

## Conformational Analysis of Organic Carbonyl Compounds. Part 6.<sup>1-5</sup> Theoretical Examination of the Conformational Properties (Ground and Transition States) and Solvent Effects on 2-Formyl-furan, -thiophene, and -pyridine

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*ab-initio* MO calculations in different AO basis sets and with full geometry optimization were performed on 2-formyl-furan, -thiophene, and -pyridine. The energy content of more stable conformations and transition states for conformer interconversion, located as saddle-points in the potential energy surface, was obtained. The relative conformer stability is correctly predicted in the STO-3G minimal basis set and in the more extended 3-21G and 6-31G (tested only for the furan derivative) basis sets, yet energy differences between conformers close to the experimental ones are obtained only when the extended sets are employed. A minor effect on the energetics of these molecules is caused by geometry optimization. On the molecular geometry the effect of AO-basis set implementation is significant only as regards the exocyclic C-C bond length, which is shorter in the larger set. An analysis of the effects which can determine the relative conformer stability shows that electrostatic interactions, estimated from calculated atomic point charges, are mainly responsible for the difference in behaviour, observed experimentally, of the conformational equilibrium in these compounds. Using the classical solvent effect theory, the contribution of electrostatic and dispersion solute-solvent interactions and cavity formation to the solvation energy of the ground- and transition-states was calculated: the most important contribution comes from electrostatic effects, as can be seen in previous approaches where only this term has been taken into account. The calculated solvation energies are strongly dependent on the dipole moments for ground- and transition-states, but nevertheless the trend of the experimental solvent effects on the conformational equilibrium is correctly predicted from a qualitative point of view, for the three derivatives examined. The effect of solvent polarity on activation energies was also obtained and enables comparison of the behaviour of the compounds examined, even though an experimental comparison and a qualitative agreement could be found only in the case of furan-2-carbaldehyde.

Studies on the conformational properties of carbonyl derivatives of aromatic compounds have been reported by us in previous papers.<sup>1-5</sup> Theoretical analysis of the applicability of MO methods used for predicting<sup>1</sup> the conformational behaviour of these molecules, and experimental determinations of conformer populations in formyl,<sup>2-4</sup> acetyl,<sup>2-4</sup> and benzoyl<sup>5</sup> derivatives of mainly five-membered heterocycles<sup>3-5</sup> have been the object of these studies.

The conformational situation of 2-formyl- and 2-acetyl-derivatives of thiophene and furan is found<sup>3,4</sup> to be largely unchanged, as regards the preferential X,O-*cis/trans* orientation of the heteroatom X and carbonyl oxygen, on passing to the corresponding benzo[*b*]furan and benzo[*b*]thiophene derivatives. In thiophene-2-carbaldehyde<sup>6,7</sup> experimental results from n.m.r.-l.i.s. (lanthanide-induced shifts) measurements show the predominant presence (>90%) of the S,O-*cis* isomer, an estimate which is in substantial agreement with those from nematic phase<sup>8</sup> and <sup>13</sup>C chemical shift<sup>9</sup> approaches, and from dipole moments and Kerr molecular constants.<sup>10,11</sup> The conformational composition does not appear to be significantly dependent upon the nature of the solvents.<sup>12,13</sup> Furan-2-carbaldehyde behaves differently however. N.m.r. spectroscopic techniques,<sup>12,14-16</sup> i.r. spectroscopy,<sup>17</sup> and dipole moments<sup>11</sup> show the O,O-*cis*, O,O-*trans* isomer ratio to be closely dependent on the polarity of the solution. In the case of pyridine-2-carbaldehyde the experimental evidence from n.m.r.<sup>18-21</sup> and microwave spectroscopy<sup>22</sup> and dipole moments<sup>23,24</sup> indicate that the N,O-*trans* isomer prevails in solution and that the solvent exerts no significant effect on this preference. From preliminary n.m.r. studies on 2-formyl-quinoline<sup>25</sup> it appears that this situation is maintained even in this molecule.

The difference in stability of the X,O-*cis/trans* isomers of these formyl heterocycles has been attributed<sup>20,26-32</sup> to a balance of several effects which, in the absence of relevant steric interactions, can be summarized as follows: (a)  $\pi$ -conjugation of the C-O bond with the heterocyclic ring and (b) stabilizing or destabilizing electrostatic interactions involving the carbonyl oxygen and the ring heteroatom. Factor (a) should, in the most favourable situation, involve<sup>3,26,27</sup> a *trans* arrangement of the C=O and the adjacent bond of the ring in which there is a higher  $\pi$ -electron density; however, this is contrasted by the degree of aromatic character or  $\pi$ -delocalization of the ring,<sup>9,11,29</sup> which is expected to be lower in furan and thiophene than in benzene and pyridine. The lower barriers for internal rotation in 2-formylpyridine<sup>20</sup> and benzaldehyde<sup>30</sup> with respect to the 2-furan<sup>9,14</sup> and 2-thiophene<sup>9</sup> analogues support this hypothesis. The effect in (b) should be closely related to the electric dipole of the conformers and should also be responsible for the influence of solvents<sup>14,26,27</sup> on their relative amounts: solvents with high dielectric constants should stabilize the more polar conformer.<sup>27</sup>

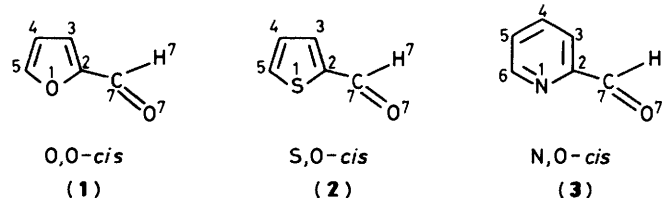
In the present study we report an estimate of the energy content of the conformers and transition states of these molecules based on *ab-initio* MO calculations. The aim was to set a reasonable upper limit for the basis set from which reliable results could be obtained regarding the relative molecular complexity of these systems. This would enable us to interpret and predict experimental behaviour. At the same time, we intended to follow the changes in the geometrical parameters of energy minimization at different levels in order to obtain conformer geometries for use as input parameters for conformational analysis, which are not experimentally available. Finally, we wished to examine the relative importance of factors (a) and (b) with regard to the stability of the X,O-*cis/trans*

ground states of 2-formyl-furan, -thiophene, and -pyridine, and to attempt a rationalization of the different relative stabilities of the ground states of these molecules to different solvents. Solvation energies were calculated by the classical approximation of the 'continuum model'<sup>33</sup> based on the solvent effect theory given by Sinanoğlu.<sup>34</sup>

### Results and Discussion

The *ab-initio* MO calculations were performed using GAUSSIAN-80 and GAUSSIAN-82 programs<sup>35</sup> on VAX-750 and CRAY-X-MP/12 computers. The internal basis sets of the programs used were STO-3G, 3-21G, and 6-31G. The molecular geometry was optimized by the gradient method given by Berny<sup>35,36</sup> and the Murtaugh-Sargent<sup>37</sup> technique, included in the standard calculation packages.<sup>35</sup>

In previous theoretical studies of the conformational properties of derivatives (1)–(3), *ab-initio* MO calculations,<sup>1,19,26,32,38,39</sup> were mainly carried out using a minimal STO-3G basis set, with partial geometry optimization.<sup>1,32,39</sup> The relative stability of X,O-*cis/trans* ground states and the energy barrier to conformer interconversion were obtained and discussed in terms of the electronic structure of these molecules. Agreement between the calculated and experimental orders of conformer stability was obtained, yet it was pointed out<sup>1,19</sup> that



basis set implementation and/or full geometry optimization seemed to be necessary to reach results more quantitatively reliable for comparison with experimental measurements. Thus we first checked the effect of optimization of all the geometrical parameters of the derivatives (1)–(3) on the minimal STO-3G and on the more extended 3-21G basis set. This was done for the X,O-*cis,trans* ground states, and also for the transition state, which was localized as a saddle-point in the potential energy surface. The final structural parameters are collected in Table 1, where the results, relative to the minimal basis set (STO-3G), have been reported only for furan-2-carbaldehyde. The differences between the structural parameters obtained in the two levels are small [as can be seen in Table 1 for derivative (1)], except for a significant reduction, from 1.50–1.45 Å, of the exocyclic C–C bond as a consequence of basis set implement-

**Table 1.** Structural parameters relative to the optimized geometries of derivatives (1)–(3)

Molecular state: <sup>a</sup> Basis set:	Compound																	
	(1)			(2)			(3)											
	<i>trans</i> -GS		<i>cis</i> -GS		TS		<i>trans</i> -GS		<i>cis</i> -GS		TS		<i>trans</i> -GS		<i>cis</i> -GS		TS	
	STO-3G	3-21G	STO-3G	3-21G	STO-3G	3-21G	3-21G	3-21G	3-21G	3-21G	3-21G	3-21G	3-21G	3-21G	3-21G	3-21G	3-21G	3-21G
<b>Bond length/Å</b>																		
X(1)–C(2)	1.380	1.380	1.380	1.377	1.380	1.378	1.796	1.791	1.800	1.327	1.330	1.328						
X(1)–C(5)	1.371	1.372	1.371	1.370	1.376	1.382	1.789	1.787	1.796									
N(1)–C(6)										1.329	1.325	1.330						
C(2)–C(3)	1.349	1.344	1.349	1.346	1.343	1.338	1.340	1.341	1.335	1.380	1.380	1.382						
C(2)–C(7)	1.501	1.449	1.501	1.451	1.524	1.487	1.458	1.452	1.485	1.479	1.484	1.500						
C(3)–C(4)	1.439 <sup>b</sup>	1.440 <sup>b</sup>	1.438 <sup>b</sup>	1.439 <sup>b</sup>	1.444 <sup>b</sup>	1.449 <sup>b</sup>	1.437 <sup>b</sup>	1.439 <sup>b</sup>	1.447 <sup>b</sup>	1.382	1.385	1.383						
C(4)–C(5)	1.343	1.345	1.343	1.346	1.339	1.339	1.339	1.340	1.334	1.385 <sup>b</sup>	1.381 <sup>b</sup>	1.384 <sup>b</sup>						
C(5)–C(6)										1.384	1.387	1.382						
C(3)–H(3)	1.079	1.067	1.079	1.066	1.078	1.065	1.069	1.071	1.070	1.069	1.071	1.071						
C(4)–H(4)	1.077	1.064	1.077	1.064	1.077	1.064	1.069	1.069	1.069	1.071	1.071	1.071						
C(5)–H(5)	1.083	1.062	1.083	1.062	1.082	1.062	1.066	1.066	1.065	1.070	1.070	1.070						
C(6)–H(6)										1.069	1.069	1.069						
C(7)–H(7)	1.103	1.082	1.103	1.085	1.104	1.082	1.083	1.085	1.083	1.082	1.087	1.084						
C(7)–O(7)	1.222	1.212	1.221	1.209	1.219	1.207	1.212	1.211	1.207	1.210	1.205	1.207						
<b>Bond angles/°</b>																		
X(1)–C(2)–C(3)	110.53	109.70	110.48	109.43	110.71	109.83	111.57	111.88	111.46	122.95	122.30	122.46						
X(1)–C(5)–C(4)	111.31	110.04	111.33	110.05	111.16	109.73	112.11	112.34	111.79									
X(1)–C(6)–C(5)										122.06	122.32	122.38						
X(1)–C(2)–C(7)	117.12	118.23	118.43	120.46	117.09	117.49	122.86	120.79	120.74	116.77	118.25	116.76						
C(2)–X(1)–C(5)	105.64	106.92	105.66	107.19	105.59	107.01	89.01	88.90	89.15									
C(2)–C(3)–C(4)										118.36	118.82	118.55						
C(2)–N(1)–C(6)										118.90	119.13	119.04						
C(2)–C(3)–H(3)	126.56	125.80	126.69	126.33	126.99	126.64	121.78	123.02	123.14	119.15	120.20	120.36						
C(3)–C(4)–H(4)										120.61	120.58	120.35						
C(4)–C(5)–H(5)	132.07	133.43	132.05	133.44	132.36	134.01	127.70	127.22	128.07									
C(5)–C(4)–H(4)	127.09	126.63	127.14	126.79	127.22	126.84	123.44	123.69	123.57									
C(5)–C(6)–H(6)										116.86	116.79	116.57						
C(6)–C(5)–H(5)										120.12	120.21	120.35						
C(2)–C(7)–H(7)	113.89	113.38	113.00	112.23	115.06	114.62	115.39	113.41	114.18	113.18	113.32	114.21						
C(2)–C(7)–O(7)	123.63	123.86	124.66	125.86	123.52	124.24	123.10	124.83	124.82	123.50	125.22	124.56						
X(1)–C(2)–C(7)–O(7)	180.00	180.00	0.00	0.00	90.41	86.02	180.00	0.00	88.95	180.00	0.00	82.31						
C(3)–C(2)–C(7)–H(7)	180.00	180.00	0.00	0.00	90.13	85.96	180.00	0.00	88.69	180.00	0.00	82.49						

<sup>a</sup> GS stands for ground state and TS for transition state, *cis* and *trans* refer, in order, to the X,O-*cis* and X,O-*trans* conformers. <sup>b</sup> A dependent parameter, shown for comparison.

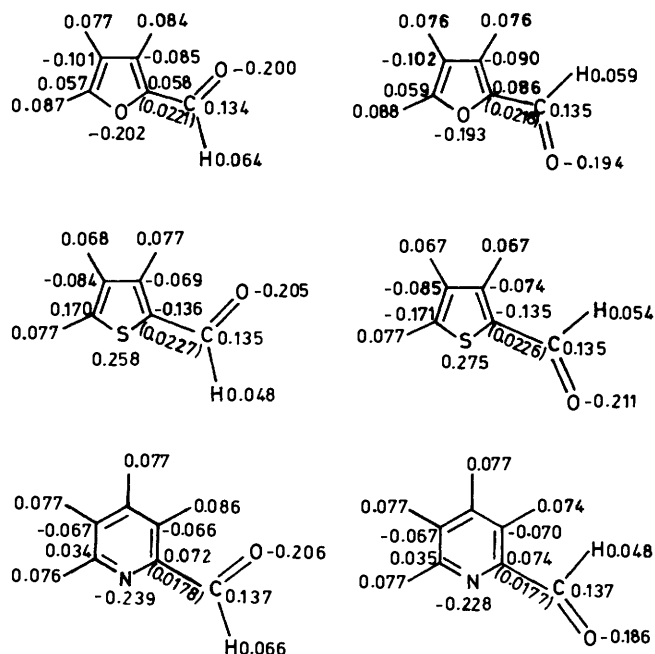


Figure.

ation. Further, as regards the transition state, the dihedral angles  $O(7)-C(7)-C(2)-O(1)$  and  $H(7)-C(7)-C(2)-C(3)$  in derivatives (1) and (3) are notably smaller than  $90^\circ$ , while the formyl group assumes an approximately perpendicular conformation in derivative (2). Apart from this peculiarity, the geometry of the formyl group is not appreciably different from that observed when the optimization is restricted to this part of the molecule in derivatives<sup>1,3,2</sup> (1) and (2). Significant differences are found for the exocyclic C-C bond length which is almost identical in derivatives (1) and (2) and slightly longer (0.02 Å) in derivative (3); this bond becomes even more relaxed in the transition state. The geometry of the heterocyclic rings approximates to that obtained in the optimization of the unsubstituted heterocycles<sup>32,40</sup> and is in satisfactory agreement with experimental values,<sup>41,42</sup> where comparison is possible.

The geometrical features of these molecules allow us to comment on the choice of the conformer geometries employed in the analysis of their conformational equilibria with the l.i.s. method. A value of 1.46 Å for the C(2)-C(7) bond distance has been employed<sup>6</sup> with satisfactory results in the l.i.s. simulation of furan-2-carbaldehyde and it seems reasonable to assume that the bond lengths and angles are very similar in the two isomeric ground states.

The results relative to the energy content of the molecules examined and the calculated dipole moments are collected in Table 2. The effect of different basis sets was tested and geometry optimization at two different levels was also performed. Relative conformer stability in agreement with that obtained experimentally was obtained even in the minimal basis set calculation (Table 2), while the calculated  $\Delta E^0$  values are significantly lower than the experimental ones (comparison refers to experimental  $\Delta G^0$  values). The effect of geometry relaxation on the energy content of the molecular ground states is small. This can also be seen by comparing the  $\Delta E^0$  relative to compound (1) in the (STO-3G//STO-3G)\* approach ( $-3.223$  kJ mol<sup>-1</sup>) with that reported in ref. 38 ( $-3.473$  kJ mol<sup>-1</sup>). Implementing the basis set (3-21G//STO-3G) or (3-21G//3-

21G) results in an increase of the  $\Delta E^0$  results which become closer to the experimental  $\Delta G^0$  values. Further implementation of the basis set (6-31G) checked for compound (1), employing molecular geometries optimized in the lower bases, 6-31G//STO-3G and 6-31G//3-21G, in the single-point approximation,<sup>43</sup> results in small and insignificant differences in the  $\Delta E^0$  values. Thus, as regards geometrical parameters, basis set implementation (within the limits here investigated) significantly influences only the exocyclic C-C bond of compounds (1)-(3), while appreciable changes are produced on the  $\Delta E^0$  values when the minimal STO-3G is extended to the larger 3-21G set. However, no further significant changes are obtained in further basis set extension or in the optimization of the molecular geometry at a higher level.

For derivative (3), as with derivative (1), basis implementation enhances the  $\Delta E^0$  value, which becomes closer to the experimental estimates (see Table 2), while for compound (2) these changes are less relevant, as a comparison among the results of STO-3G and 44-31G calculations has also shown.<sup>32</sup>

The choice of an appropriate basis set appears to be of greater relevance in the calculation of the energy barrier for internal rotation,  $\Delta E^*$ . The  $\Delta E^*$  values obtained in the STO-3G set are lower than the experimental estimates, while basis 3-21G enhances the calculated value, as shown in Table 2. While for derivatives (1) and (2) these estimates become closer to the experimental energy barriers, for derivative (3) the calculated value in the implemented basis set seems to exceed the experimental estimate significantly. The effect of further basis set extension, tested for compound (1), shows that with respect to the lower 3-21G set, 6-31G only slightly decreases the  $\Delta E^0$  value ( $\sim 1.6$  kJ mol<sup>-1</sup>), while  $\Delta E^*$  decreases significantly (5.9 kJ mol<sup>-1</sup>), closely approximating to the experimental barrier. In the 6-31G basis set it is also possible to confirm that geometry optimization at a level higher than that carried out for the STO-3G set leads to minor changes in the  $\Delta E^0$  and  $\Delta E^*$  values. The choice of the basis set thus seems to be important in the calculation of the transition state energy and these calculated values seem to be reliable only when extended sets are employed.

Dipole moments relative to ground and transition states were also obtained and are collected in Table 2. The correct

\* The basis set on the left is that employed in MO calculations while that on the right refers to the level of the optimized geometry employed.

Table 2. Calculated nuclear repulsion energy ( $E_N$ ), total SCF energy  $E(\text{RHF})$ , and dipole moments for the *trans*, *cis* ground states and for the transition state of compounds (1)–(3) in different basis sets

Compound	Basis set <sup>a</sup>	Molecular state <sup>b</sup>	$E_N/\text{a.u.}$	$E(\text{RHF})/\text{a.u.}$	$\mu/D$	$\mu_{\text{exp.}}/D$	$\Delta E^0 = E_{\text{trans}} - E_{\text{cis}}$ $\text{kJ mol}^{-1}$	$\Delta G_{\text{exp.}}^0/\text{kJ mol}^{-1}$	$\Delta E^*/(E_{\text{TS}} - E_E)$ $\text{kJ mol}^{-1}$	$\Delta G_{\text{exp.}}^*/\text{kJ mol}^{-1}$	
(1)	STO-3G//STO-3G	<i>trans</i> -GS	269.102 374	-336.982 179	1.83	3.23 <sup>c</sup>	-3.223	-8.37 <sup>d</sup>	26.095	25 <sup>d</sup> ; 35.573 <sup>e</sup>	
		<i>cis</i> -GS	269.955 180	-336.980 945	2.41	3.93 <sup>c</sup>		-2.55 <sup>f</sup>		45.57 <sup>f</sup>	
		TS	268.602 816	-336.972 190	1.79						
	3-21G//STO-3G	<i>trans</i> -GS		-339.439 124	3.39		-12.503		52.837		
		<i>cis</i> -GS		-339.434 338	4.49						
		TS		-339.418 898	3.39						
	3-21G//3-21G	<i>trans</i> -GS	271.304 700	-339.442 284	3.48		-12.654		54.979		
		<i>cis</i> -GS	271.860 078	-339.437 440	4.52						
		TS	270.202 383	-339.421 238	3.40						
	6-31G//STO-3G	<i>trans</i> -GS		-341.197 168	3.84		-11.591		47.871		
		<i>cis</i> -GS		-341.192 731	5.18						
		TS		-341.178 843	3.92						
6-31G//3-21G	<i>trans</i> -GS		-341.199 983	3.93		-11.019		49.093			
	<i>cis</i> -GS		-341.195 712	5.23							
	TS		-341.181 190	3.93							
(2)	STO-3G//STO-3G	<i>trans</i> -GS	325.735 682	-656.321 728	2.01	2.5 <sup>g</sup>	+3.610	0.647 <sup>h</sup> ; 5.1–6.8 <sup>c</sup>	25.039	42.478 <sup>h</sup>	
		<i>cis</i> -GS	327.911 992	-656.323 110	1.97	3.5 <sup>g</sup>					
		TS	325.577 717	-656.313 525	1.73						
	3-21G//STO-3G	<i>trans</i> -GS		-660.558 700	3.13		+3.790		45.428		
		<i>cis</i> -GS		-660.560 151	4.30						
		TS		-660.542 760	3.34						
	3-21G//3-21G	<i>trans</i> -GS	324.615 523	-660.564 119	3.08		+2.800		45.768		
		<i>cis</i> -GS	326.961 102	-660.565 191	4.49						
		TS	323.625 838	-660.547 667	3.45						
	(3)	STO-3G//STO-3G	<i>trans</i> -GS	323.388 509	-354.868 603	2.44	3.91 <sup>i</sup>	-9.971	-3.6 <sup>i</sup> ; -3.0 <sup>m</sup>	26.280	31.44 <sup>i</sup> ; 32.22 <sup>m</sup>
			<i>cis</i> -GS	323.254 460	-354.864 786	3.74	5.3 <sup>i</sup>		-20.08 to -28.46 <sup>n</sup>		18.83 <sup>n</sup>
			TS	322.332 269	-354.858 543	3.12					
3-21G//STO-3G		<i>trans</i> -GS		-357.402 247	3.79		-27.166		55.515		
		<i>cis</i> -GS		-357.391 848	5.53						
		TS		-357.380 996	4.64						
3-21G//3-21G		<i>trans</i> -GS	327.357 913	-357.406 424	3.75		-27.461		56.906		
		<i>cis</i> -GS	326.823 847	-357.395 912	5.44						
		TS	325.811 340	-357.384 635	4.61						

<sup>a</sup> See text. <sup>b</sup> GS, TS, *trans* and *cis* as in Table 1. <sup>c</sup> F. Mönig, H. Dreizler, and H. D. Rudolph, *Z. Naturforsch.*, 1965, **20a**, 1323. <sup>d</sup> Ref. 14: vapour phase. <sup>e</sup> K. I. Dahlquist and S. Forsen, *J. Phys. Chem.*, 1965, **69**, 4062; 10% in dimethyl ether solution. <sup>f</sup> Ref. 10. <sup>g</sup> Ref. 9: solvent  $\text{CD}_2\text{Cl}_2$ ; <sup>h</sup> Ref. 22. <sup>i</sup> Ref. 21: solvent  $\text{CHCl}_2\text{-CCl}_2\text{F}_2$  (1/1). <sup>m</sup> Ref. 20: solvent  $\text{CCl}_3\text{F}_2\text{-CHCl}_2$ . <sup>n</sup> Ref. 19: the  $\Delta G^0$  values refer to the vapour phase and  $\Delta G^*$  (*trans*  $\rightarrow$  *cis*) to the pure liquid. <sup>o</sup> Ref. 18: vapour phase.

**Table 3.** Electrostatic interactions calculated from *ab-initio* point charges (STO-3G//STO-3G approach) on atoms, using equation (1). The  $\Delta E$  values refer to  $E_{trans} - E_{cis}$  and are expressed in kJ mol<sup>-1</sup>

Compound	$\Delta E_{ES}^a$	$\Delta E_{H(7)-C(3)}$	$\Delta E_{H(7)-H(3)}$	$\Delta E_{H(7)-X}$	$\Delta E_{O(7)-C(3)}$	$\Delta E_{O(7)-H(3)}$	$\Delta E_{O(7)-X}$	$\Sigma^b$
(1)	-5.402	0.457	-0.387	-2.330	1.009	-2.675	-2.574	-6.500
(2)	5.968	0.711	-0.643	0.467	0.605	-2.826	7.062	5.376
(3)	-7.922	-0.006	0.025	-4.126	1.523	-4.531	-1.671	-8.786

<sup>a</sup> Refers to the contribution of all the atoms of the molecule. <sup>b</sup> This summation extends over the terms of the six preceding columns.

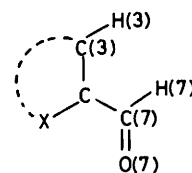
order of ground-state polarity is predicted, the best agreement between calculated and experimental values being given by 3-21G calculations, even though values overestimating the experimental measurements are obtained (Table 2). Smaller and larger basis sets give lower and higher values of dipole moments. This trend was also evidenced in molecules of smaller size<sup>44</sup> and seems to be related to the charge distribution given by the different basis sets; the more extended combinations having the tendency to enhance charge separation in molecules. In the minimal basis set the values relative to the ground states of compound (2) are the reverse of the experimental values.

From the calculated energy terms, nuclear repulsion  $E_N$  and total SCF energies  $E(RHF)$ , and also from charge densities and overlap populations, a comparative examination of the factors affecting the different stabilities of *trans/cis* ground states in derivatives (1)–(3) is feasible. For these quantities refer to Table 2 and the Figure. The trend of the nuclear repulsion terms shows that only in compound (1) do they follow the stability order of the two conformers, whereas the reverse order is found for derivatives (2) and (3). These terms are balanced by electronic effects in the total energy content of the molecules, therefore significant dependence of the relative *trans/cis* stability on steric factors can be ruled out, at least as regards derivatives (2) and (3). Conjugative and electrostatic effects should thus contribute largely to the final stability of ground states. The extent of  $\pi$ -conjugation can be deduced from the amount of  $\pi$ -character of the exocyclic C–C bond, while an estimate of electrostatic interactions can be obtained from atomic charges. Since atomic charges and overlap populations are closely dependent on the basis set, these conclusions must be considered only qualitatively, and the discussion will be based on the electron distribution obtained in the STO-3G//STO-3G approach, for the reasons specified above. The  $\pi$ -overlap relative to exocyclic C–C bond,  $\eta_{C-C}$ , for derivative (3) is lower than in (1) and (2), yet in the three derivatives  $\eta_{C-C}$  is slightly higher for the X,O-*trans* conformation. The extent of conjugation should thus be higher in derivatives (1) and (2) than in compound (3), while in the two conformers of each molecule the  $\eta_{C-C}$  values are very close, indicating that  $\pi$ -conjugation should not greatly affect their relative stabilities. The difference in conformer stability in these molecules is thus expected to depend mostly on electrostatic interactions particularly between the heteroatom of the ring and the carbonyl oxygen.

Two schemes have been previously employed<sup>45,46</sup> for an approximate estimate of molecular electrostatic interactions: one based on point-charges and the other based on dipole-dipole interactions. The former approximation has been used here and the coulomb interactions,  $E_{ES}$ , are calculated from equation (1):  $q_i, q_j$  are the charges centred on the single atoms,

$$E_{ES} = \sum \frac{q_i q_j}{r_{ij}} \quad (1)$$

where  $i$  and  $j$  represent all the pairs of atoms, excluding those directly bonded, and those bonded to a common atom. The  $E_{ES}$  values, reported in Table 3, show a trend which agrees with



experimental values and also with the calculated total energy, as regards the relative stability of X,O-*cis/trans* conformers. The analysis of single additive contributions to  $E_{ES}$ , restricted to the vicinity of the formyl group, shows that the X,O atoms in derivatives (1) and (3) are mutually repulsive and in derivative (2) are attractive. For the hydrogen atom of the formyl group these terms are of opposite sign when referring to the interaction with the ring carbon C(3) and H(3) respectively, yet they are almost entirely balanced. The remaining terms determine the electrostatic contributions to the energy difference between the X,O-*cis* and X,O-*trans* conformers. Electrostatic interactions thus turn out to be responsible for the relative energy difference  $\Delta E^0$ , but the significant contributions are not confined to direct interactions between the electric charges on the X and O atoms.

**Solvent Effects on Conformational Equilibria.**—The electrostatic properties of a molecule are important in determining its ability to interact with solvents. In the case of a molecule having conformers with different charge distributions, *i.e.* different dipole moments, the conformer composition in both liquid and vapour phase may change in solvents of different polarity. This was found to be the case with furan-2-carbaldehyde and not, or at least to a considerably lesser extent, of thiophene- and pyridine-2-carbaldehyde. A quantitative account of this behaviour for derivative (1) and of the solvent dependence of the  $\Delta E^0$  and  $\Delta E^*$  values has been given by Abraham and Sivers<sup>14</sup> in terms of the classical theory of dielectrics. This has also been applied to derivative (3).<sup>18</sup> Application of an SCF MO LCAO approach at a semi-empirical level to derivative (1) gave<sup>47</sup> results closely similar to those from classical theory when the self-consistent reactive field model<sup>48</sup> (SCRf) was employed.

A different classical approach to solute-solvent interactions involves calculation of the interaction of a solute molecule with its entire environment, using a continuum model for the solvent. Following the procedure of Sinanoğlu,<sup>34</sup> the solvation energy is divided into three contributions: electrostatic solute-solvent interactions, dispersion solute-solvent interactions, and the energy required for cavity formation. This approach has been applied<sup>33b</sup> to derivative (1) and it was found that inclusion of additional terms beside the electrostatic solute-solvent interactions reproduces the principal trend of solvation energies as in the Abraham treatment,<sup>14</sup> but the magnitude of the solvent effect is somewhat overestimated. Since our aim was to compare the effects of solvation on the relative stability of the conformers of compounds (1)–(3) and on their activation energies as a function of solvent polarity, we preferred not to restrict solute-solvent interactions to electrostatic terms, but rather to

**Table 4.** Calculated (see text) solvent-effect energy contribution ( $\text{kJ mol}^{-1}$ ) to the ground states,  $\Delta E_{\text{sol}}(E_{\text{cis}} - E_{\text{trans}})$ , and to the activation energy  $\Delta E_{\text{sol}}^{\ddagger}$  for the internal rotation process in compounds (1)–(3). The terms  $\Delta E_c$ ,  $\Delta E_d$ ,  $\Delta E_e$ , and  $\Delta E_s$  refer to equation (3)

Solvent ( $\epsilon$ )	Compound																					
	$\Delta E_c$	$\Delta E_d$	$\Delta E_e$	$\Delta E_s$	$\Delta E_{\text{sol}}$		$\Delta E_{\text{sol}}^{\ddagger}$	(2)		(3)												
					$(\Delta E_{\text{v}})^b$	$(\Delta E_{\text{v}})^c$		$\Delta E_{\text{sol}}^{\text{sol}}$	$\Delta E_{\text{sol}}^{\text{sol}}$	$\Delta E_{\text{sol}}^{\text{sol}}$												
					(-12.654)	(-6.278)		$(\Delta E_{\text{v}})^b$	$(\Delta E_{\text{v}})^b$	$(\Delta E_{\text{v}})^b$												
Cyclohexane (2.01)	-1.95	1.15	4.57	3.77	-8.38	-2.51	13.41	68.39	11.73	63.82	$(E_{\text{TS}} - E_{\text{cis}})$	$\Delta E_{\text{sol}}^{\text{sol}}$	$(\Delta E_{\text{v}})^b$	$\Delta E_{\text{sol}}^{\text{sol}}$	$(\Delta E_{\text{v}})^b$	$(E_{\text{TS}} - E_{\text{trans}})$	$\Delta E_{\text{sol}}^{\text{sol}}$	$(\Delta E_{\text{v}})^b$	$\Delta E_{\text{sol}}^{\text{sol}}$	$(\Delta E_{\text{v}})^b$	(56.91)	69.95
Carbon tetrachloride (2.23)	-2.06	1.34	5.20	4.48	-7.67	-1.79	13.63	68.61	12.77	64.69												69.95
Benzene (2.27)	-2.25	1.30	5.31	4.36	-7.79	-1.91	15.81	70.78	13.21	67.03												72.34
Chloroform (4.81)	-2.09	1.35	9.16	8.41	-3.74	2.13	17.88	72.86	20.04	73.89												72.17
1,1,2,2-Tetrachloroethane (8.20)	-2.40	1.38	11.04	10.01	-2.14	3.74	22.17	77.15	23.88	80.59												75.74
Acetone (20.70)	-1.80	1.04	12.94	12.18	0.03	5.90	21.27	76.25	27.19	82.44												73.25
Methanol (32.63)	-1.53	1.12	13.44	13.04	0.88	6.76	18.87	73.85	27.73	80.68												70.36

<sup>a</sup>  $\Delta E_{\text{sol}}^{\ddagger}$  is the difference between the energy of the transition state and that of the more stable conformer in the different solvents;  $\Delta E_{\text{sol}}^{\ddagger}$  is defined by the analogous equation (3) for the activation energy.

<sup>b</sup> Calculated value (3-21G//3-21G). <sup>c</sup> Experimental value, see Table 2.

calculate the effect of dispersion interactions and cavity formation also, in order to compare their relative importance on the total effect.

The energy difference between two conformers in solution,  $\Delta E_{\text{sol}}$ , can be expressed as the sum of the energy difference in the vapour phase,  $\Delta E_v$ , and a term representing the difference in solvation energy between the conformers,  $\Delta E_s$ . The  $\Delta E_v$  value

$$\Delta E_{\text{sol}} = \Delta E_v + \Delta E_s \quad (2)$$

has been determined experimentally for a number of molecules and could, in principle, be the result of 'accurate' quantum-mechanical calculations. The  $\Delta E_s$  term was calculated from equation (3), where the terms  $\Delta E_e$ ,  $\Delta E_d$ , and  $\Delta E_c$ , refer, in order, to the difference in the energy involved in the two conformers in electrostatic interactions between permanent and induced dipole moments, in dispersion interactions, and in cavity formation. The single terms appearing in equation (3) were

$$\Delta E_s = \Delta E_e + \Delta E_d + \Delta E_c \quad (3)$$

calculated from the known computational schemes<sup>33b</sup> and parameters reported in the literature.<sup>33,49</sup> The radius of the solute cavity was determined from the molecular volume<sup>33</sup> by employing molecular geometries calculated with the 3-21G//3-21G scheme for each conformer. Dipole moments were also derived from these levels of calculations. The results of solvation energy calculations are collected in Table 4: the single terms appearing in equation (3) are reported only for compound (1). These values show that  $\Delta E_d$  and  $\Delta E_c$  are of opposite sign and almost cancel each other out, while  $\Delta E_e$  is the determining factor of  $\Delta E_s$ , as is also found in other molecules.<sup>33a</sup> This confirms the importance of the charge distribution of the solute molecules, both in determining the most stable conformation in the vapour phase and the change in energy of the different conformers as a function of solvent polarity. If comparison is made with the  $\Delta E_s$  values obtained from the classical theory of dielectrics,<sup>14</sup> those reported in Table 4 for compound (1) are in close agreement, in contrast with the lower values calculated from dipole moments from the STO-3G//STO-3G scheme or by employing experimental values. Since our purpose was a comparative survey of solvent effects on the relative stability of the conformers of derivatives (1)–(3), reference will be made only to the results reported in Table 4.

The solvation energy  $\Delta E_s$  increases in derivatives (1)–(3) with solvent polarity. For compound (1),  $\Delta E_v$  and  $\Delta E_s$  are of opposite sign in all solvents and the resultant  $\Delta E_{\text{sol}}$  is positive or negative according to the absolute magnitude. The data in Table 4 show that the  $\Delta E_{\text{sol}}$  is negative (O,O-*trans* more stable) in solvents with low polarity and positive in more polar solvents. On qualitative grounds, this agrees with the experimental observations<sup>14</sup> and is also reproduced by classical dielectric theory.<sup>14</sup> The stability inversion of O,O-*cis* and O,O-*trans* conformers occurs in media of dielectric constant of *ca.* 20 and *ca.* 3.5 when  $\Delta E_v$  values of  $-12.654$  (calculated) and  $-6.278$  kJ mol<sup>-1</sup> (experimental; see Table 2) respectively are used. According to the values calculated by Abraham<sup>14</sup> and in agreement with experimental results, this change should occur in solvents of dielectric constant of *ca.* 5.

For compound (2),  $\Delta E_s$  and  $\Delta E_v$  are of the same sign, and increased solvent polarity causes an increase in stability of the S,O-*cis* conformer which prevails in the vapour phase. Solvent effects are thus expected to be quite small and this corresponds to experimental observations.<sup>13</sup>

For compound (3)  $\Delta E_s$  and  $\Delta E_v$  are of opposite sign and the higher stability of the O,O-*trans* form in the vapour phase can be reversed by polar solvents. As with derivative (1), the  $\Delta E_s$

and  $\Delta E_v$  values are critical for predicting the range of solvent polarities in which inversion of conformer stability should occur. From the results obtained it can be concluded that this inversion is likely to occur in solvents of higher polarity than in the case of derivative (1). Experimental measurements indicate that while the N,O-*trans* conformer prevails<sup>17–21</sup> in media over a range at polarity, small changes are likely to occur<sup>18</sup> in the N,O-*cis/trans* ratio in highly polar solvents (acetone and dimethyl sulphoxide) yet the N,O-*trans* conformer should not fall below 90%. Classical theory of dielectrics predicts<sup>18</sup> only a small decrease in the N,O-*trans* population in polar solvents.

While the trend of Table 4 is in qualitative agreement with experiment, from a quantitative point of view the change of conformer population with solvent polarity, when predicted, occurs in a dielectric constant range not entirely coincident with experiment: the choice of dipole moment, energy content of the conformers in the vapour phase, and radius of the solute cavity determine the calculated trend.

Application of this procedure to the solvation energy of transition states also enables the effects of solvent polarity on the energy barrier to be estimated. The results, obtained by employing the dipole moments of the transition state from the 3-21G//3-21G approach, are reported in Table 4 and show that for compounds (1)–(3) increased solvent polarity augments the energy barrier for internal rotation; for derivative (2) this enhancement is larger than for derivatives (1) and (3). A comparison with experimental results is possible<sup>14</sup> only for compound (1) and, from a qualitative point of view, can be considered satisfactory. In the dielectric constant range considered ( $\leq 32.6$ )  $\Delta E^*$  increases 6–8 kJ mol<sup>-1</sup> on going from the vapour to the pure liquid ( $\epsilon$  41.9) and this is reproduced<sup>14</sup> more quantitatively by classical dielectrics theory. For compound (2) the solvation effect on the energy barrier appears to be rather large, but unfortunately no experimental results are available for discussion of this observation. The  $\Delta E_s^*$  values are probably overestimated owing to the choice of dipole moments, as occurs for the  $\Delta E_s$  values.

In conclusion, this comparative study of solvent effects in derivatives (1)–(3) shows that for furan- and pyridine-2-carbaldehyde a mobile equilibrium should be expected with a change of stability from the less polar X,O-*trans* to the more polar X,O-*cis* conformer with increasing solvent polarity, in a different range of dielectric constant for the two molecules. For derivative (1) this is in agreement with experimental findings,<sup>14,27,50</sup> but from a qualitative point of view only. For derivative (3) it was found<sup>18</sup> that the N,O-*trans* form predominates to the extent of  $\geq 90\%$  even in solvents of high polarity (*e.g.* dimethyl sulphoxide). The equilibrium in thiophene-2-carbaldehyde should be only slightly perturbed by solvent polarity, the S,O-*cis* form being more stable in all solvents, in agreement with experimental evidence.<sup>9,12,13,51</sup> As regards the calculated solvent effects on the energy barriers for *cis/trans* interconversion, the results show that they become greater with increased solvent polarity and that the effect is more significant for derivative (2). Only for derivative (1) is experimental evidence available<sup>7,14</sup> and this is in agreement with the calculated trend.

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#### References

- Part 1, R. Benassi, L. Schenetti, and F. Taddei, *J. Chem. Soc., Perkin Trans. 2*, 1979, 545.

- 2 Part 2, R. Benassi, U. Folli, D. Iarossi, L. Schenetti, and F. Taddei, *J. Chem. Soc., Perkin Trans. 2*, 1981, 228.
- 3 Part 3, R. Benassi, U. Folli, D. Iarossi, L. Schenetti, and F. Taddei, *J. Chem. Soc., Perkin Trans. 2*, 1983, 911.
- 4 Part 4, R. Benassi, U. Folli, D. Iarossi, L. Schenetti, and F. Taddei, *J. Chem. Soc., Perkin Trans. 2*, 1984, 1479.
- 5 Part 5, R. Benassi, U. Folli, D. Iarossi, L. Schenetti, and F. Taddei, *J. Chem. Soc., Perkin Trans. 2*, 1987, 351.
- 6 R. J. Abraham, P. J. Chadwick, and F. Sancassan, *Tetrahedron*, 1982, **38**, 1485.
- 7 D. Casarini, L. Lunazzi, and D. Macciantelli, *J. Chem. Soc., Perkin Trans. 2*, 1985, 1839.
- 8 L. Lunazzi and C. A. Veracini, *J. Chem. Soc., Perkin Trans. 2*, 1973, 1739.
- 9 L. Lunazzi, G. Placucci, C. Chatgililoglu, and D. Macciantelli, *J. Chem. Soc., Perkin Trans. 2*, 1984, 819.
- 10 J. Fernandez Bertran, E. Ortiz, and L. Ballester, *J. Mol. Struct.*, 1973, **17**, 161.
- 11 C. L. Cheng, I. G. John, G. L. D. Ritchie, P. H. Gore, and L. Farnell, *J. Chem. Soc., Perkin Trans. 2*, 1975, 744.
- 12 J. Fernandez Bertran and M. Rodriguez, *Org. Magn. Reson.*, 1974, **6**, 525.
- 13 S. R. Salman, *Org. Magn. Reson.*, 1982, **20**, 151.
- 14 R. J. Abraham and T. M. Sivers, *Tetrahedron*, 1972, **28**, 3015.
- 15 B. R. Larson, F. Nicolaisen, and J. T. Nielsen, *Acta Chem. Scand.*, 1972, **26**, 1736.
- 16 D. J. Chadwick, *J. Chem. Soc., Perkin Trans. 2*, 1976, 451.
- 17 F. A. Miller, W. G. Fateley, and R. E. Witkowski, *Spectrochim. Acta*, 1967, **23A**, 891.
- 18 W. Danchura, T. Schaefer, J. B. Rowbotham, and D. J. Wood, *Can. J. Chem.*, 1974, **52**, 3986.
- 19 G. Conti, M. Longeri, E. Matteoli, and C. Petrongolo, *J. Chem. Soc., Perkin Trans. 2*, 1975, 1673.
- 20 G. Cerioni, L. Lunazzi, and D. Macciantelli, *J. Chem. Soc., Perkin Trans. 2*, 1976, 1791.
- 21 T. Drakenberg, *J. Chem. Soc., Perkin Trans. 2*, 1976, 147.
- 22 Y. Kawashima, M. Suzuki, and K. Kuzima, *Bull. Chem. Soc. Jpn.*, 1975, **48**, 2009.
- 23 R. J. W. Le Fèvre and P. J. Stiles, *J. Chem. Soc. B*, 1966, 420.
- 24 C. L. Cheng and G. L. D. Ritchie, *J. Chem. Soc., Perkin Trans. 2*, 1973, 1461.
- 25 R. Benassi, U. Folli, D. Iarossi, L. Schenetti, and F. Taddei, unpublished results.
- 26 I. A. John, L. Radom, and L. D. Ritchie, *J. Chem. Soc., Perkin Trans. 2*, 1977, 1601.
- 27 V. N. Sheinker, A. D. Garnovskii, and O. A. Osipov, *Russ. Chem. Rev. (Engl. Transl.)*, 1981, **50**, 336.
- 28 V. Galasso, *Mol. Phys.*, 1973, **26**, 81.
- 29 L. Kaper and T. De Boer, *Spectrochim. Acta*, 1970, **A26**, 2171; L. Kaper and T. J. De Boer, *ibid.*, 1971, **A27**, 261; M. C. Fournié-Zaluski, B. P. Roques, and C. Chatain-Cathaud, *Org. Magn. Reson.*, 1975, **7**, 160.
- 30 D. Boicelli, L. Lunazzi, and D. Macciantelli, *Tetrahedron Lett.*, 1975, 1205.
- 31 B. Roques, S. Combrisson, C. Riche, and C. Pascard-Billy, *Tetrahedron*, 1970, **26**, 3555; B. Roques and M. C. Fournié-Zaluski, *Org. Magn. Reson.*, 1971, **3**, 305.
- 32 J. Kao and L. Radom, *J. Am. Chem. Soc.*, 1979, **101**, 311.
- 33 (a) D. L. Beveridge, M. M. Kelly, and R. J. Radna, *J. Am. Chem. Soc.*, 1974, **96**, 3769; (b) F. Birnstock, H. J. Hofman, and H. J. Köhler, *Theor. Chim. Acta*, 1976, **42**, 311.
- 34 O. Sinanoğlu, *Adv. Chem. Phys.*, 1968, **12**, 283; *Theor. Chim. Acta*, 1974, **33**, 279; in 'Molecular Interactions,' eds. M. Ratajczak and W. J. Orville-Thomas, Wiley, Chichester, 1982, vol. 3.
- 35 GAUSSIAN-80: An *ab-initio* Molecular Orbital Program; J. S. Binkley, R. A. Whiteside, R. Krishnan, D. Seeger, D. J. De Fries, H. B. Schlegel, S. Topiol, L. R. Kahn, and J. A. Pople, *QCPE*, 1981, **13**, 406; GAUSSIAN-82. Release A: J. S. Binkley, K. Ragavachari, D. J. De Fries, H. B. Schlegel, R. A. Whiteside, G. Fluder, J. M. Frisch, R. Seeger, and J. A. Pople, Carnegie-Mellon University.
- 36 H. B. Schlegel, *J. Comput. Chem.*, 1982, **3**, 214.
- 37 B. A. Murtaugh and R. W. H. Sargent, *Comput. J.*, 1980, **13**, 185.
- 38 C. Petrongolo, *Chem. Phys. Lett.*, 1976, **42**, 512.
- 39 I. G. John and L. Radom, *J. Am. Chem. Soc.*, 1978, **100**, 3981.
- 40 F. Bernardi, A. Bottoni, and A. Mangini, *Gazz. Chim. Ital.*, 1977, **107**, 57.
- 41 W. R. Harbarger and S. H. Bauer, *Acta Crystallogr.*, 1970, **26B**, 1010; R. A. Bonham and F. A. Momany, *J. Phys. Chem.*, 1963, **67**, 2474; B. Bak, D. Christensen, L. Mansen-Nygaard, and J. Rastrup-Andersen, *J. Mol. Spectrosc.*, 1961, **7**, 58.
- 42 'Tables of Interatomic Distances and Configuration in Molecules and Ions,' ed. L. Sutton, The Chemical Society, London, Special Publications nos. 11 and 18, 1958 and 1965.
- 43 T. Oie, G. H. Loew, S. K. Burt, and R. D. MacElroy, *J. Am. Chem. Soc.*, 1983, **105**, 2221.
- 44 S. Binkley, J. A. Pople, and W. J. Hehre, *J. Am. Chem. Soc.*, 1980, **102**, 940; M. S. Gordon, J. S. Binkley, J. A. Pople, N. J. Pietro, and W. J. Hehre, *ibid.*, 1982, **104**, 2797.
- 45 J. M. Lehn and G. Ourisson, *Bull. Soc. Chim. Fr.*, 1963, 1113.
- 46 L. J. Collins and D. N. Kirk, *Tetrahedron Lett.*, 1970, 1547; R. J. Abraham and Z. L. Rossetti, *ibid.*, 1972, 4965.
- 47 C. Weiss and I. A. Abronin, *Izv. Akad. Nauk. SSSR, Ser. Khim.*, 1984, 364 (*Chem. Abstr.*, 1984, **100**, 191025).
- 48 O. Tapia, in 'Molecular Interactions,' eds. H. Ratajczak and W. J. Orville-Thomas, Wiley, Chichester 1982, vol. 3; O. Tapia and O. Goscinski, *Mol. Phys.*, 1975, **29**, 1653.
- 49 Lange, 'Handbook of Chemistry,' Handbook Publishers, Inc., Sandusky, Ohio, 1956; T. Halicioglu and A. Sinanoğlu, *Ann. N.Y. Acad. Sci.*, 1969, **158**, 308.
- 50 C. Chatgililoglu, L. Lunazzi, D. Macciantelli, and G. Placucci, *J. Am. Chem. Soc.*, 1984, **106**, 5252.
- 51 V. N. Sheinker, E. G. Merinova, M. E. Perel'son, and O. A. Osipov, *Zh. Obsch. Khim.*, 1976, **46**, 1582 (*Chem. Abstr.*, 1976, **85**, 192098).

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