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Theoretical and Infrared Investigation of the Conformations of 1,3-Dihaloacetones

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The conformational equilibria for 1,3-difluoro- (DFA), 1,3-dichloro- (DCA), and 1,3-dibromo-acetone (DBA) have been determined through IR spectroscopy, ab initio calculations at the B3LYP/6-311++G(2df,2p) level, and solvation calculations. The C=O stretching frequencies of DFA, DCA, and DBA in the vapor phase were calculated theoretically and compared to the experimental C=O frequencies in solvents with varying polarities. The theoretical calculations also gave the energy minima and thus the conformational equilibria of these molecules in the vapor phase in terms of the rotamers **1** (cis/cis), **2** (cis/gauche), **3** (cis/trans), **4** (gauche/gauche), **5** (gauche/gauche′), and **6** (trans/trans). For DFA, the stable conformers in the vapor phase are **1**, **3**, and **5**, conformer **3** being the most stable. The conformer ratio in solution changes from circa 12% for **1**, 85% for **3**, and 3% for **5** in CCl_4 to 34% for **1** and 66% for **3** in CH_3CN. For DCA, the most stable forms are the same as those for DFA, but in this case conformer **5** is the most stable form in the vapor phase. In solution the equilibrium changes from circa 58% for **3** and 42% for **5** in CCl_4 to 37% for **1**, 57% for **3**, and 6% for **5** in CH_3CN. For DBA, the most stable conformers in the vapor phase are **1**, **2**, and **5**, conformer **5** again being the most stable form. In solution the population changes from circa 36% for **2** and 64% for **5** in CCl_4 to 29% for **1**, 57% for **2**, and 14% for **5** in CH_3CN. The conformer populations in both the vapor phase and the solvents studied can be explained quantitatively from the ab initio and solvation calculations.

I. Introduction

1,3-Dihaloacetones have been widely used as starting materials in organic synthesis.[1−3] They are also very important compounds in bioorganic chemistry.[4−8] A remarkable example is the use of 1,3-difluoro-2-propanol, the major ingredient of the pesticide Gliftor, easily converted to 1,3-difluoroacetone, which acts as a toxic agent in the Krebs' cycle.[8] 1,3-Difluoroacetone enters the cycle as fluoroacetylCoA and is then converted to (−)-erythrofluorocitrate, which is not recognized by the enzyme aconitate hydratase, and the biological reaction sequence is interrupted.

Despite the importance and applications of 1,3-dihaloacetones in organic and bioorganic chemistry, there are only a few reports on the determination of their conformations. Furthermore, the available studies disagree as to which are the stable conformers in both the vapor and condensed phases.

The simple α-halogenated ketones XCH_2COR exist in solution and in the vapor phase as mixtures of trans and cis rotamers for the fluoro derivative[9−11] (Figure 1a) and cis and gauche forms for the chloro, bromo, and iodo derivatives[12] (Figure 1b). For the 1,3-dihalogenated ketones XCH_2COCH_2X (X = F, Cl, and Br), the presence of a second, symmetrically substituted, halogen atom increases the number of possible rotational isomers (Figure 2).

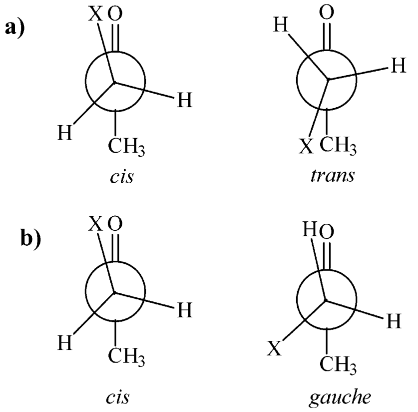

Figure 1. Stable conformers for haloacetones: (a) X = F, (b) X = Cl, Br, and I.

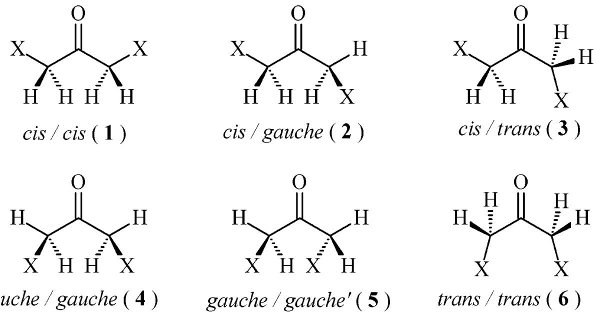

Figure 2. Possible rotamers for 1,3-dihaloacetones (X = F, Cl, and Br).

For 1,3-difluoroacetone, studies utilizing theoretical methods, as well as IR, NMR, and microwave spectroscopies,[13−17] show different results for the conformer stabilities in gas or liquid phases, and a general agreement has not yet been reached, since all of the **1**−**5** (Figure 2) forms have been invoked to be the

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TABLE 1: Intensities (*I*) and Carbonyl Frequencies ($\nu_{C=O}$ cm^{-1}) in the Fundamental and First Overtone IR spectra for DFA, DCA, and DBA in Selected Solvents

	$\nu_{C=O}$ fundamental								$\nu_{C=O}$ first overtone					
	CCl_4		$CHCl_3$		CH_2Cl_2		CH_3CN		CCl_4		$CHCl_3$		CH_2Cl_2	
compound	$\nu_{C=O}$	*I*	$\nu_{C=O}$	*I*	$\nu_{C=O}$	*I*	$\nu_{C=O}$	*I*	$\nu_{C=O}$	*I*	$\nu_{C=O}$	*I*	$\nu_{C=O}$	*I*
DFA	1740	0.004												
	1759	0.132	1754	0.126	1754	0.182	1754	0.177	3499	0.116	3492	0.094	3491	0.125
	1769	0.019	1760	0.036	1763	0.039	1761	0.092	3523	0.008	3515	0.003	3510	0.011
DCA	1730	0.088	1727	0.039	1727	0.040	1728	0.010	3440	0.064	3433	0.028	3433	0.024
	1748	0.119	1743	0.131	1743	0.185	1743	0.095	3476	0.090	3468	0.111	3468	0.103
			1760	0.006	1758	0.027	1755	0.062					3494	0.015
DBA	1720	0.108	1717	0.080	1717	0.063	1717	0.021	3421	0.088	3417	0.054	3417	0.049
	1739	0.061	1736	0.085	1736	0.098	1737	0.083	3460	0.042	3454	0.050	3454	0.056
			1758	0.008	1757	0.015	1756	0.042					3496	0.015

TABLE 2: Dihedral Angles (θ_1 and θ_2), Energies, and Dipole Moments at the B3LYP/6-311++G(2df,2p) Level and IR C═O Frequency ($\nu_{C=O}$) and Its Intensity ($I_{\nu_{C=O}}$) at the B3LYP/6-311++G(d,p) Level for the Stable Forms[a]

	DFA				DCA				DBA			
conformer	**3**	**5**	**1**	**6**	**5**	**3**	**1**	**4**	**5**	**2**	**1**	**4**
θ_1[a]	180	141.8	0.0	180.0	123.6	1.5	0.0	101.1	108.4	−6.6	0.0	92.9
θ_2[a]	0	−141.8	0.0	180.0	−126.3	174.3	0.0	−101.1	−108.4	108.7	0.0	−92.9
energy /kcal mol^{-1}	0.00	1.30	3.30	3.70	0.0	0.72	2.40	4.26	0.00	2.01	3.55	4.07
dipole moment /D	2.66	0.06	4.68	0.63	0.64	2.35	4.21	3.20	1.43	3.30	3.97	3.22
$\nu_{C=O}$ /cm^{-1} [b]	1758.6	1743.3	1776.5	1721.8	1730.5	1748.1	1777.3	1731.3	1724.4	1746.1	1770.3	1723.4
$I_{\nu_{CdO}}$ /km mol^{-1}	163.1	150.6	160.8	129.4	183.1	140.7	112.0	164.5	189.8	142.9	94.3	171.8

[a] $\theta_1 = X_1{-}C{-}C{=}O$ and $\theta_2 = O{=}C{-}C{-}X_2$, where X = F (DFA), Cl (DCA), and Br (DBA). [b] Values obtained through multiplying the calculated frequencies by 0.96 (the correction factor).

most stable conformation. In the same way, studies for 1,3-dichloro- and 1,3-dibromo-acetone present divergent results when comparing the methods used for their conformational analyses.[18−21]

In order to establish a suitable tool to deduce the stable conformers and their geometries, energy differences and C═O vibrational frequencies, we have applied a methodology based on combining IR measurements in solution with theoretical calculations at a reasonably high level in the present investigation. These data allowed us to assign the C═O absorptions for the stable rotamers and deduce their populations in solvents of varying polarities, despite the uncertainties of the direct measurement of the band intensities, since each rotamer may have a different molar absorptivity.[22]

II. Experimental Section

Compounds. 1,3-Difluoroacetone (DFA) was synthesized according to a procedure described in the literature,[23] based on the reaction of 1,3-difluoro-2-propanol, sodium dichromate, and sulfuric acid in water. 1,3-Dichloroacetone (DCA) and 1,3-dibromoacetone (DBA) were obtained commercially from Acros Organics and used without further purification.

Infrared Spectra. The infrared spectra of DFA, DCA, and DBA (Figures 3−5) were recorded on a BOMEM MB-100 spectrometer using CCl_4, $CHCl_3$, CH_2Cl_2, and CH_3CN solutions of 0.02 mol L^{-1}, in a NaCl cell with a spacer of 0.5 mm for the C═O stretching bands in the fundamental mode (Table 1) and in a quartz cell with 10.0 mm of optical length for the first overtone region. The spectra were recorded with 64 scans and resolutions of 1 cm^{-1}. The intensities of the C═O bands for each conformer were measured after band deconvolution through the Grams program, available in the BOMEM equipment, which utilizes Lorentzian and Gaussian functions.

Computational Methods. The geometries and relative electronic energies (ΔE) for the stable conformers of DFA, DCA, and DBA in the isolated state were obtained through the B3LYP method with the 6-311++G(2df,2p) basis set, available in the Gaussian 98 package.[24] The dihedral angles for each stable form, energies, and dipole moments are shown in Table 2. The density functional theory frequency calculations from the optimized geometries were carried out at the B3LYP/6-311++G(d,p) level for each stable form (Table 2). In order to obtain a better coherence between the experimental and calculated C═O stretching wavenumbers, a correction factor due to anharmonicity effects[25] was obtained. This is a common practice in the literature, due to the differences between the experimental values and the corrected calculated frequencies, since the frequency sequences are maintained and can help in the assignment of the principal vibrations to each conformer. This was accomplished by taking acetone, a reference molecule which does not present conformational isomerism, and estimating the carbonyl group stretching wavenumber at the B3LYP/6-311++g(d,p) level and recording its experimental value for the neat liquid. The ratio $\nu_{C=O(exp)}/\nu_{C=O(calc)}$ for the C═O stretching band of acetone gave a correction factor of 0.96 (1718 cm^{-1}/1786 cm^{-1}), which was applied to the 1,3-dihaloacetones, giving the calculated frequencies of Table 2.

Solvation Energies. The solvation energy in any solvent for each conformer can be predicted by the theory developed by Abraham and Bretschneider.[26] In this treatment, the solvation energy of any molecule in state A is the difference between the energy in the vapor phase (E_A^V) and in any solvent (E_A^S) of relative permittivity ϵ. This is given in terms of the dipolar (k_A) and quadrupolar (q_A) reaction-field terms plus a direct dipole−dipole term, to take into account the breakdown of the Onsager reaction-field theory in very polar media.[26] The input for the program consists of simply the geometry data (from Gaussian), since the dipole and quadrupole moments plus the solute radius and refractive index are calculated by the MODELS program.[26] For each conformer a similar equation is obtained differing only in the values of the dipole and quadrupole terms. If the experimental E^S can be obtained through the relative intensities from the IR spectra, one can obtain E^V by extrapolation, the relative conformer vapor state energy, and this may be compared with the Gaussian electronic energies.

III. Results and Discussion

The joint use of infrared spectroscopy and theoretically calculated frequencies for 1,3-dihaloacetones allowed us to assign the C═O stretching frequencies for their possible rotamers and estimate their population in solvents of different polarities. The C═O vibration is very adequate here, since it has a strong absorption in a clear infrared region, and it should be born in mind that the C═O stretching mode experiences different shifts in different solvents, as can be seen in Table 1.

1,3-Difluoroacetone. The theoretical calculations for DFA showed four energy minima, and their energies and dipole moments are shown in Table 2. According to the calculations, conformer **3** (Figure 2) is the most stable one in the vapor phase and has a dipole moment smaller than conformer **1** but larger than the other two forms (**5** and **6**), which present almost zero dipole moments (Table 2). Conformer **5** is the second most stable form in the vapor phase.

It would be expected that conformer **5** is present in small amounts in a nonpolar solvent, for example, CCl_4, but it vanishes in the remaining solvents, due to its very low dipole moment. Despite the high energy of conformer **1**, its dipole moment (4.68 D) is large enough to produce a reasonable percentage in solvents with moderate and high polarities. Conformer **3** has a moderate dipole moment (2.66 D), and thus it makes sense to expect a similar behavior pattern in all solvents, that is, a representative population from the vapor phase to solvents with high relative permittivity. Because of the high energy (ΔE = 3.70 kcal mol^{-1}) and the low dipole moment (0.63 D) of conformer **6**, its population should be negligible in both the vapor and condensed phases.

The carbonyl frequencies in the IR spectra for DFA (Figure 3) show the trends mentioned above. The first overtone region has also been analyzed to prevent interference from Fermi resonance in the fundamental C═O stretching vibration, although these band shapes do not show such a combination effect.

From a comparison of the calculated and experimental C═O fundamental frequencies, the absorption for each conformer was assigned, due to the strict correlation between the data (Tables 1 and 2). The major preference for one conformer is evident (Figure 3). The analytically deconvoluted bands in CCl_4 revealed the presence of three vibrational frequencies. The first one at 1740 cm^{-1} is due to conformer **5**, the second and strongest one, at 1759 cm^{-1}, is assigned to conformer **3**, and the last one, at 1769 cm^{-1}, is a shoulder corresponding to conformer **1**. In the remaining solvents, which are more polar than CCl_4, the absorption due to conformer **5** vanishes and the more polar **3** and **1** forms remain in solution, the band for **1** being easily noted in CH_3CN (Figure 3g).

The intensity ratios between the rotamer frequencies allow an approximate qualitative conformational analysis, as each rotamer has a distinct molar absorptivity for C═O absorption, since this bond, as with any other, presents different characteristics when changing conformation and solvent.[22,27] Evidence for the molar absorptivity dependence with conformation is given by the data in Table 2, which shows the calculated IR intensities for the C═O stretching of all rotamers, where substantial differences are observed. The use of the same extinction coefficients for different conformations is very often carried out to estimate the percentages of rotamers by IR at a single temperature, and this procedure is usually well accepted. With this consideration, the experimental intensities (Table 1) were applied to estimate the populations, which varied from 3% of **5**, 85% of **3**, and 12% of **1** in CCl_4 to 66% of **3** and 34% of **1** in CH_3CN. A complete analysis may be found in Table 3. These results are consistent with the methylene bending mode analysis and dipole moment determinations in CCl_4 by Maury et al.,[16] whose evaluation indicated **3** as the only form present in this solution. In solvents with a high dielectric constant, like CH_3CN, Shapiro et al.,[17] through their NMR studies, deduced that the conformational mixture has a high proportion of **1**, due to its large dipole moment, in agreement with our results.

1,3-Dichloroacetone. The theoretical calculations for DCA also showed four energy minima, as in DFA, but the rotamer stabilities and dipole moments present a different sequence (Table 2). Now, conformer **5** (Figure 2) is the most stable one in the vapor phase and has the smallest dipole moment (0.64 D), and should be stable in nonpolar and moderately polar solvents. Conformer **3** is the second most stable form (ΔE = 0.72 kcal mol^{-1}) in the vapor phase and has a moderate dipole moment (2.35 D). Thus, it may be expected that this conformer displays a similar behavior pattern in all solvents, that is, a representative population from the vapor phase to solvents with high relative permittivities.

Conformer **1** is the third stable form (ΔE = 2.40 kcal mol^{-1}) in the vapor phase and shows the highest dipole moment (4.21 D). It should thus be expected that conformer **1** appears in a reasonable amount in solvents with moderate and high polarities. Conformer **4** has the highest energy (ΔE = 4.26 kcal mol^{-1}) and a relatively low dipole moment (3.20 D) and, thus, its population should be negligible in both the vapor and condensed phases.

We should therefore expect two carbonyl frequencies in the IR spectra for DCA in CCl_4 (nonpolar solvent) solution and three for the remaining solvents. In fact, the experimental carbonyl frequencies in the IR spectra for DCA (Figure 4) are in agreement with the theoretical data. By comparison of the calculated and experimental C═O fundamental frequencies, the absorption for each conformer was easily assigned, due to the strict correlation between these data (Tables 1 and 2). The major preference for one conformer in all solvents is evident (Figure 4). The analysis of the fundamental carbonyl region in CCl_4 (Figure 4a) revealed the presence of two vibration frequencies. The first one at 1730 cm^{-1} is due to conformer **5**, and the second and highest one, at 1748 cm^{-1}, refers to conformer **3**. In the remaining solvents, which are more polar than CCl_4, the absorption due to conformer **5** has a decreased intensity and a shoulder appears at a high frequency, due to conformer **1**.

The intensity ratios of the bands allow a qualitative conformational analysis. The measured populations varied from 42% of **5** and 58% of **3** in CCl_4 to 6% of **5**, 57% of **3**, and 37% of **1** in CH_3CN. The complete figures are found in Table 3. It can be observed for DCA (Table 3) that the population of conformer **3** increases from CCl_4 to CH_2Cl_2, as expected due to its moderate dipole moment (2.35 D), but in a polar solvent, namely, CH_3CN, the population of conformer **3** decreases and that of conformer **1**, presenting the highest dipole moment (4.21 D), is favored. The disagreement between these data and the literature is probably due to the uncertainties and inconclusive results obtained through the methods used,[18−21] particularly the molecular mechanics calculations,[21] which gave the **1**, **2**, and **5** structures as the stable forms.

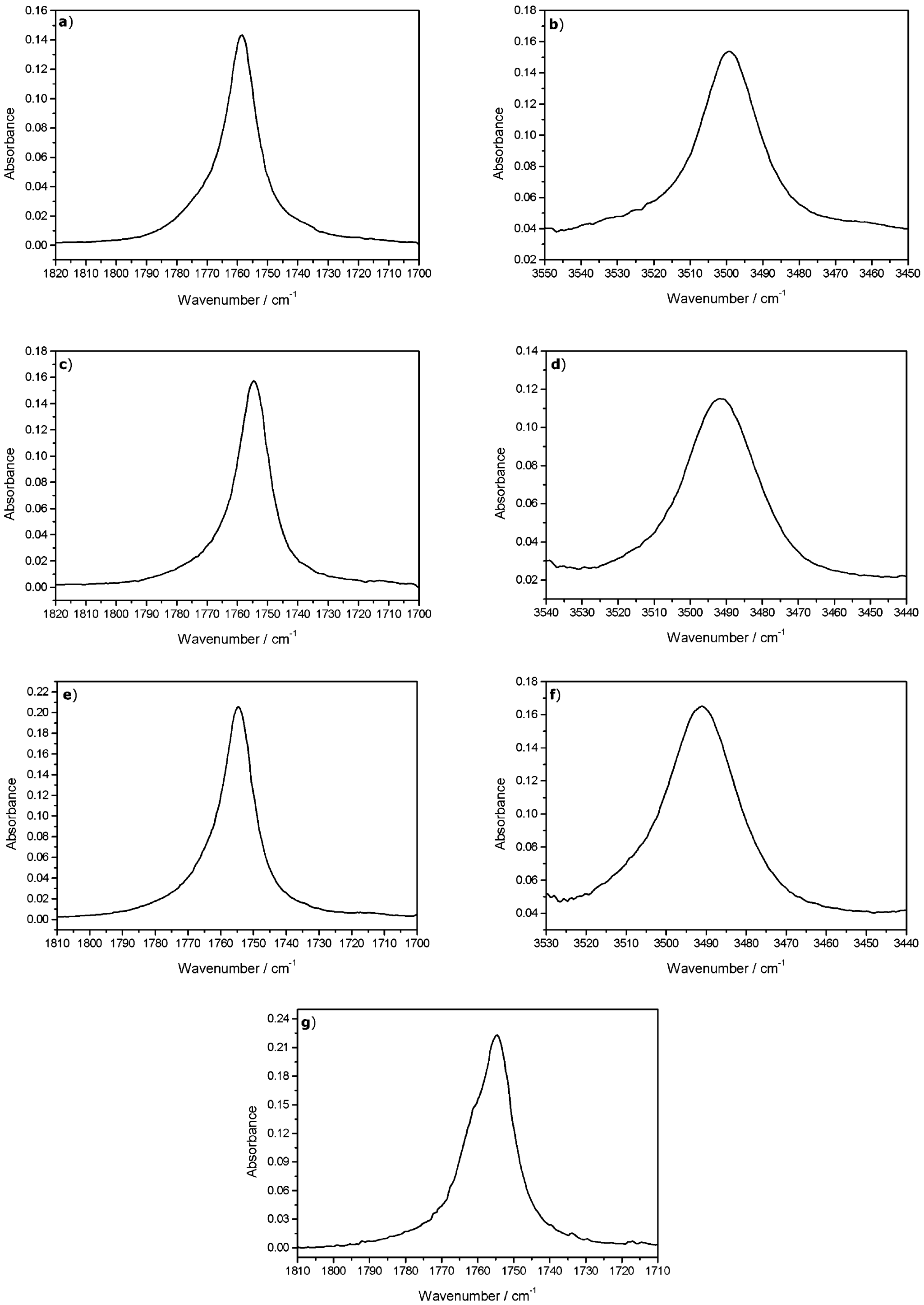

Figure 3. Carbonyl absorption band in the IR spectrum of 1,3-difluoroacetone in (a) CCl_4, (b) CCl_4 (first overtone), (c) $CHCl_3$, (d) $CHCl_3$ (first overtone), (e) CH_2Cl_2, (f) CH_2Cl_2 (first overtone), and (g) CH_3CN.

TABLE 3: Conformer Percentages for DFA, DCA, and DBA Obtained from the Intensity Ratios of the Fundamental C=O Frequencies in the IR Spectra

	DFA			DCA			DBA		
solvent	**1**	**3**	**5**	**1**	**3**	**5**	**1**	**2**	**5**
CCl_4	12	85	3		58	42		36	64
$CHCl_3$	22	78		4	74	22	5	49	46
CH_2Cl_2	18	82		11	73	16	8	56	36
CH_3CN	34	66		37	57	6	29	57	14

1,3-Dibromoacetone. The conformational behavior for DBA is quite different in comparison to DFA and DCA, since one of the four stable structures is a cis−gauche (**2**) form instead of the cis−trans (**3**) form present in DFA and DCA. One of the main peculiarities of **2** is its higher dipole moment, in comparison to **3** of DFA and DCA, and as a consequence, **2** is more stabilized with increasing solvent polarity than **3**.

According to the theoretical calculations, conformer **5** in DBA is the most stable one in the vapor phase and also has the smallest dipole moment (1.43 D), while **2** is the second most stable form with a dipole moment of 3.30 D, significantly higher than **5**. It is then expected that the population of **5** decreases with increasing solvent polarity, and in contrast, **2** must be present in significant percentage in solvents with moderate and high polarities.

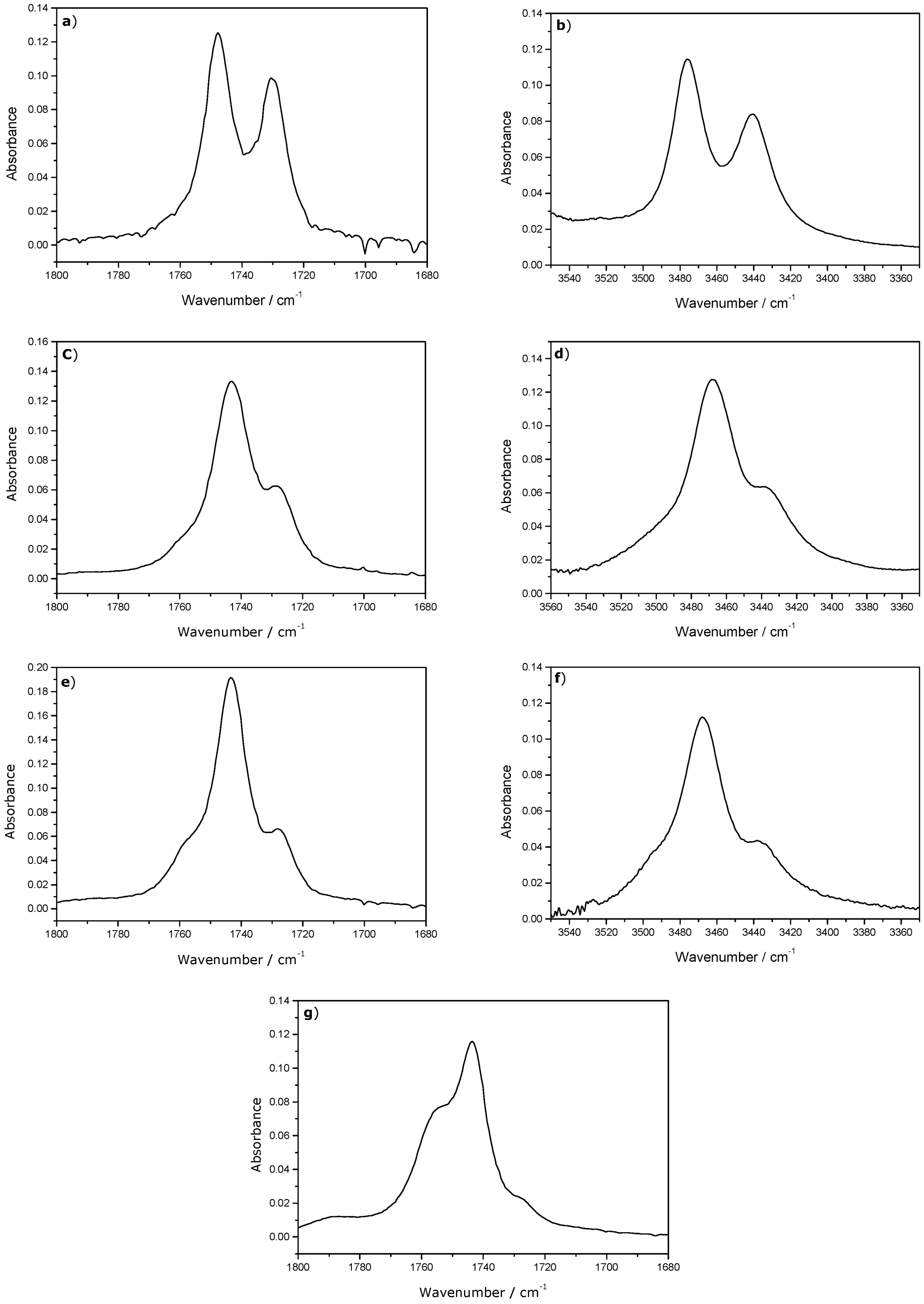

Figure 4. Carbonyl absorption band in the IR spectrum of 1,3-dichloroacetone in (a) CCl_4, (b) CCl_4 (first overtone), (c) $CHCl_3$, (d) $CHCl_3$ (first overtone), (e) CH_2Cl_2, (f) CH_2Cl_2 (first overtone), and (g) CH_3CN.

According to the theoretical data (Table 2), rotamer **1** appears as the third stable form (ΔE = 3.55 kcal mol^{-1}) but with a high dipole moment (3.97 D). Therefore, an appreciable amount of **1** is expected in polar solvents, while conformer **4**, which presents the highest energy (4.07 kcal mol^{-1}) and has an intermediate dipole moment (3.22 D), should not be observed in both the vapor and condensed phases.

The bands in the IR spectra for DBA (Figure 5) in the fundamental and first overtone C═O region in CCl_4 solution are noted, with a third absorption appearing at a higher wavenumber for $CHCl_3$ solution. A detailed comparison between the experimental and calculated fundamental carbonyl frequencies (Tables 1 and 2) allows us to assign the C═O band with the lowest wavenumber (1720 cm^{-1} in CCl_4) to rotamer **5**. The band with an intermediate frequency (1739 cm^{-1} in CCl_4) is attributed to **2**, while the band with the highest wavenumber (1758 cm^{-1} in $CHCl_3$) refers to **1**. The calculated smallest value for the carbonyl frequency is referred to rotamer **4**, which cannot be taken into account in the experimental spectrum, as mentioned above, due to its high energy and relatively low dipole moment.

The rotational equilibrium for DBA in various solvents (Table 3), obtained through the intensity measurements in the experimental infrared spectra, demonstrates the expected behavior, that is, the less polar and most stable rotamer in the vapor phase (**5**) has a decrease in percentage on going from CCl_4 (64%) to CH_3CN (14%), while the second most stable form in the vapor phase (**2**) becomes the major one in $CHCl_3$. It is also interesting

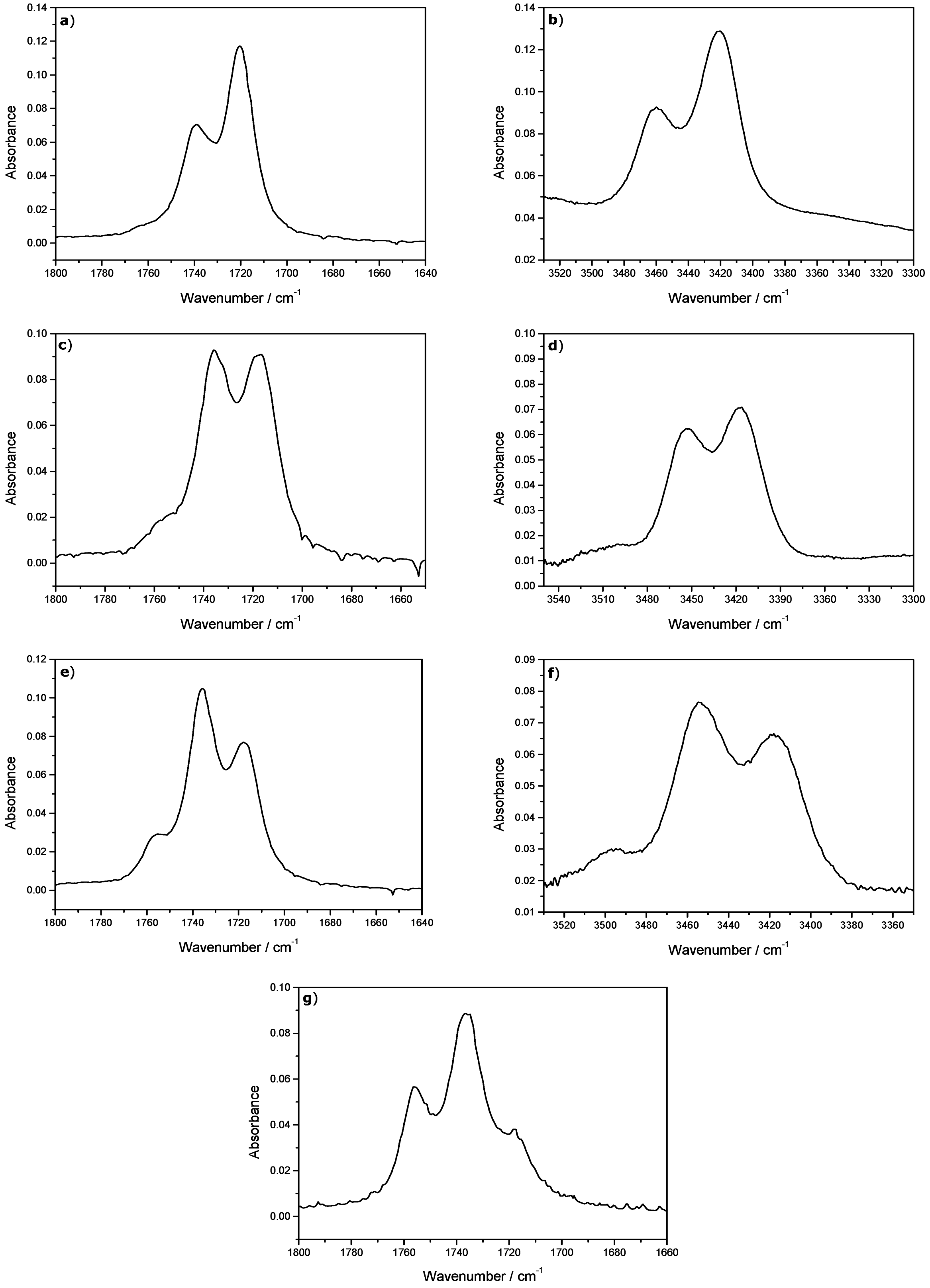

Figure 5. Carbonyl absorption band in the IR spectrum of 1,3-dibromoacetone in (a) CCl_4, (b) CCl_4 (first overtone), (c) $CHCl_3$, (d) $CHCl_3$ (first overtone), (e) CH_2Cl_2, (f) CH_2Cl_2 (first overtone), and (g) CH_3CN.

that conformer **1**, similarly to what was observed in DFA and DCA, has a high energy in the vapor phase and in CCl_4 but appears in $CHCl_3$ and has an important contribution for the conformational equilibrium of DBA in CH_3CN.

Solvation Calculations. The solvation calculations can now be combined with the experimental conformer populations to give a quantitative account of the dependence of the conformational equilibria on the solvent polarity. The conformer populations in any solvent immediately give the conformer energies in that solvent from the Boltzmann equation, provided the statistical weights of the conformers are included. These are 1, 4, 2, 2, 2, and 1 for conformers **1**, **2**, **3**, **4**, **5**, and **6**,

TABLE 4: Solvation Energies ($E^V - E^S$) and Vapor State Conformer Energies (E^V) (kcal mol^{-1}) in 1,3-Dihaloacetones[a,b]

	DFA				DCA				DBA			
solvent	**1**	**3**	**5**	**6**	**1**	**3**	**4**	**5**	**1**	**2**	**4**	**5**
vapor	3.3[c]	0.0	1.7		3.9[d]	0.0		0.0	3.7[d]	1.6		0.0
CCl_4	3.19	1.46	1.19	1.48	2.53	1.09	1.48	0.72	2.22	1.37	1.35	0.70
$CHCl_3$	5.48	2.48	1.98	2.49	4.41	1.88	2.58	1.20	3.92	2.41	2.39	1.18
CH_2Cl_2	6.77	3.06	2.42	3.05	5.49	2.32	3.22	1.46	4.90	3.02	3.00	1.45
CH_3CN	9.03	4.09	3.22	4.05	7.32	3.10	4.32	1.94	6.54	4.05	4.04	1.93

[a] From MODELS. [b] From IR intensities and solvation energies. [c] ± 0.5. [d] ± 0.1.

respectively. In this treatment, the experimental conformer energy difference is the Gibbs energy, which is one of the determining factors of the relative intensities in the infrared spectra. It is approximated to the differences in solvation energy, since contributions to the free energy due to zero-point energy, higher vibrational states, and pdV terms, as well as ΔS, are canceled in this approximation. The conformer energy in any solvent (E^S) can be combined with the solvation energy in that solvent ($E^V - E^S$, Table 4) to give the vapor state conformer energy (E^V). These energy values are given in Table 4 (top line). The vapor state conformer energy will be independent of the solvent used if both the populations and the solvation calculations are accurate. For DFA there was a significant spread in the values of E^V (± 0.5 kcal mol^{-1}), but for DCA and DBA it was just ± 0.1 kcal mol^{-1}.

The extrapolated values of E^V (Table 4) for the conformers detected in solution can be compared directly with the values given by the ab initio calculations in Table 2. For DFA the values for conformers **1, 3**, and **5** are 3.3, 1.3, and 0.0 kcal mol^{-1} (ab initio) and 3.3, 1.7, and 0.0 (extrapolated). For DCA the corresponding values are 2.4, 0.7, and 0.0 versus 3.9, 0.0, and 0.0 and for DBA for **1, 2**, and **5** the values are 3.5, 2.0, and 0.0 versus 3.7, 1.6, and 0.0. The generally good agreement between these sets of values is strong support for the procedure adopted here, including the assumptions made in this derivation, such as molar absorptivity effects in the IR data, as mentioned earlier.[22,27]

Conformational Preferences. The stability of the 1,3-dihaloacetones is governed essentially by classical effects, namely steric and electrostatic factors. However, nonclassical effects have also been frequently invoked to explain the stabilities of some systems, which are similar to the ones presented here, and thus, we would expect an appreciable dependence of the conformer stabilities due to the occurrence of orbital interactions.

The high stability of the main gauche−gauche′ (**5**) form, for DCA and DBA (and also for DFA), is the one where the two halogens, as well as the halogen and the carbonyl oxygen, are not eclipsed. Such interactions would lead to high steric and dipolar energies, as shown by **6**, which is not present in DCA and DBA and must be negligible for DFA. The same is true for **4**, which also has the two halogens facing each other. Conformer **4** is not present in DFA and is negligible for DCA and DBA.

For DFA, the lowest energy of conformer cis−trans (**3**) can be explained by the nonclassical interaction n_F-n_O via the σ^*_{C-C} orbital, known to stabilize the cis conformation in fluoroacetaldehyde.[28] This would also explain why conformer **2** is the most stable conformer for DBA, although for DBA the predominant effect, which favors **2** in relation to **3**, must be the relief of the steric strain between the C-1 (bearing a cis Br atom) and the bromine atom in C-3, which is gauche in conformer **2**, and thus not in the same plane as in **3**. Additional evidence for the stability of the cis and trans arrangements (**3** for DFA and DCA and **2** in DBA) are the corresponding structures of fluoroacetone, which occurs as an equilibrium between the cis and trans forms, the trans being favored in the vapor phase.[9]

The stabilization of the *axial* halogen in halocyclohexanones, against the natural *equatorial* preference, has been explained by a better donation of the n_X orbital from the halogen into the empty π^*_{CO} orbital of the carbonyl group. Therefore, it is expected that the $n_X-\pi^*_{CO}$ interactions, involving the gauche-halogen atom, lead to lower energies of conformer **5** in DFA and DCA and also of **5** and **2** in DBA.[28]

For DFA, the cis−trans (**3**) form is the most stable one in the vapor phase, although the dipolar and steric repulsions between one fluorine atom and the carbonyl oxygen are destabilizing. Besides the arguments presented above to explain the extra stability of this form in DFA, which is 1.3 kcal mol^{-1} more stable than **5**, there may also be an electrostatic attractive interaction, such as hydrogen bonding, involving the trans F atom and the hydrogens from the other methylene group. Theoretical support for this is given by a comparison between the calculated distance between the fluorine and those hydrogen atoms and the sum of the van der Waals radii of these atoms. The calculated distance is 2.63 Å, while the sum of the F and H van der Waals radii[29] is 2.67 Å, suggesting the occurrence of this attractive interaction. Similar attractive interactions leading to short hydrogen-to-heteroatom distances have been reported.[30,31]

Obviously, the MO considerations presented above are relevant in vacuo but also in condensed phases. However, in a solvent cage, the electrostatic interaction between solute and solvent can become the main factor, which leads to the stabilization of the more polar rotamer with increasing solvent polarity, as can be observed from the data in Table 3.

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