

Conformational Analysis of Organic Carbonyl Compounds. Part 10.† *Ab-initio* MO Calculations of the Conformational Properties of 3-Formyl-furan, -thiophene, and -pyrrole

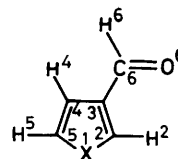
Rois Benassi, Ugo Folli, Luisa Schenetti, and Ferdinando Taddei*
 Dipartimento di Chimica, Università, Via Campi 183, 41100 Modena, Italy

The relative stability of the conformers of 3-formyl-furan, -thiophene, and -pyrrole, and the changes in conformational composition in solutions of different polarity, have been studied using theoretical methods. The total electronic energy of the ground states and that of the transition state for conformer interconversion were calculated with *ab-initio* MO methods (GAUSSIAN-82) in different AO basis sets. The energy difference between the conformers changes remarkably as a function of the AO basis sets and, as a general rule, the X,O-*trans* form is increasingly preferred in the more extended basis sets. Geometry relaxation shows that the most significant changes occur on passing from the minimal STO-3G to the 3-21G basis while further implementation fails to produce appreciable changes. The molecular parameter most affected is the exocyclic C-C bond distance which becomes shorter (from 1.50 to 1.46 Å) and approaches experimental values determined for structurally similar compounds. The calculated electronic structures of these molecules indicate that the relative stability of their conformers is a balance of conjugative interactions, polar character of the conformers, and local electrostatic interactions between the atoms of the formyl group and those of the ring; these effects give a different result in the different calculated schemes. Conformer populations were obtained by solving the Schrödinger equation for the hindered rotor and compared with those available from experimental studies. For the 3-formyl-furan and -thiophene derivatives the X,O-*trans* conformer predominates, in agreement with experimental results; for the furan derivative this conformer population increases on employing energy values from extended basis sets. For 3-formylpyrrole the N(H),O-*cis* form is energetically preferred; only to a small extent when energies from large basis sets (6-31G) are employed this conformer is favoured. Reaction field theory was applied in order to study the behaviour of the conformational equilibrium in media of different polarity and the results are compared with those of experimental studies, showing that the trends are qualitatively predicted for the three molecules examined.

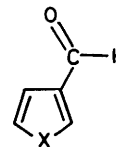
The conformational properties of 2-formyl derivatives of five-membered heterocycles have been studied extensively using experimental¹⁻⁴ and theoretical⁵⁻⁸ methods. A solvent-dependent conformational equilibrium has been demonstrated for furan-2-carbaldehyde.⁹ The relative amount of O,O-*cis*- and O,O-*trans* conformers, the former of higher polarity and lower stability, depends⁹ on the polarity of the medium, the O,O-*trans* form being predominant in the vapour phase.¹⁰ The relative stability of the conformers has been predicted with *ab-initio* MO calculations^{5,6,11,12} while classical theory of solvent effects shows^{5,9,12} that dipolar electrostatic interactions are responsible for determining the higher stability of the O,O-*cis* form in polar solution. For thiophene-2-carbaldehyde, the more polar S,O-*cis* conformation is found to be the more stable form from MO calculations^{5,7} and in the vapour phase¹³ and in solutions of different polarity it predominates (>90%).¹⁴⁻¹⁶ The amount of S,O-*cis* form increases slightly with solvent polarity^{14,16} and, from a theoretical study⁵ of solvent effect, this seems to depend on the electrostatic dipolar contribution to the solvation energy. For pyrrole-2-carbaldehyde the less polar N(H),O-*cis* form was predicted^{8,11} to be the more stable conformer with *ab-initio* MO calculations and this result is in agreement with experimental measurements.^{1-3,17}

For the 3-formyl derivatives of furan, thiophene, and pyrrole, experimental results obtained in different media sug-

gest^{1,16,17} that the X,O-*trans* conformation is preferred. The effect of solvents has been investigated by us¹⁶ for furan- and thiophene-3-carbaldehyde and have shown that for these molecules the amount of the less polar X,O-*trans* conformer increases, even to a small extent, with an increase in the polarity of the solution.



X,O-*cis*



X,O-*trans*

- (1) X = O
- (2) X = S
- (3) X = NH

From *ab-initio* MO calculations^{6-8,11} in the minimal STO-3G basis set the two conformers of compounds (1)–(3) showed a close energy content (not higher than 1.6 kJ mol⁻¹), and only for the thiophene derivative was a higher stability for the X,O-*trans* form predicted. This being the situation, we undertook a theoretical study of compounds (1)–(3), employing MO *ab-initio* calculations in different AO basis sets in order to tackle

† Part 9, preceding paper.

a number of still unsolved problems. Firstly to verify whether the lower stability found^{6,8,11} for the X,O-*trans* form of compounds (1) and (3), apparently in contrast with experimental findings, is a limitation of the minimal STO-3G basis set. Secondly, to set up a reasonable model to explain the conformational behaviour of these molecules based on their calculated electronic structure. Finally, to rationalize the changes in the conformational composition in compounds (1) and (2) in media of different polarity, and to predict whether in derivative (3) the higher stability of the N(H),O-*cis* form found from calculations may be reversed in media of increasing polarity in order to account for its observed behaviour.¹⁸ Classical reaction field theory¹⁹ is employed for exploring solvent effects.

Results from ab-initio MO Calculations.—*Ab-initio* MO calculations were performed using the GAUSSIAN-82 program²⁰ on a CRAY-X-MP/12 computer. The basis sets of the program used were STO-3G, 3-21G, 6-31G, and 6-31G*. The molecular geometry was optimized by the gradient method²¹ included in the standard calculation package.²⁰ Fully relaxed molecular geometries were obtained for the X,O-*cis* and X,O-*trans* conformers and for the transition state (localized as the saddle point in the potential energy surface) relative to *cis-trans* interconversion.

The effect of basis set extension on molecular geometry relaxation was first checked on compound (1) by performing geometry relaxation at the STO-3G, 3-21G, and 6-31G levels. On extending the AO basis set over the minimal STO-3G, significant changes occur only for the C(3)–C(6) bond distance, which passes from 1.50 (STO-3G) to 1.46 Å (3-21G) and shows no appreciable further change in the 6-31G basis set. In the transition state (TS) the most significant change on implementing the AO basis set is on the C(3)–C(6) bond distance, slightly longer (0.03 Å) than in the ground states, which decreases from 1.52 (STO-3G) to 1.48 Å (3-21G and 6-31G).

For compounds (2) and (3) geometry relaxation was limited to the 3-21G basis set and the most significant change with respect to the minimal STO-3G scheme is again the shortening of the C(3)–C(6) bond distance. This behaviour was also observed⁵ in the 2-formyl derivatives of furan and thiophene and the value of 1.45–1.46 Å, obtained in basis sets greater than the minimal STO-3G, is closer to the experimental values^{13,20,21} for carbonyl derivatives of five-membered heterocycles. Bond lengths and bond angles referring to the 3-21G approach are reported in Table 1 for compounds (1)–(3). Direct comparison with the experimental geometries of these molecules is not possible; however, calculated bond distances and bond angles are reasonably close to those of the formyl group and of the heterocyclic rings of structurally similar compounds.^{13,22,23} The geometrical features of the two conformers of each compound are quite close except for the exocyclic angles made by the C(3)–C(6) with the ring, which are significantly different in the *cis* and *trans* forms. In the transition state, besides the lengthening of the C(3)–C(6) bond distance with respect to the ground states, the most relevant characteristic is that the plane of the carbonyl group and that of the heterocyclic ring are not exactly perpendicular, the carbonyl oxygen being slightly twisted toward the C(2)–H(2) bond.

The behaviour of the relative energy of the conformers for different choices of AO basis sets is reported in Table 2. For the three compounds examined the larger sets increase the relative stability of the X,O-*trans* form. For compound (1) the minimal STO-3G approach predicts, as previously reported,^{6,11} a higher stability for the O,O-*cis* conformer, while progressive basis set implementation inverts the stability of the conformers and makes the O,O-*trans* form increasingly more stable. For compound (2) the S,O-*trans*-conformer is the more stable form but while in the STO-3G scheme the conformers are almost

isoenergetic, the relative energy (ΔE) increases in the larger basis sets. The N(H),O-*cis* conformer is the more stable form in the case of compound (3) and the conformers become progressively isoenergetic by extending the AO basis set. Less relevant appears the effect of geometry relaxation on the relative conformer energy in levels higher than the minimal STO-3G, as can be observed in Table 2, and this was also found⁵ for the corresponding furan- and thiophene-2-carbaldehyde.

In acyl derivatives of five-membered heterocycles the relative stability of the two conformers can be rationalized in terms of an oversimplification of the electronic effects which results from two factors: (i) the degree of conjugation of the C=O bond with the ring, which seems^{1,11,24} to have a maximum stabilizing effect when the C=O and the C=C bond of the ring with higher π character are in an *s-trans* arrangement, and (ii) electrostatic interactions, which relate either to the dipole moment of the conformers (the less polar conformer being preferred¹ in non-polar media and in the case of isolated molecules) or to the balance^{5,7} of attractive and repulsive interactions due to local charges on the atoms of the acyl group and of the ring. Within this scheme, the relative stability of the conformers of compounds (1)–(3) can be tentatively correlated to their electronic fine-structure with the aim of also trying to understand the fluctuations in the results given by the different AO basis sets.

The π bond orders relative to the C(3)–C(6) bond (η), calculated ($\mu_{\text{calc.}}$) and empirical dipole moments ($\mu_{\text{emp.}}$) of the conformers, and the difference between electrostatic interactions in the two conformers [$\Delta = (\Sigma_{\text{cis}} - \Sigma_{\text{trans}})$] are reported in Table 3. The values of η are greater in the X,O-*trans* than in the X,O-*cis* form of compounds (1) and (2) in the larger basis sets, while the opposite holds for compound (3). These quantities thus indicate the role played by π -conjugation among the C=O bond and the ring on the conformational stability of these compounds. The calculated dipole moments refer to the 3-21G approach, since larger sets tend^{5,25} to overestimate dipole moments. They show that the X,O-*cis* form of compounds (1) and (2) is the more polar one; for the latter compound the reversed order of polarity of the conformers is found in the STO-3G basis set. Thus, at least in non-polar media, the dipole character of compounds (1) and (2) favours the X,O-*trans* conformer. The reverse is true for compound (3). Negative values of the electrostatic interactions constant (Δ) indicate a predominance of attractive interactions and suggest that the X,O-*cis* form of compounds (1) and (3) should be favoured. For compound (2) the preferred conformer depends on the basis set employed; the S,O-*trans* form being more stable in the 3-21G.

In conclusion, from the electronic structure of compounds (2) and (3) it can be deduced that conjugative effects, the dipolar character of the conformers, and electrostatic interactions operate to stabilize one conformer. For compound (1) a balance of electrostatic and conjugative effects determines the relative stability of the conformers. The relative weight of these factors depends on the choice of AO basis set.

The energy required to interchange conformers through the transition-state (ΔE^*) is given in Table 2. These values increase on extending the basis set but fluctuations are observed in the different approaches. Experimentally, the free energy of activation is known¹⁵ only for derivative (2) (measured in solution) and this is more accurately compared with calculated values in the next section where the effects of solvents are discussed. At this stage we anticipate that the calculated energy barrier is of the order of magnitude of the experimental value¹⁵ (35.6 kJ mol⁻¹) in the extended 6-31G basis set.

Thermodynamic Equilibrium between Conformers and Solvent Effect.—Comparison of conformer populations determined experimentally with the energy difference values between the

Table 1. Total electronic molecular energy E (a.u.), bond lengths (Å), and bond angles ($^\circ$) obtained in the 3-21G basis set for ground and transition states (TS) of compounds (1)–(3)

Molecular parameter	(1)			(2)			(3)		
	O,O- <i>cis</i> -339.439 977	O,O- <i>trans</i> -339.440 176	TS -339.424 371	S,O- <i>cis</i> -660.562 500	S,O- <i>trans</i> -660.564 154	TS -660.547 219	N(H),O- <i>cis</i> -319.743 056	N(H),O- <i>trans</i> -319.741 995	TS -319.724 293
E									
C(2)-C(3)	1.345	1.345	1.340	1.340	1.339	1.335	1.365	1.366	1.359
C(2)-X	1.363	1.364	1.376	1.779	1.784	1.792	1.359	1.362	1.373
C(3)-C(4) ^a	1.449	1.447	1.451	1.445	1.446	1.450	1.434	1.431	1.433
C(3)-C(6)	1.456	1.454	1.485	1.468	1.466	1.493	1.450	1.450	1.484
C(4)-C(5)	1.338	1.336	1.339	1.334	1.332	1.335	1.355	1.353	1.358
C(5)-X	1.389	1.392	1.378	1.800	1.804	1.794	1.386	1.387	1.375
C(6)-O	1.213	1.212	1.209	1.211	1.211	1.208	1.216	1.214	1.210
C(6)-H(6)	1.084	1.085	1.084	1.085	1.085	1.084	1.086	1.088	1.086
C(2)-H(2)	1.062	1.063	1.062	1.066	1.067	1.066	1.065	1.066	1.065
C(4)-H(4)	1.066	1.064	1.065	1.070	1.068	1.069	1.067	1.065	1.066
C(5)-H(5)	1.061	1.061	1.062	1.065	1.065	1.065	1.064	1.064	1.065
N-H							0.995	0.995	0.994
X-C(2)-C(3)	109.9	109.8	109.9	111.9	111.7	111.9	108.1	108.0	108.1
C(4)-C(5)-X	109.5	109.5	109.8	111.4	111.5	111.8	107.9	107.9	108.0
C(2)-X-C(5)	107.4	107.2	107.2	89.4	89.3	89.2	109.5	109.4	109.3
C(2)-C(3)-C(6)	125.2	127.7	127.7	122.3	124.5	124.2	124.2	126.5	126.7
C(3)-C(6)-H(6)	124.2	123.9	125.0	124.3	123.5	124.9	124.7	124.8	125.4
C(3)-C(6)-O	114.4	114.7	114.4	114.4	114.8	114.2	114.4	114.3	114.6
H(6)-C(4)-C(5)	126.8	127.8	127.1	123.4	124.6	123.6	126.4	127.3	126.5
C(4)-C(5)-H(5)	134.2	134.4	133.5	128.2	128.4	127.7	130.7	130.9	130.2
C(2)-C(2)-H(2)	132.3	133.1	133.3	125.9	127.3	127.5	129.0	130.0	130.1
C(5)-N-H							125.1	125.2	125.4
O-C(6)-C(3)-C(2)	0.0	180.0	92.2	0.0	180.0	91.0	0.0	180.0	92.1
H(6)-C(6)-C(3)-C(2)	180.0	0.0	-88.7	180.0	0.0	-89.7	180.0	0.0	-88.6

^a Dependent parameter.

Table 2. Relative energy of ground states, $\Delta E(E_i - E_c)$,^a and energy barrier for conformer interconversion ΔE^* (refers to the more stable conformer) obtained for compounds (1)–(3) in different AO basis sets (kJ mol⁻¹)

Computing approach ^b	(1)		(2)		(3)	
	ΔE	ΔE^*	ΔE	ΔE^*	ΔE	ΔE^*
(STO-3G//STO-3G)	0.22	21.57	-0.06	22.40	1.35	25.27
(3-21G//STO-3G)	-0.53	39.43	-3.43	42.29	2.23	46.83
(3-21G//3-21G)	-0.52	41.29	-4.35	44.24	2.77	49.01
(6-31G//3-21G)	-1.92	38.05	-4.09	38.83	1.24	44.27
(6-31G*/3-21G)	-2.54	37.14	-4.19	37.62	0.17	42.20
(6-31G//6-31G)	-2.00	38.24				
(6-31G*/6-31G)	-3.12	37.27				

^a The symbols *t* and *c* stand for X,O-*trans* and X,O-*cis*. ^b According to standard notation the basis set on the right refers to the level of geometry relaxation.

Table 3. Calculated and empirical dipole moments, μ (10⁻³⁰ Cm), π bond orders, η , and electrostatic interactions (kJ mol⁻¹), $\Delta(\Sigma_{cis} - \Sigma_{trans})$, between the atoms of the formyl group and of the heterocyclic ring, in derivatives (1)–(3). Calculations refer to different AO basis sets

Compound	$\mu_{calc.}$		μ_{emp}	$\eta[C(3)-C(6)]$			$\Delta(\Sigma_{cis} - \Sigma_{trans})^a$	
	STO-3G	3-21G		STO-3G	3-21G	6-31G	STO-3G	3-21G
(1)	O,O- <i>cis</i>	6.14	10.62	9.34 ^b	0.1183	0.1101	0.1255	
	O,O- <i>trans</i>	4.81	7.89	8.07 ^b	0.1157	0.1103	0.1290	-2.89
(2)	S,O- <i>cis</i>	6.69	10.09	9.91 ^c	0.1192	0.1067		
	S,O- <i>trans</i>	7.16	7.12	8.64 ^c	0.1166	0.1104		-0.01
(3)	N(H),O- <i>cis</i>	10.62	15.54	14.7 ^d	0.1274	0.1383		
	N(H),O- <i>trans</i>	13.23	19.01	17.3 ^d	0.1248	0.1364		-1.85

^a The summation Σ , referred to the X,O-*cis* and X,O-*trans* forms, is expressed⁷ as $\Sigma q_i q_j / r_{ij}$, where q are atomic charges and r interatomic distances [i are the atoms of the formyl group and j those C(2), C(4), H(2), H(4), and X of the ring]. Negative values of Δ indicate either prevailing attractive interactions or the presence of minor repulsive interactions in the X,O-*cis* form. ^b D. M. Bertin, C. Chatain-Cathaud, and M.-C. Fournié-Zaluski, *C.R. Hebd. Seances Acad. Sci. Ser. C.*, 1972, **274**, 1112: from dipole moments in benzene solution. ^c A. S. Kuzharov, V. N. Sheinker, E. G. Derecha, O. A. Osipov, and D. Ya. Movshovich, *Zh. Obshch. Khim.*, 1974, **44**, 2008: from dipole moments in carbon tetrachloride. ^d Ref. 17: from dipole moments in benzene solution.

ground states of the conformers obtained from quantum mechanical calculations is an intriguing task owing to at least two factors. The first is due to the fact that a homogeneous comparison can only be achieved between free energy differences (ΔG°) measured at the same temperature. Secondly, the experimental results normally refer to dense media and of different permittivity, whereas comparisons with calculated quantities refer to isolated molecules or, at least, to the vapour phase. Knowledge of the behaviour of the conformational composition in different solvents should thus be acquired.

In order to obtain ΔG° values from *ab-initio* energies the outline of the procedure previously employed¹² for furan-2-carbaldehyde was adopted. The internal rotational potential was computed by fitting the energy values to a Fourier series [equation (1)]. For compound (1) energy values corresponding

$$V(\alpha) = \sum_n \frac{1}{2} V_n (1 - \cos n\alpha) \quad (1)$$

to the torsional angles α (45° and 135°) relative to the ground states and transition state were employed. The energies relative to the two torsional angles were obtained in the approximation of the flexible rotor.²⁶ The value of $\alpha = 0^\circ$ is that of the more stable conformer, therefore the supplementary angle of the dihedral angles reported in Table 1 was employed for compounds (1) and (2). Expansion of equation (1) for $n = 3$ and 4 was performed and the V_n s were not significantly different in the two approximations, as can be seen in Table 4 for the energy values from the 3-21G basis set. Furthermore, the calculated thermodynamic quantities obtained in the two truncations differ in the limit of the errors of their experimental determination. For determination of the energy values from the 6-31G and 6-31G* approaches only three values were employed

(ground states and transition state) and truncation for $n = 3$. The values of $V(\alpha)$ were introduced into the Schrödinger equation of the hindered rotor by employing values of I_{red} (reduced moment of inertia) calculated²⁷ for different α values and the equation solved²⁸ employing free rotor basis functions. From normalized eigenfunctions $[\psi_i(\alpha)]$ (101 basis functions ensured a satisfactory convergence limit in the calculations) and eigenvectors (ϵ_i) the probability distribution was obtained¹² and integrated between two maxima of the potential energy curve to give the conformer population.

A number of calculated populations relative to the more stable conformer are reported in Table 5 together with the free energy difference ΔG° (298 K) and enthalpy difference, ΔH° (298 K), obtained from the Gibbs-Helmholtz equation. For compounds (1) and (2) the X,O-*trans* conformation is the major conformer. Extension of the AO basis set, for compound (1), has the effect of increasing the population of the O,O-*trans* conformer (n_t), nevertheless this remains an underestimate with respect to the experimental result even when energies are from 6-31G* basis set. The value of n_t for compound (2) decreases slightly with basis set extension and reaches a slight excess with respect to the experimental values. For compound (3) the N(H),O-*cis* form prevails even though in larger AO basis sets almost equal amounts of the two conformers are obtained.

Several experimental results concerning the conformational properties of derivatives (1)–(3) were obtained in dense media, therefore a knowledge, even at an approximate level, of the behaviour of conformer populations in different solvents is necessary. For derivatives (1) and (2) the less polar X,O-*trans* form is the preferred conformation¹⁶ in different solvents and increases in polar solutions, a behaviour that requires an explanation within the theories of solvent effect. For compound

Table 4. Calculated results relative to V_n of equation (1) for derivatives (1)–(3) (kJ mol⁻¹)

Compound	Basis set	V_1	V_2	V_3	V_4
(1)	(3-21G//3-21G)	-1.0287	40.9697	1.5518	0.3972
	(3-21G//3-21G)	-0.9525	41.1650	1.5912	
	(6-31G*//3-21G)	0.3511	35.8109	2.1850	
(2)	(3-21G//3-21G)	2.5399	42.0485	1.8157	0.3689
	(3-21G//3-21G)	2.6384	42.1171	1.8249	
	(6-31G*//3-21G)	2.1893	35.5039	2.0011	
(3)	(3-21G//3-21G)	3.5543	47.5846	-0.7839	0.2190
	(3-21G//3-21G)	3.5775	47.6710	-0.7394	
	(6-31G*//3-21G)	1.6477	42.0639	-1.4808	

Table 5. Calculated populations relative to the more stable^a conformer, ΔG° (298 K) (kJ mol⁻¹) and ΔH° (298 K) obtained from *ab-initio* MO energies in different AO basis sets

Basis set	(1)			(2)			(3)		
	n_t	ΔG° ($t \rightarrow c$)	ΔH°	n_t	ΔG° ($t \rightarrow c$)	ΔH°	n_c	ΔG° ($c \rightarrow t$)	ΔH°
(3-21G//3-21G) ^b	0.53	0.32	-0.40	0.83	3.94	1.47	0.76	2.74	0.43
	(0.95 ± 0.02) ^d			(0.76 ± 0.02) ^d					
(3-21G//3-21G) ^c	0.54	0.43	-0.28	0.84	4.00	1.53	0.76	2.88	0.58
(6-31G//3-21G) ^c	0.66	1.60	0.62	0.81	3.61	1.57	0.63	1.36	0.41
(6-31G*//3-21G) ^c	0.71	2.17	1.31	0.82	3.69	1.64	0.53	0.35	0.30
(6-31G//6-31G) ^c	0.75	2.71	1.36						
(6-31G*//6-31G) ^c	0.75	2.71	0.89						

^a n_t and n_c are the populations of the X,O-*trans* and X,O-*cis* conformers. ^b Equation (1) $n = 4$. ^c Equation (1) $n = 3$. ^d Experimental value extrapolated into the vapour phase.¹⁶

(3) the N(H),O-*trans* form is the predominant conformer in solution¹⁸ (>95%) even though theoretical results predict a higher stability for the N(H),O-*cis* form.

A classical approach to solute-solvent interactions can be made using the reaction field theory.¹⁹ The difference between conformer energies in solution ($\Delta E_{\text{sol.}}^\circ$) is partitioned in two terms, according to equation (2), where $\Delta E_{\text{vap.}}^\circ$ and $\Delta E_{\text{solv.}}^\circ$ refer

$$\Delta E_{\text{sol.}}^\circ = \Delta E_{\text{vap.}}^\circ + \Delta E_{\text{solv.}}^\circ \quad (2)$$

to the vapour phase and to the contribution due to the solvent, respectively. The term $\Delta E_{\text{solv.}}^\circ$ can be expressed as the sum of three terms,¹⁹ the electrostatic contribution ($\Delta E_{\text{el.}}^\circ$), solvent dispersion interactions ($\Delta E_{\text{disp.}}^\circ$), and the energy required for cavity formation ($\Delta E_{\text{cav.}}^\circ$). The last two terms, appearing in equation (3), were found^{5,29} to be of opposite sign and almost

$$\Delta E_{\text{solv.}}^\circ = \Delta E_{\text{el.}}^\circ + \Delta E_{\text{disp.}}^\circ + \Delta E_{\text{cav.}}^\circ \quad (3)$$

cancel each other out, while $\Delta E_{\text{el.}}^\circ$ reproduces the principal trend of solvation energies. For derivatives (1)–(3) only $\Delta E_{\text{el.}}^\circ$ and the terms entering into its factorization [equation (4)] are reported

$$\Delta E_{\text{el.}}^\circ = \Delta E_{\text{d}}^\circ + \Delta E_{\text{q}}^\circ + \Delta E_{\text{qd}}^\circ \quad (4)$$

here and discussed. In equation (4), $\Delta E_{\text{d}}^\circ$, $\Delta E_{\text{q}}^\circ$, and $\Delta E_{\text{qd}}^\circ$ represent^{12,30} dipolar, quadrupolar, and dipolar-quadrupolar contributions. The molecule was oriented in a system of cartesian axes with origin in the centre of mass and directed along the inertial axis. The same origin was adopted for the dipole and quadrupole moment of the molecule. The molecular volume was determined by describing a solid having dimensions dx , dy , and dz , obtained from the largest values of the co-ordinates of the atoms and adding the van der Waals radii of the atoms occupying the outer extreme positions in the molecule. This approach was

adopted since unrealistic molecular volumes are obtained with different approximations.¹⁹ Dipole and quadrupole moments used here are those from *ab-initio* calculations in the 3-21G basis set. The results are given in Table 6.

The values of $\Delta E_{\text{solv.}}^\circ$ assimilated to free energy differences, were then added to the ΔG° values reported in Table 5 (6-31G*//3-21G) and the $\Delta G_{\text{sol.}}^\circ$ thus obtained was employed for evaluating conformer populations reported in Table 6. In a different approach $\Delta E_{\text{sol.}}^\circ$ for the different conformations was fitted to a potential function $V(\alpha)$ of equation (1) relative to the different solvents, then conformer populations were derived from the probability distribution as described above. The populations obtained in this way, collected in Table 6 for comparison, are identical to those obtained directly from the $\Delta E_{\text{sol.}}^\circ$ between ground states. The assumption of considering $\Delta E_{\text{sol.}}^\circ$ close to $\Delta G_{\text{sol.}}^\circ$ is therefore acceptable for conformers of molecules of the type considered here (entropy factors are in fact negligibly small).

The data reported in Table 6 show that for compounds (1) and (2) the larger contribution to solvation energy is represented by the quadrupole term ($\Delta E_{\text{q}}^\circ$) which is opposite in sign to the dipole term ($\Delta E_{\text{d}}^\circ$) and increases in value in polar solution. The stability of the X,O-*trans* conformer should thus increase in more polar solutions. This behaviour is reversed with respect to that found⁵ for the 2-formyl derivatives of furan and thiophene, especially for the former,^{5,9} where the dipolar term is responsible for the larger stability of the X,O-*cis* form in polar solvents. The calculated populations follow the trend of experimental values, yet they appear underestimated for compound (1) and slightly overestimated for compound (2). The choice of $\Delta E_{\text{vap.}}^\circ$ (or $\Delta G_{\text{vap.}}^\circ$) is one of the sources of the quantitative disagreement between calculated and experimental values.

For compound (3), the trend of solvation energy shows that dipolar and quadrupolar contributions almost balance each

Table 6. Calculated contributions, according to equation (4), to solvation energy of ground and transition states (values in kJ mol⁻¹) and populations of the *n_i* conformer for derivatives (1)–(3) (298 K)

Compound	Solvent ^b	$\Delta E_{\text{d}}^{\text{c}}$	$\Delta E_{\text{q}}^{\text{c}}$	$\Delta E_{\text{qd}}^{\text{c}}$	$\Delta E_{\text{el}}^{\text{c}}$	$\Delta E_{\text{sol}}^{\text{c}}$	n_i	n_i^{d}	$n_i(\text{exp})^{\text{e}}$	ΔE^*	ΔE^{*f}
(1) ^a	A	-0.55	1.46	0.00	0.91	3.08	0.78	0.77	0.94	38.58	38.07
	B	-0.74	1.94	0.01	1.21	3.38	0.80	0.79		39.07	38.45
	C	-0.78	2.02	0.01	1.25	3.42	0.80	0.79		39.15	38.51
	D	-1.95	4.89	0.11	3.05	5.22	0.89	0.88		42.10	41.00
	E	-2.54	6.26	0.14	3.86	6.03	0.92	0.91	0.97	43.49	42.75
	F	-3.14	7.60	0.66	5.12	7.29	0.95	0.94		45.40	44.51
	G	-3.30	7.95	2.19	6.84	9.01	0.97	0.97	0.98	47.39	46.26
Compound (2) ^a	A	-0.37	0.87	0.00	0.50	4.19	0.84	0.84	0.79	37.87	37.52
	B	-0.49	1.17	0.00	0.68	4.37	0.85	0.85		37.96	37.60
	C	-0.51	1.21	0.01	0.71	4.40	0.85	0.85		37.97	37.61
	D	-1.30	2.94	0.06	1.70	5.39	0.90	0.89	0.82	38.48	37.49
	E	-1.71	3.76	0.07	2.12	5.81	0.91	0.91		38.70	37.72
	F	-2.12	4.57	0.37	2.82	6.51	0.93	0.93	0.84	39.04	38.07
	G	-2.24	4.78	1.37	3.91	7.60	0.96	0.95		39.49	38.56
Compound (3) ^g	A	-0.92	1.06	0.00	0.14	0.49	0.45	0.45		43.64	43.01
	B	-1.24	1.41	-0.02	0.15	0.50	0.45	0.45		44.12	43.36
	C	-1.29	1.47	-0.02	0.16	0.51	0.45	0.45		44.23	43.42
	D	-3.28	3.56	-0.20	0.08	0.43	0.46	0.46		47.28	46.51
	E	-4.30	4.55	-0.33	-0.08	0.27	0.47	0.47		48.75	47.85
	F	-5.36	5.53	-0.99	-0.82	-0.47	0.55	0.54	0.95	51.32	50.33
	G	-5.64	5.78	-1.75	-1.61	-1.26	0.63	0.62		53.83	52.59

^a ΔG° (*t* → *c*). ^b A, Cyclohexane, $\epsilon = 2.01$; B, carbon tetrachloride, $\epsilon = 2.23$; C, benzene, $\epsilon = 2.27$; D, chloroform, $\epsilon = 4.81$; E, tetrachlorethane, $\epsilon = 8.20$; F, acetone, $\epsilon = 20.70$; G, methanol, $\epsilon = 32.63$. ^c $\Delta G_{\text{vap}}^{\circ}$ was taken from Table 5 and refers to the 6-31G*/3-21G approach. ^d Obtained from the potential function in different solvents, see text. ^e From ref. 16. ^f Obtained as difference between the lowest rotational level of ground state and the first rotational level common to the two ground states. ^g ΔG° (*c* → *t*). ^h From ref. 25. ⁱ The values relative to solvents F and G are referred to the X,O-*trans* ground state.

other. The same conformer should prevail in the vapour phase and in media of low polarity [this is the less polar N(H),O-*cis* conformer]. In solutions of high permittivity the opposite is true, and this seems due to the increasing weight of the $\Delta E_{\text{d}}^{\text{c}}$ and $\Delta E_{\text{qd}}^{\text{c}}$ terms, which are favourable to the increase of the amount of the more polar N(H),O-*trans* form. The calculated population in acetone is nevertheless significantly smaller than the experimental value, as shown in Table 6.

Equations (2)–(4) were also employed to estimate the behaviour towards solvent effects of the energy barrier relative to the conformer interconversion process. The ΔE^* s refer to the transition state and to the more stable ground states. For the ΔE_{vap}^* values, reference was made to the ΔE^* s in Table 2 (6-31G*/3-21G approach). The energy barrier increases with the polarity of the medium, more significantly for derivatives (1) and (3).

By employing the eigenvalues of equation (2) in the different solvents, the energy barrier for conformer interconversion is obtained from the lowest rotational level of the ground state and the first level common to the two ground states. These values of ΔE^* , listed in Table 6, are slightly lower than the difference between transition-state and ground-state energies. For a comparison with experimental results, the differences between the two sets of values are not significant. An experimental value of the free energy of activation has been reported¹⁵ for compound (2) and amounts to 35.6 kJ mol⁻¹ (¹³C d.n.m.r.; CHFCl₂-CF₂Cl₂). This measurement should be compared with those calculated in solvents C and D, in Table 6, and appears in satisfactory agreement.

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