0.7)	−31.6 (−0.6)	506.3 (+4.1)
DMSO	**1a**[a]	extd	578.5	−47.0	−77.7	136.5	−42.8	547.6	−13.3	−28.2	19.4	−22.1	525.4
		endo	582.4 (+3.9)	−53.3 (−6.3)	−77.0 (+0.7)	141.6 (+5.1)	−35.4 (+7.4)	558.2 (+10.6)	−14.8 (−1.5)	−26.5 (+1.7)	17.5 (−1.9)	−23.9 (−1.8)	534.3 (+8.9)
	1b[a]	extd	614.1	−54.9	−80.1	105.6	−42.3	542.3	−12.6	−30.5	20.2	−22.9	519.4
		endo	618.4 (+4.3)	−61.7 (−6.8)	−79.4 (+0.7)	110.9 (+5.3)	−35.2 (+6.9)	552.9 (+10.6)	−14.6 (−2.0)	−29.0 (+1.5)	18.1 (−2.1)	−25.5 (−2.6)	527.4 (+8.0)
	1c	extd	652.6	−65.7	−82.8	72.1	−43.0	533.2	−12.8	−32.2	20.4	−24.6	508.6
		endo	652.4 (-0.2)	−70.0 (−4.3)	−82.0 (+0.8)	75.5 (+3.4)	−35.1 (+7.9)	540.8 (+7.6)	−14.0 (−1.2)	−31.0 (+1.2)	18.6 (−1.8)	−26.4 (−1.8)	514.5 (+5.9)
		exo	649.4 (-3.2)	−66.6 (−0.9)	−82.4 (+0.4)	74.2 (+2.1)	−36.6 (+6.4)	538.0 (+4.8)	−13.4 (−0.6)	−31.2 (+1.0)	18.9 (−1.5)	−25.6 (−1.0)	512.3 (+3.7)

[a] No exo local minimum found.

of **1** is, in vacuum, an energetically unfavorable process and that only the endo processes correspond to local minima since we were unable to locate any "stable" exo conformation. The total energy values also clearly show that progressive substitution of the furfurylic position decreases the extended-folded energy gap because the first methyl group (**1a** to **1b**) lowers it 0.5 kcal/mol while the second one (**1b** to **1c**) lowers it an additional 2.7 kcal/mol. These results, which are in qualitative agreement with corresponding experimental data, indicate that the *gem*-dimethyl effect is not a simple additive phenomenon. The particular case of the monomethyl derivative **1b** deserves further comment. This compound indeed bears an asymmetric center on the tether that splits both the "endo" and "exo" modes into two diastereomeric approaches, putting the methyl group in either a pseudoequatorial or pseudoaxial position. Experimentally, the cyclization is diastereoselective[3] and takes place, as expected, through the pseudoequatorial transition state. Preliminary calculations have confirmed that this approach is significantly preferred over the pseudoaxial one; therefore, we have limited our computations to only this case in the following study.

A close examination of the different values reported for the first three entries of Table 3 details the role of the various physicochemical contributions in vacuum. For **1a** and **1b**, the dispersion term is the only one significantly in favor of the molecular folding. It corresponds to the expected improvement of the through-space interactions between unsaturated fragments. Specific for triene **1c** is the fact that the repulsion does not increase with folding, probably because of the decrease of the steric repulsion between the *gem*-dimethyl group and the closer carbonyl group plus a furan β-proton (as can be seen in Figure 2B). As a consequence, the dispersion term does not favor the folding of this compound since both contributions (Rep and Disp) run parallel. The variation of the torsion term (Tor) was also of interest since it takes into account the conjugative stabilization between the different unsaturated fragments of the molecule. It turns out that this factor does not vary much with substitution and thus does not contribute significantly to the *gem*-dialkyl effect. The results obtained in the absence of solvent, i.e., corresponding to a "pure" *gem*-dialkyl effect, show that, within the framework of the folding as a pretransition state (or N.A.C.) hypothesis, the van der Waals forces (Rep + Disp) are the leading terms for IMDA cyclizations.

The values for **1a**−**c** in $CHCl_3$ (Table 3) show that (i) "stable" exo conformers can be found for **1b** and **1c** and are more stable than the corresponding endo arrangements; (ii) the conformations in $CHCl_3$ are very similar to those obtained in vacuum, and therefore, the intramolecular energies differ at most by 0.3 kcal/mol from the corresponding results in vacuum; and (iii) for all three compounds, the solvent effect decreases the folding energies of the endo conformers, that is, the energy difference between the folded and extended arrangements, by 1.4−1.8 kcal/mol. The results for **1a**−**c** in DMSO are qualitatively similar to the previous ones with the following differences: (i) only **1c** leads to a "stable" exo form, and (ii) the folding energy decrease is, as expected from experimental data, larger than in $CHCl_3$. Examination of the solvation energy contributions indicates that, in both solvents, the electrostatic plus polarization term (El + Pol) and the cavitation (Cav) energies contribute to the stabilization of the folded forms while

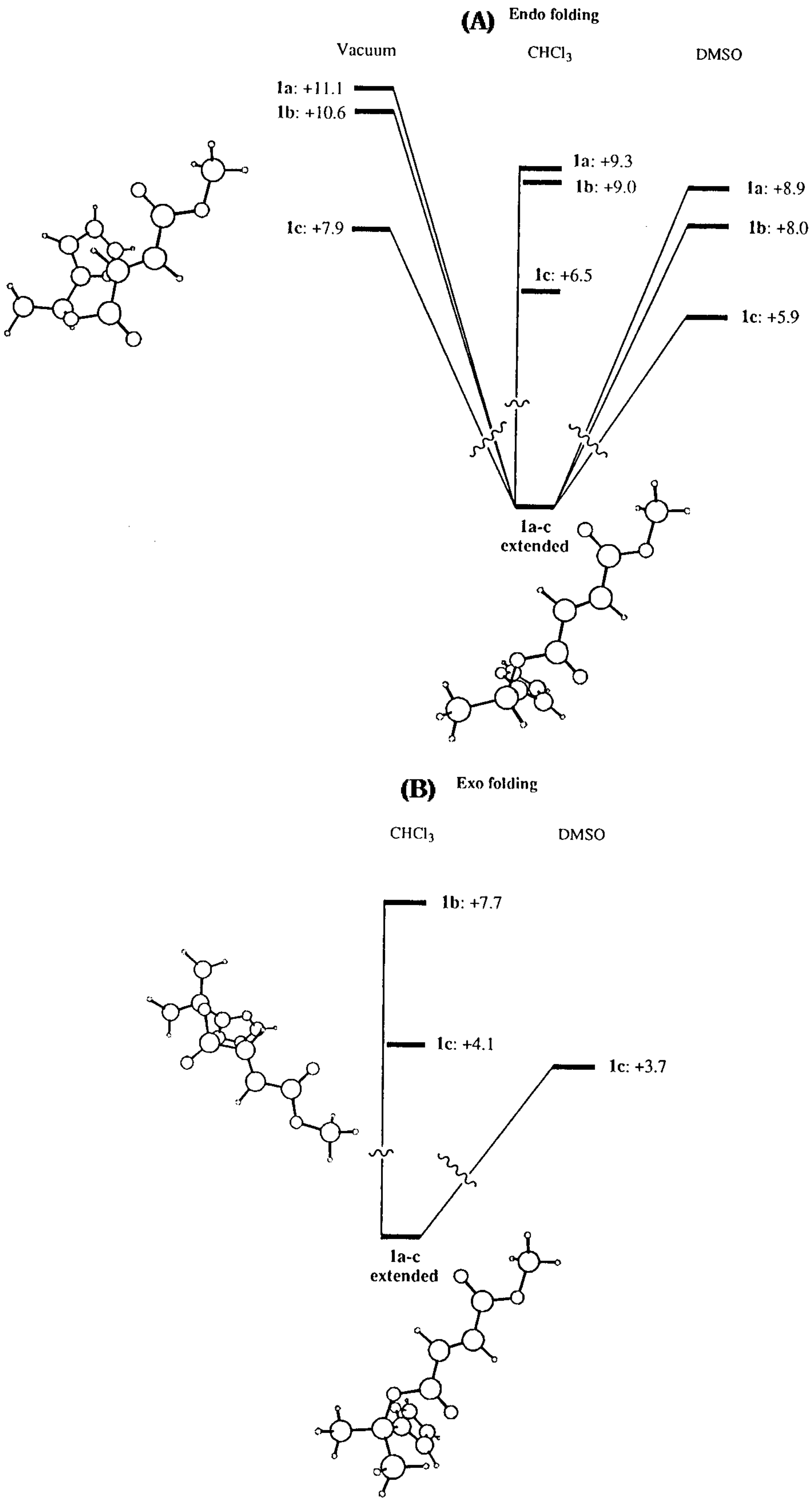

Figure 2. (A) SIBFA relative energies of the extended and endo-folded conformers of fumarates **1a**–**c** in vacuum, $CHCl_3$, and DMSO. The molecular drawings are restricted to **1b** in vacuum. (B) SIBFA relative energies of the extended and exo-folded conformers of fumarates **1b**,**c** in $CHCl_3$ and DMSO. The molecular drawings are restricted to **1c** in $CHCl_3$.

the sum of the dispersion and repulsion terms tend to hinder this process. The comparison of the solvation internal energies in $CHCl_3$ and DMSO shows that their numerical similarity comes from the cancellation of variations, in opposite directions, of the different contributions. The larger absolute E_{solv} values calculated in $CHCl_3$ are due to the larger cavitation energy in DMSO, while the variation of this quantity, upon folding, is similar in the two solvents. Noteworthy is the favorable E_{solv} variation with increasing dielectric constant that

Table 4. AM1 Energies (kcal/mol, Not Including ZPE) of Furanic Derivatives 1a−c and 4a−c under Their Extended ("Extd") Conformations Plus the "Endo" (2a−c and 5a-c) and "Exo" (3a−c and 6a−c) Stereoisomers of Their Lactones Together with the Corresponding Transition States

compd	conf	E [$\Delta(E)^a$]	TS [$\Delta(E)^b$]	compd	conf	E [$\Delta(E)^a$]	TS [$\Delta(E)^b$]
1a	extd	−142.5		**4a**	extd	−106.7	
2a	endo	−140.0 [2.5]	−106.4 [36.1/33.6]	**5a**	endo	−107.7 [−1.0]	−71.7 [35.0/36.0]
3a	exo	−122.0 [20.5]	−95.8 [46.7/26.2]	**6a**	exo	−93.0 [13.7]	−64.2 [42.5/38.8]
1b	extd	−145.4		**4b**	extd	−109.7	
2b	endo	−144.3 [1.1]	−110.3 [35.1/34.0]	**5b**	endo	−111.4 [−1.7]	−75.9 [33.8/35.5]
3b	exo	−126.1 [19.3]	−99.5 [45.9/26.6]	**6b**	exo	−97.1 [12.6]	−68.9 [40.8/28.2]
1c	extd	−144.7		**4c**	extd	−110.5	
2c	endo	−145.2 [−0.5]	−111.9 [32.8/33.3]	**5c**	endo	−113.4 [−2.9]	−77.7 [32.8/35.7]
3c	exo	−127.5 [17.2]	−101.1 [43.6/26.4]	**6c**	exo	−98.9 [11.6]	−70.4 [40.1/28.5]

[a] Difference between enthalpies of formation of products and starting material. [b] Activation barrier with respect to (1) the extended conformation and (2) the corresponding lactone.

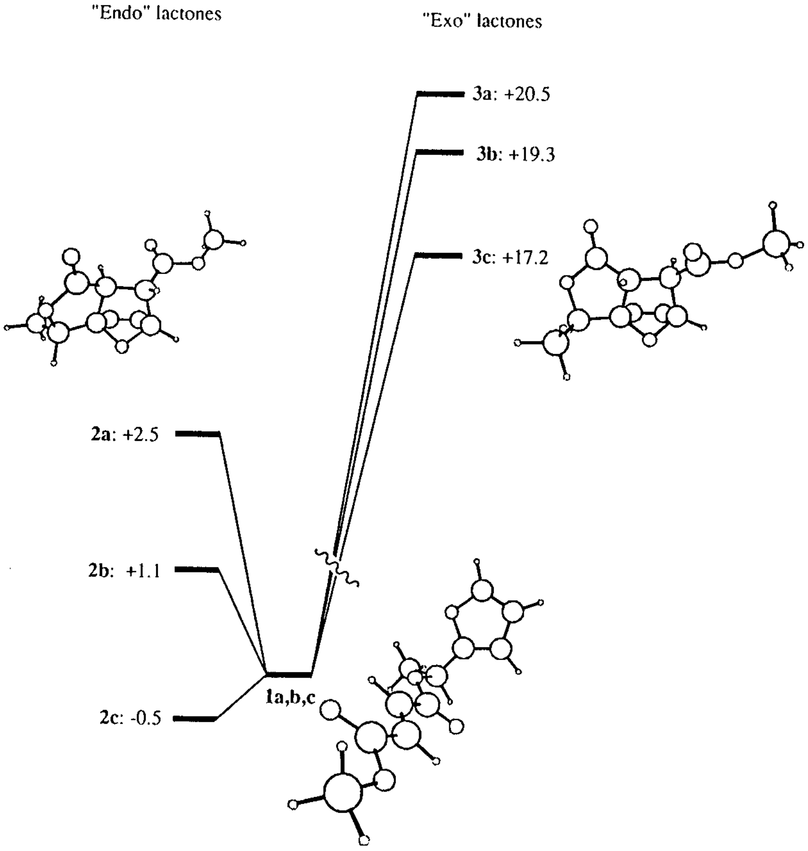

Figure 3. AM1 relative energies of the endo and exo lactones **2a**−**c** and **3a**−**c** with respect to the corresponding extended fumarates **1a**−**c**. The molecular drawings are restricted to **1b**, **2b**, and **3b**.

supports the hypothesis of the more polar pretransition state stabilized by more polar solvents,[3] although the El + Pol term takes very similar values in both solvents. One also notes that the preference for the exo folding over the endo stems mainly from intramolecular factors. The repulsion and electrostatic contributions are indeed less unfavorable to the exo than to the endo mode, and the sum of these two effects is not counterbalanced by the dispersion factor, which tends to promote the endo process. On the contrary, the contribution of E_{solv} decreases the energy difference between the two approaches. These results are summarized in Figure 2. For a given conformer, the geometrical arrangements obtained in vacuum, $CHCl_3$, or DMSO are so similar that we decided to display only one graphical representation per conformer in Figures 2 and 5. The constant decrease of the energy level of the folded conformers with substitution (going from **a** to **b** to **c**) and solvent (going from vacuum to $CHCl_3$ to DMSO) is especially evident for the endo mode (Figure 2A). The dramatic energy drop due to the *gem*-dialkyl effect (**1c**) with respect to a monoalkyl substituent on the tether (**1b**) is also evident. Figure 2B, depicting the exo folding, while very limited, presents the same overall pattern.

The improved stability of the exo-folded forms seems to yield products that do not correspond to those obtained experimentally. In order to understand the origin of this discrepancy, we carried out a set of AM1 calculations on the lactones **2a**−**c** and **3a**−**c**, the results of which are shown in Table 4 and Figure 3. These results show that the "endo" epimers **2** are favored over the "exo" ones **3** by more than 17 kcal/mol in all three cases. Therefore, the preference for the exo-folded conformers is a thermodynamic deadend since the corresponding products lie at much too high an energy to be of significance in a reversible reaction such as the cyclization studied here.

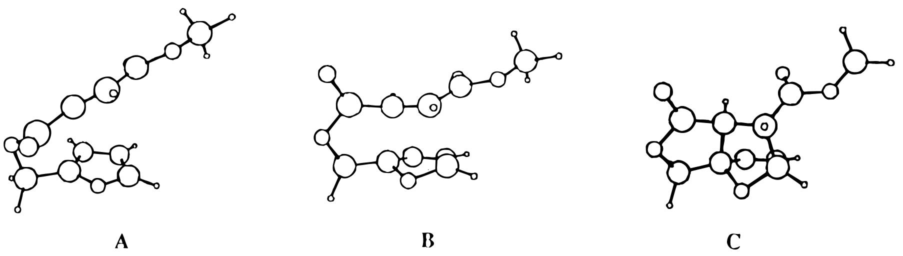

Figure 4. Molecular drawings of (a) SIBFA-folded conformation for **1a**; (b) **1a** → **2a** AM1 transition state; (c) AM1 final endo lactone **2a**.

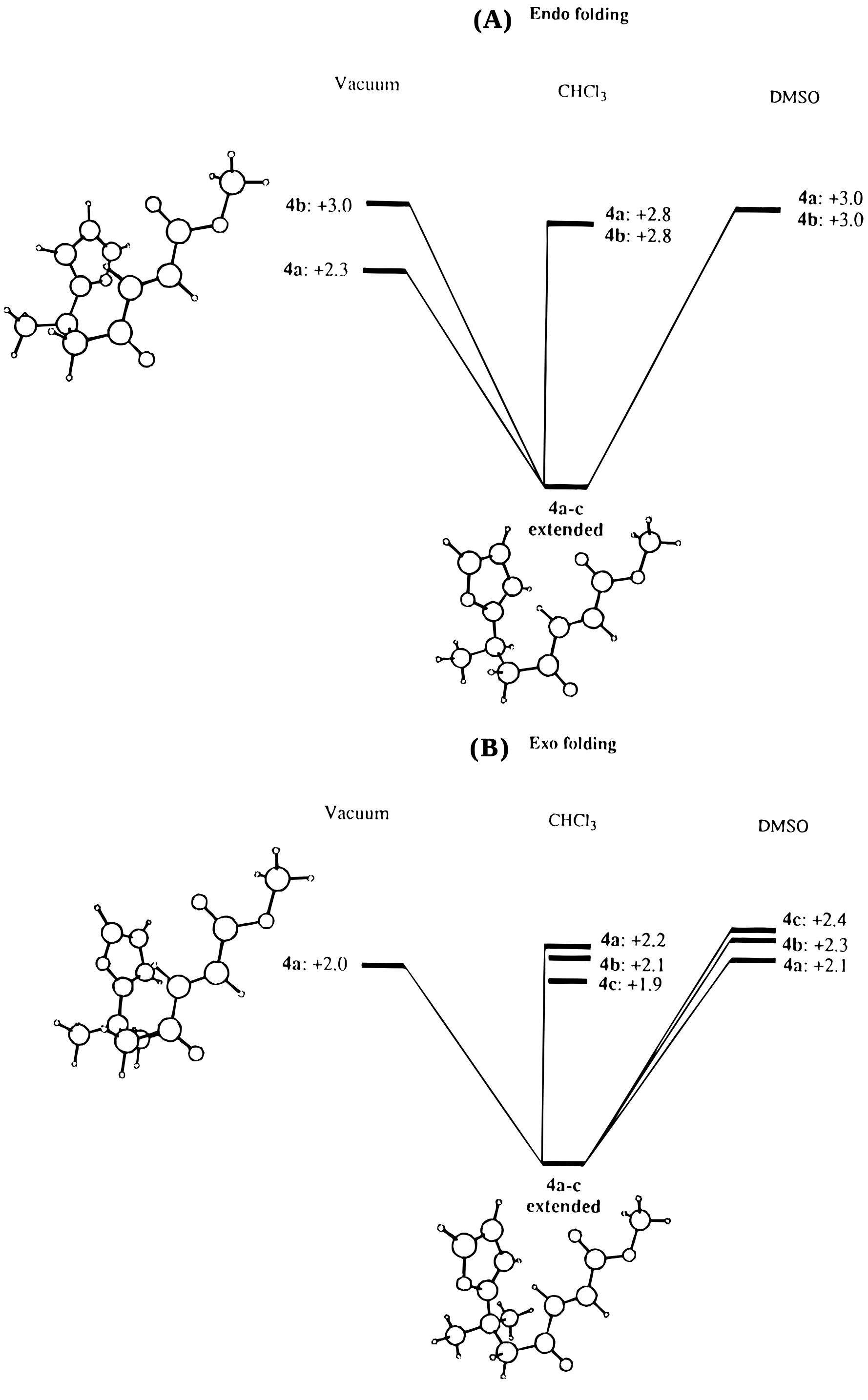

Figure 5. (A) SIBFA relative energies of the extended and endo-folded conformers of 2-furfuryl ketones **4a,b** in CHCl$_3$ and DMSO. The molecular drawings are restricted to **4b** in vacuum. (B) SIBFA relative energies of the extended and exo-folded conformers of 2-furfuryl ketones **4a**–**c** in vacuum, CHCl$_3$, and DMSO. The molecular drawings are restricted to **4c** in CHCl$_3$.

The substitution of the furfurylic position exerts a definite influence on the final products since the IMDA reaction (**1** → **2**) is decreasingly endothermic (+2.5 and 1.1 kcal/mol for **1a** and **1b**, respectively) and even

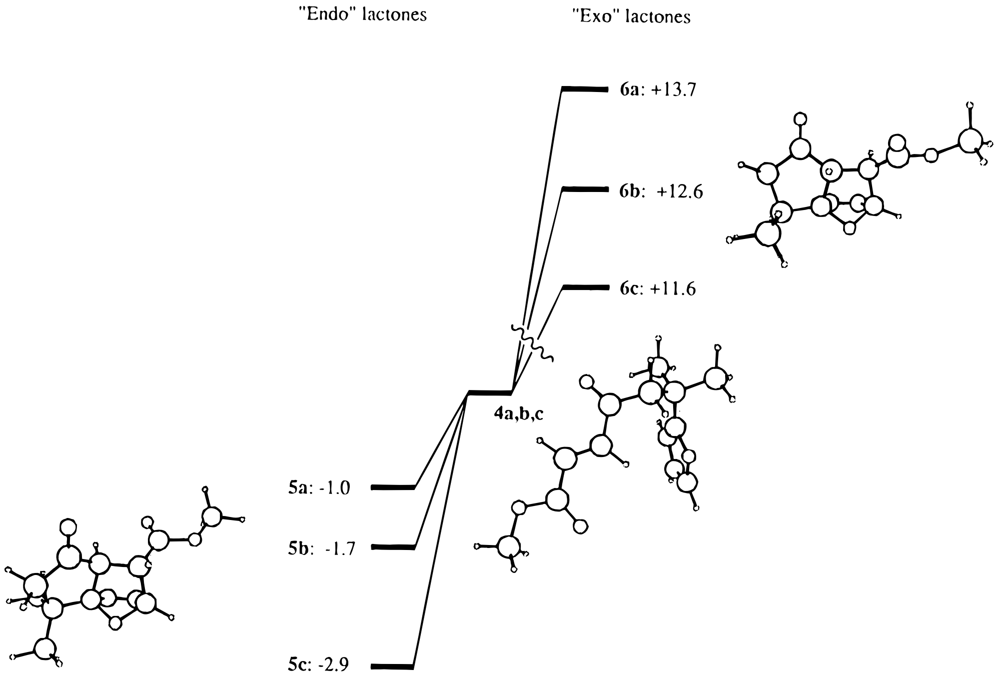

Figure 6. AM1 relative energies of the *endo*- and *exo*-cyclopentanones **5a**−**c** and **6a**−**c** with respect to the corresponding extended 2-furfuryl ketones **4a**−**c**. The molecular drawings are restricted to **4c**, **5c**, and **6c**.

becomes exothermic (by −0.5 kcal/mol) for **1c** → **2c** (Figure 3), as reported.[3b] A comparable effect is at work for the hypothetical "exo" lactones **3**. It should be mentioned that *no "stable" endo- or exo-folded conformers could be obtained from AM1 computations*. This result, partly due to the underestimation of the rotational barriers by AM1, confirms the importance of the dispersion/correlation term, which is not taken into account at the SCF level, in the stabilization of the folded pretransition states.

The values concerning the transition states obtained from AM1 computations show that the substituent effect decreases the activation energy for the formation of the endo lactones by 1.0 (for **1b** → **2b**) and 3.3 (for **1c** → **2c**) kcal/mol. These values are close to the corresponding SIBFA folding variation energies in Table 3 (0.5 and 3.2 kcal/mol, respectively). It is worth noting that, as experimentally observed for this reversible reaction, the activation energy barrier is almost identical when starting from a trienic system (starting material) or from endo lactones (product). We also see that the tabulated values concerning the exo species indicate a much higher activation energy (42−47 instead of 32−37 kcal/mol). Finally, the AM1 activation energies have numerical values within the range of those obtained from *ab initio* computations for model Diels−Alder reactions[27] but significantly larger than the measured ones.[3b] Figure 4 shows that the major conformational difference between the endo-folded conformation **1a** and its transition state to the tricyclic lactone **2a** is the distorsion from planarity of both the tethering ester group and the furan ring oxygen. The difference between this TS and **2a** concerns the terminal ester moiety and the pyramidalization of the furan α-carbons. Therefore, the transition state adopts, as expected, a conformation that lies somewhere between those of the folded reactant and of the product.

It is interesting then to compare the theoretical results obtained here to the experimental ones, first with regard to the *gem*-dialkyl effect. The activation enthalpy ($\Delta H^{\ddagger}_{298}$) for the cyclization of **1a**−**c** in CD_3CN is reported in ref 3b. Going from **1a** to **1b** and from **1a** to **1c** produces a decrease in $\Delta H^{\ddagger}_{298}$ of 1.4 and 4.9 kcal/mol, respectively, values that should be compared to those we have calculated (for pretransition states) of 0.3 and 2.8 kcal/mol in $CDCl_3$ and 0.9 and 3.0 kcal/mol in DMSO. Considering that the dielectric constant of CD_3CN (ϵ = 37.9) is between $CDCl_3$ (ϵ = 4.7) and DMSO (ϵ = 48.9), our results qualitatively account for the phenomenon but somewhat underestimate its size. Regarding the solvent effect, the same paper reports a kinetic rate ratio of 3200/220/8 for **1a**/**1b**/**1c** when going from toluene to DMSO.[3b] The corresponding values calculated from the data in Table 3 going from $CHCl_3$ to DMSO (~2/5/3) support the solvent effect but are in this case totally out of range. Obviously, in considering this kinetic data, we are reaching the limits of the approach and/or the computational method chosen for this problem.

The results concerning the keto esters **4** are reported in Table 5 and Figure 5. The energy differences between the stable endo and extended conformers are found to be significantly smaller than in the previous diester case, by an average factor of 2. We also see that a comparison of the extended and the endo-folded forms can only be made for **4a** and **4b**. As in the case of the fumarates, the exo-folded conformers are found to be more stable than the endo ones. But in the present case, the "extended" conformers already exhibit some folding, as can be seen in Figure 5. More important with respect to the experimental data is the absence in our theoretical results of any significant decrease of the folding energy upon methyl substitution. A slight decrease is seen only when **4a** and **4b** are in DMSO, but it is negligible. The "absence" of alkyl effect in these compounds has a dual origin. The dispersion term decreases on folding for **4b** while it increases in the case of **4a** and the electrostatic destabilization of the folded forms is larger for **4b** than for the unsubstituted 2-furfuryl keto ester **4a**. These two features are opposite to the corresponding data in the

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(27) Goldstein, E.; Beno, B.; Houk, K. N. *J. Am. Chem. Soc.* **1996**, *118*, 6036.

Table 5. SIBFA and Solvent Contributions (kcal/mol) to Conformational Energy Minima of Keto Esters 4a−c under Their Threshold “Extended” (“Extd”), “Endo”, and “Exo” Conformations in vacuum, Chloroform, and Dimethyl Sulfoxide (ΔE in Parenthesis)

solvent	compd	conf	Rep	Disp	Pol.	Elec	Tor	E_{intra}	El + Pol	Disp + Rep	Cav	E_{solv}	total
none	**4a**	extd	424.5	−60.0	−65.4	−32.7	−35.8	230.5					230.5
		endo	423.2 (−1.3)	−60.1 (−0.1)	−64.3 (+1.1)	−32.0 (+0.7)	−34.1 (+1.7)	232.8 (+2.3)					232.8 (+2.3)
		exo	417.7 (−6.8)	−54.7 (+5.3)	−63.6 (+1.8)	−31.0 (+1.7)	−35.9 (−0.1)	232.5 (+2.0)					232.5 (+2.0)
	4b[b]	extd	483.5	−74.3	−71.3	−53.5	−35.6	248.8					248.8
		exo	472.2 (−11.3)	−64.6 (+9.7)	−69.9 (+1.4)	−49.9 (3.6)	−36.0 (−0.4)	251.8 (+3.0)					251.8 (+3.0)
	4c[a,b]	extd	523.3	−82.6	−72.5	−78.0	−35.6	254.5					254.5
$CHCl_3$	**4a**	extd	423.9	−59.6	−65.3	−32.6	−35.6	230.8	−13.4	−25.9	9.5	−29.9	200.7
		endo	423.4 (−0.5)	−60.2 (−0.6)	−64.4 (+0.9)	−32.1 (+0.5)	−33.9 (+1.7)	232.8 (+2.0)	−19.9 (−6.5)	−25.4 (+0.5)	9.0 (−0.5)	−29.3 (+0.6)	203.5 (+2.8)
		exo	417.2 (−6.7)	−54.3 (+5.3)	−63.6 (+1.7)	−31.0 (+1.6)	−35.9 (−0.3)	232.4 (+1.6)	−13.4 (0.0)	−25.6 (+0.3)	9.3 (−0.2)	−29.6 (+0.3)	202.9 (+2.2)
	4b	extd	483.2	−74.1	−71.3	−53.4	−35.6	248.8	−12.2	−26.3	9.5	−28.9	219.9
		endo	476.1 (−7.1)	−68.2 (+5.9)	−71.2 (+0.1)	−50.5 (+2.9)	−33.9 (+1.7)	252.3 (+3.5)	−12.8 (−0.6)	−26.4 (−0.1)	9.5 (0.0)	−29.6 (−0.7)	222.7 (+2.8)
		exo	472.1 (−11.1)	−64.4 (+9.7)	−69.9 (+1.4)	−49.9 (+3.5)	−36.0 (−0.4)	251.9 (+3.1)	−13.0 (−0.8)	−26.4 (−0.1)	9.6 (+0.1)	−29.9 (−1.0)	222.0 (+2.1)
	4c[b]	extd	522.9	−82.2	−72.5	−77.9	−35.7	254.6	−12.1	−28.0	9.9	−30.2	224.4
		exo	511.9 (−11.0)	−73.0 (+9.2)	−70.9 (+1.6)	−74.2 (+3.7)	−36.1 (−0.4)	257.7 (+3.4)	−13.1 (−1.0)	−28.2 (−0.2)	9.9 (0.0)	−31.4 (−1.2)	226.3 (+1.9)
DMSO	**4a**	extd	424.5	−60.1	−65.4	−32.7	−35.8	230.5	−12.9	−29.2	18.1	−24.0	206.5
		endo	424.2 (−0.3)	−60.8 (−0.7)	−64.3 (+1.1)	−31.9 (+0.8)	−34.2 (+1.6)	233.0 (+2.5)	−12.4 (+0.5)	−28.6 (−0.6)	17.5 (−0.6)	−23.5 (+0.5)	209.5 (+3.0)
		exo	417.6 (−6.9)	−54.7 (+5.4)	−63.6 (+1.8)	−31.0 (+1.7)	−35.9 (−0.1)	232.5 (+2.0)	−12.8 (+0.1)	−29.0 (−0.2)	17.9 (−0.2)	−23.9 (+0.1)	208.6 (+2.1)
	4b	extd	482.8	−73.8	−71.2	−53.3	−35.6	248.8	−11.7	−30.0	18.3	−23.3	225.5
		endo	475.4 (−7.4)	−67.4 (+6.4)	−72.4 (−1.2)	−50.6 (+2.7)	−34.1 (+1.5)	250.7 (+1.9)	−12.6 (−0.9)	−30.0 (0.0)	18.2 (−0.1)	−24.4 (−1.1)	226.3 (+3.0)
		exo	471.8 (−11.0)	−64.2 (+9.6)	−69.9 (+1.3)	−49.9 (+3.4)	−35.9 (−0.3)	251.9 (+3.1)	−12.5 (−0.8)	−30.1 (−0.1)	18.3 (0.0)	−24.1 (−0.8)	227.8 (+2.3)
	4c[b]	extd	521.8	−81.5	−72.4	−77.7	−35.6	254.6	−11.9	−31.9	18.8	−25.0	229.7
		exo	511.5 (−10.3)	−72.5 (+9.0)	−70.9 (+1.5)	−74.3 (+3.4)	−36.0 (−0.4)	257.8 (+1.2)	−12.6 (−0.7)	−31.9 (0.0)	18.9 (+0.1)	−25.7 (−0.7)	232.1 (+2.4)

[a] No exo local minimum found for this compound. [b] No endo local minimum found for this compound.

case of the fumarates **2**. Moreover, as shown in Table 5, E_{solv} does not increase on folding in many cases. This fact, which is responsible for the absence of a solvent effect, is due to the minor variation of the El + Pol term, a result presumably due to the fact that ketones are less polar than esters. Therefore, in the present case, the SIBFA results are unable to predict satisfactorily the *gem*-dialkyl effect that, although less pronounced than for the fumarates, is still observed. No experimental information is available regarding the solvent effects in the cyclizations of **4**.

The AM1 data for cyclic ketones **5** and **6** are reported in Table 4 and Figure 6. The latter shows that this computational method leads, as SIBFA does, to some bending for the extended forms. From the tabulated values for the three compounds, it can be seen that the endo cyclization is exothermic and the energy gain increases with substitution. As in the cases of the fumarates, the exo adducts are highly unstable; therefore, the more stable exo-folded conformers correspond again to a deadend. On thermodynamic grounds, we see that the *gem*-dialkyl stabilization of the energy of formation of the adducts is less important for the cyclopentanones **5** than for the lactones **2**, which is in complete agreement with experiment. On kinetic grounds, the values of Table 4 concerning the AM1 transition states for ketones **4** exhibit a variation upon alkylation totally parallel to that obtained for the fumarates and thus overestimate the *gem*-dialkyl effect for these compounds.

Concluding Remarks

The hypothesis that there is a relationship between the stabilization of the folded conformers, considered as pretransition states, and the kinetic parameters of the IMDA reaction of the 2-furfuryl fumarates **2** is supported by SIBFA molecular mechanics and AM1 computations that are able to give a reasonable explanation for the observed *gem*-dialkyl effect. These calculations are also able to reproduce qualitatively the role of polar solvents in this reaction. The analysis of the different energetic contributions clearly emphasizes the role of van der Waals forces in the variation of the folding energy, a feature that limits the use of methods neglecting correlation such as AM1, for understanding the kinetics of such reactions. Because the pretransition state (or N.A.C.[8]) is more polar than the extended conformer, its solvation internal energy variation is larger, as proposed earlier.[3b] However, these computations and/or the working hypothesis seem to underestimate the observed effects. These limitations of our theoretical approach could explain the poor account obtained in the case of ketones **4**, which are also not properly described by the AM1 approach. Nevertheless, the calculations carried out on the final products are in good agreement with the corresponding experimental data. These results indicate that such an approach is able to accurately describe the general trends in the substituent and solvent effects in IMDA reactions and thus could provide useful information on related systems[12,13,28] as well as promote the efficient design of compounds taking advantage of these and comparable effects.

Acknowledgment. We thank Prof. K. N. Houk (UCLA) for fruitful discussions. Computations were

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performed on an RS6000/370 workstation (purchased thanks to a grant of the Conseil Régional de Haute-Normandie to J.M.) and at the Institut de Développement des Ressources Informatiques Scientifiques (IDRIS, Orsay). The assistance of a NATO-NSF travel grant to M.E.J. is gratefully acknowledged.

Supporting Information Available: Figure S1 and Tables S1−S3 giving the values for all of the dihedral angles in the methyl furfuryl fumarate derivatives **1a**−**c** and the methyl 4-ketopenten-2-oate derivatives **4a**−**c** in all of the various conformation (extended, endo, and exo) (4 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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