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The Conformation of 2-Phenylpropionaldehyde and Alkyl 1-Phenylethyl Ketones as Evidenced by Ab Initio Calculations. Relevance of the CH/π and CH/O Interactions in Stereochemistry[#]

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Ab initio MO calculations were carried out for the conformation of 2-phenylpropionaldehyde **1** and related ketones $CH_3CH(C_6H_5)$–CO–R (R = CH_3 **2**, C_2H_5 **3**, *i*-C_3H_7 **4**, and *t*-C_4H_9 **5**) at the MP2/6-311G(d,p)//MP2/6-31G(d) level. The conformation whereby the alkyl group R is synclinal to the phenyl group (rotamer **a**, C_6H_5–C–CO–R torsion angle ϕ 64–93°) has been found to be the most stable. The second most favorable one has been shown to have R flanked by the benzylic methyl group and C_6H_5 (rotamer **b**: ϕ 282–297°). The difference in the enthalpy between **a** and **b** has been calculated to be 1.58, 2.16, 2.19, 2.08, and 4.89 kcal mol^{-1}, respectively, for **1**, **2**, **3**, **4**, and **5**. The C_6H_5/R antiperiplanar conformation (rotamer **c**) has been shown to be the least stable for **1** (ϕ 171°) and is not at an energy minimum for **2**–**5**. In rotamers **a** and **b**, short interatomic distances have been shown between one of the alkyl hydrogens and the phenyl group. In rotamer **a**, a short distance has been calculated between one of the hydrogens of the benzylic methyl group and the carbonyl oxygen. The ab initio results are compatible with those obtained by NMR measurements. Contributions of the CH/π and CH/O interactions to the conformational equilibria have been invoked to accommodate the above results. Instability of rotamer **c** may be due to the unfavorable electrostatic interaction of the C=O dipole vs the quadrupole of the phenyl group. Conformational energies of methyl formate **6**, *N*-methylformamide **7**, and propionaldehyde **8** were also calculated to examine the effect of the CH/O interaction in carbonyl compounds. The results are consistent with the notion that the CH/O interaction is important in stabilizing the CH_3/O eclipsed conformation.

Previously, one of the authors and his co-workers studied, by NMR experiments, the conformation of 2-phenylpropionaldehyde **1** and related ketones $CH_3CH(C_6H_5)$–CO–R: 2-phenyl-3-butanone **2** (R = CH_3), 2-phenyl-3-pentanone **3** (C_2H_5), 2-methyl-4-phenyl-3-pentanone **4** (*i*-C_3H_7), and 2,2-dimethyl-4-phenyl-3-pentanone **5** (*t*-C_4H_9).[1] They found that **1**–**5** prefer the conformation in which the alkyl group R is synclinal to the phenyl group (Ph) and antiperiplanar to the benzylic methyl group C^1H_3 (to avoid confusion, the benzylic methyl group is denoted hereafter as C^1H_3). (rotamer **a** in Fig. 1: Ph/R torsion angle ϕ ca. 60°). The next most stable conformation was suggested to have the alkyl group flanked by C^1H_3 and Ph (rotamer **b**: ϕ ca. 300°). The Ph/R antiperiplanar conformation (rotamer **c**: ϕ ca. 180°) was not shown to prevail in solution.[2] The above result was obtained by studying NMR chemical shifts induced by lanthanoide-shift-reagent (LSR). This conclusion, however, was at variance from the results obtained by the molecular mechanics method.

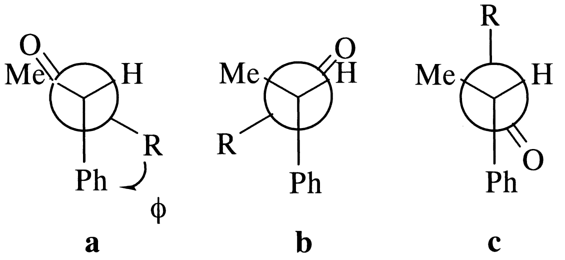

Fig. 1. Three staggered conformations (**a**, **b**, and **c**) of 2-phenylpropionaldehyde **1** $CH_3CH(C_6H_5)$–CO–R (R = H), 2-phenyl-3-butanone **2** (CH_3), 2-phenyl-3-pentanone **3** (C_2H_5), 2-methyl-4-phenyl-3-pentanone **4** (*i*-C_3H_7), and 2,2-dimethyl-4-phenyl-3-pentanone **5** (*t*-C_4H_9). ϕ : R/Ph torsional angle.

The force-field calculation (MM2) predicted that, in **1**–**5**, rotamer **a** is energetically the most favorable.[3] This agreed with the LSR results but the calculation suggested that rotamer **c** was the next most stable. Rotamer **c**, however, has not been shown to prevail in experiments. To investigate the reason for the above discrepancy and to elucidate the principle governing the conformation of these molecules, we carried out high-level ab initio calculations of the relevant compounds. In order to confirm the effect of the putative CH_3/C=O interaction,[1] higher-level calculations were performed for simple model compounds CH_3–X–(C=O)H (Fig. 2): methyl formate **6** (X = O),

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[#] A comprehensive literature list for the CH/π interaction is available on the following website. http://www.tim.hi-ho.ne.jp/dionisio

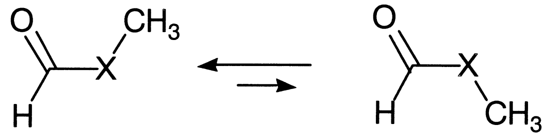

Fig. 2. Two stable rotamers of methyl formate **6** (X = O), *N*-methylformamide **7** (X = NH), and propionaldehyde **8** (X = CH_2).

N-methylformamide **7** (X = NH), and propionaldehyde **8** (X = CH_2).

Method

The Gaussian 98 program[4] was used. The basis sets implemented in the program were employed without modification. Electron correlation energies were calculated by applying the second order Møller-Plesset perturbation theory. For **1–5**, geometry of the molecules was optimized at the HF/6-31G(d) and the MP2/6-31G(d) level of approximation. Using these geometries, single point calculations were performed at the MP2/6-311G(d,p) level to estimate the energies of conformers. Atomic charge distributions were calculated by electrostatic potential fitting according to the scheme of Merz–Singh–Kollman[5] using the MP2/6-311G(d,p) wave functions.

For methyl formate **6**, *N*-methylformamide **7**, and propionaldehyde **8**, geometry optimizations were performed at the MP2/6-311++G(d,p) level, and single point calculations were performed at the CCSD(T)/6-311++G(d,p) level. Vibrational frequencies were calculated using the analytical second derivatives at the same level of the geometry optimization for each conformer. Using these results, the thermal energy corrections were added to the total energy at 298.15 K and 1 atmosphere of pressure, using the principal isotope for each element type. To estimate atomic charge distributions more precisely, they were calculated by the theory of Atoms in Molecules (AIM) by Bader[6] using AIM2000.[7]

Results and Discussion

Conformation of 2-Phenyl-3-butanone and Its Homologues. Table 1 shows relative steric energies of the stable conformations of $CH_3CH(C_6H_5)$–CO–R **1–5** and torsional angles at the potential minima.

First, the torsional potential of Ph–C–CO–R bond was calculated for 2-phenyl-3-butanone **2** (R = CH_3). The geometry was optimized at the MP2/6-31G(d) level. Relative steric energies were then calculated at the MP2/6-311G(d,p) level. The MP2 potentials show that the molecule has two stable conformations, **a** and **b** (Fig. 3). In the most stable conformation **a** (Ph–$C^2H(C^1H_3)$–$C^3(=O)$–C^4H_3 torsion angle ϕ 77°), C^4H_3 is synclinal to Ph and antiperiplanar to C^1H_3. This suggests that the CH/π interaction[8] between C^4H_3 and Ph π-ring is responsible for stabilizing this conformation. In support of this, the distance between one of the three hydrogens in C^4H_3 and the *ipso*-carbon in Ph is 2.85 Å. In rotamer **a**, C–C^1H_3 and C=O bonds are nearly eclipsed. The CH/O interaction[9] may also be responsible for stabilizing this geometry. The distance between a hydrogen in C–C^1H_3 and the C=O oxygen is in fact shown very short, 2.63 Å.

Table 1. Relative Steric Energies (in kcal mol^{-1}) of the Stable Conformations of $CH_3CH(C_6H_5)$–CO–R **1–5** Calculated by the Ab Initio Method (MP2/6-311G(d,p)//MP2/6-31G(d)). Optimized Torsion Angles R/Ph, ϕ/° Are Given in the Parentheses

	Rotamer **a**	Rotamer **b**	Rotamer **c**
H (**1**)	0 (64)	1.58 (302)	2.06 (171)
CH_3 (**2**)	0 (77)	2.16 (283)	
C_2H_5 (**3**)	0 (79)	2.19 (282)	
i-C_3H_7 (**4**)	0 (71)	2.08 (297)	
t-C_4H_9 (**5**)	0 (93)	4.89 (289)	

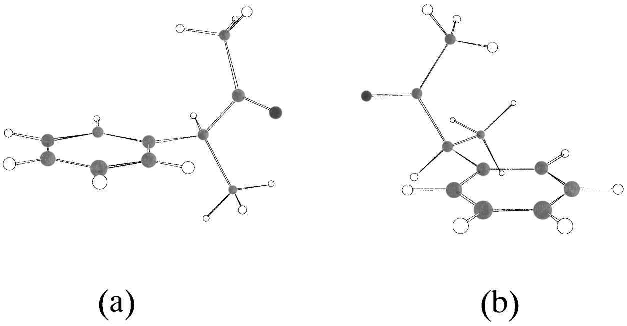

Fig. 3. Optimized structures of 2-phenyl-3-butanone **2**. (a) Rotamer **a**, (b) rotamer **b**.

In the next most stable conformation (**b**: ϕ 283°), C^4H_3 is flanked by Ph and C^1H_3. The CH/π interaction seems to work in stabilizing rotamer **b** also; the distance between a hydrogen in C^4H_3 and the *ipso*-carbon is 2.86 Å. Rotamer **b** has been calculated to be 2.16 kcal mol^{-1} less stable than rotamer **a**. This may reflect the absence of stabilizing C^1H_3/O interaction in rotamer **b**. In this geometry, C^1H_3 is remote from C=O and no effective C^1H_3/O interaction can occur. In conformation **b**, attractive interaction may occur between the methine hydrogen (C^2H) and the carbonyl oxygen. The electron charge of C^2H (Table 2: vide infra), however, is considerably lower than those of C^1H_3. This implies that the intramolecular CH/O hydrogen bond is not formed in such a situation. For C^2H, formation of a 4-membered CH/O ring is expected with the C=O group, while for C^1H_3 a more effective 5-membered interaction may occur. One may also argue that the steric congestion, R vs C^1H_3, is severer than in **a**, so as to destabilize rotamer **b**.

The optimized geometries of **3** (R = C_2H_5), **4** (*i*-C_3H_7), and **5** (*t*-C_4H_9) have shown that these compounds are also stable in conformations **a** and **b** (Fig. 4). In rotamer **a**, the distance between a hydrogen next to the CO moiety (α-CH or C^4H) and the *ipso*-carbon is 2.83 and 2.77 Å, respectively, for **3** (ϕ 79°) and **4** (70°). For the *t*-butyl analog **5**, the torsional angle ϕ increases to 93° and the distance of a hydrogen of the *t*-butyl group (β-CH) from the *ipso*-carbon is 2.91 Å. This is reasonable from stereochemical considerations. The distance between one of the three CHs in C^1H_3 and the C=O oxygen is 2.62, 2.65, and 2.57 Å, respectively, for **3**, **4**, and **5**, these values suggest involvement of the CH/O hydrogen bonding.[1]

In rotamer **b** (ϕ 282–297°), the alkyl group R is flanked by Ph and C^1H_3. As in the case of **2**, rotamer **b** is less stable (2.19 and 2.08 kcal mol^{-1}) than **a** when R = C_2H_5 and *i*-C_3H_7. This is reasonable since the stabilizing C^1H_3/O interaction cannot

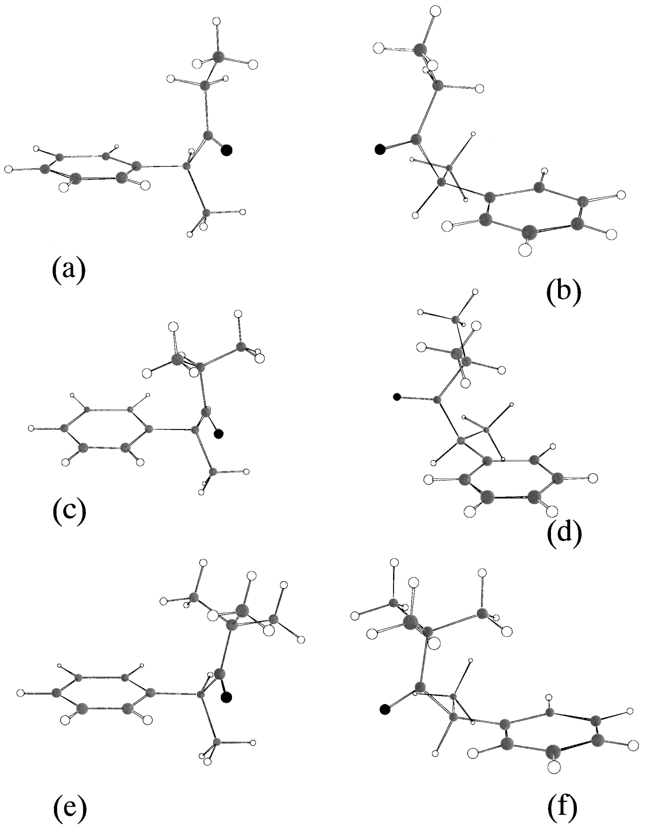

Fig. 4. Optimized structures of 2-phenyl-3-pentanone **3**, 2-methyl-4-phenyl-3-pentanone **4**, and 2,2-dimethyl-4-phenyl-3-pentanone **5**. (a) Rotamer **a** of **3**, (b) rotamer **b** of **3**, (c) rotamer **a** of **4**, (d) rotamer **b** of **4**, (e) rotamer **a** of **5**, (f) rotamer **b** of **5**.

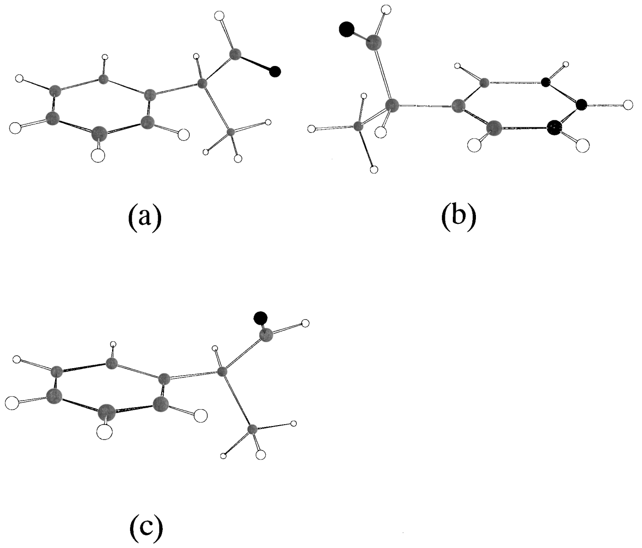

Fig. 5. Optimized structures of 2-phenylpropionaldehyde **1**. (a) Rotamer **a**, (b) rotamer **b**, (c) rotamer **c**.

Table 2. Atomic Charge Distributions Calculated by the Electrostatic Potential Fitting According to the Scheme of Merz–Singh–Kollman. The Conformation of $CH_3CH(C_6H_5)$–CO–R **1**–**5** Was Obtained by MP2/6-311G(d,p)//MP2/6-31G(d) Level Calculations

	Rotamer	O	H [a)]	H [b)]
R				
H (**1**)	**a**	−0.487	+0.249	−0.014
	b	−0.514	+0.330	+0.039
	c	−0.492	+0.248	+0.005
CH_3 (**2**)	**a**	−0.561	+0.308	+0.020
	b	−0.593	+0.311	+0.058
C_2H_5 (**3**)	**a**	−0.536	+0.273	+0.006
	b	−0.563	+0.246	+0.056
i-C_3H_7 (**4**)	**a**	−0.542	+0.305	+0.014
	b	−0.585	+0.299	+0.039
t-C_4H_9 (**5**)	**a**	−0.552	+0.357	+0.090
	b	−0.574	+0.283	+0.046

a) Summation of the atomic charges of three hydrogen atoms in C^1H_3.

b) Methine CH in $C^1H_3C^2H$.

occur in this geometry. In rotamer **b** also, a short CH/π distance is noted between an *α*-CH and the *ipso*-carbon: 2.83 and 2.77 Å, respectively, for **3** and **4** (2.75 Å for a *β*-CH/Ph in **5**). When R = *t*-C_4H_9, rotamer **b** is ca. 4.89 kcal mol^{-1} less stable than **a**. An unfavorable environment due to steric congestion (*t*-Bu vs C^1H_3) may be the reason of the relative instability of rotamer **b** of **5**.

Conformation of 2-Phenylpropionaldehyde. The geometry optimization of 2-phenylpropylaldehyde **1** (R = H) shows that this molecule is in three stable conformations. The optimized geometries are shown in Fig. 5. In the most stable conformation **a** (ϕ 64°), the C–C^1H_3 and C=O groups are nearly eclipsed (shortest CH/O distance 2.72 Å). In the second stable conformation **b** (ϕ 302°), C–C^1H_3 is remote from the C=O group. The calculated energy difference between rotamers **a** and **b** (1.58 kcal mol^{-1}) is about 0.6 kcal mol^{-1} smaller than in the cases of ketenes **2**–**4**. Rotamer **c** (ϕ 171°), where the C=O and C–Ph bonds are eclipsed is the least stable.

The fact that rotamer **c** is not found in **2**–**5** and is least stable in **1** may be interpreted on the ground of unfavorable electrostatic interaction of the carbonyl group with the phenyl ring. The C=O/Ph eclipsed conformation is unstable due to the interaction between the C=O dipole and the quadrupole of Ph, which is destabilizing. We do not know the exact reason for the discrepancy between **1** and **2**–**5**, but the result may reflect the difference in the electronic character of the C=O bond of the aldehyde and ketones. Atomic charge distributions of the three possible rotamers of **1**–**5**, calculated by electrostatic potential fitting [MP2/6-311G(d,p)//MP2/6-31G(d)] according to the scheme of Merz–Singh–Kollman, are shown in Table 2. The electron charge of the carbonyl oxygen atom has in fact been found to be −0.49 for **1** and −0.54 to −0.56 for **2**–**5**. An alternative explanation is that rotamer **c** of **1** is least stable due to the unfavorable C=O/Ph interaction, whereas rotamer **a** can be stabilized by a C^1H_3/O interaction, which is favorable. The stability of rotamer **b** falls between **a** and **c**.

Effect of the Electron Correlation on the CH/π and CH/O Distance. In Table 3 are listed CH/π and CH/O distances calculated for the stable conformations of **1**–**5**, obtained by the HF/6-31G(d) and MP2/6-31G(d) level optimizations. It is re-

Table 3. Comparison of the (a) CH/π and (b) CH/O Distances of the Stable Conformations of $CH_3CH(C_6H_5)–CO–R$ **1**–**5**, Obtained by Two Different Methods of Optimization

(a) CH/π Distance (in Å) between One of the Hydrogens Next to C=O (α–CH; β–CH for **5**) in the Alkyl Group R and the *ipso*-Carbon of the Phenyl Group Ph

	HF [a)]	MP2 [b)]	Δ [c)]
Rotamer **a**			
R			
CH_3 (**2**)	2.929	2.853	0.076
C_2H_5 (**3**)	2.929	2.830	0.099
i-C_3H_7 (**4**)	2.885	2.770	0.115
t-C_4H_9 (**5**)	3.105	2.910	0.195
Rotamer **b**			
R			
CH_3 (**2**)	2.911	2.864	0.047
C_2H_5 (**3**)	2.887	2.826	0.061
i-C_3H_7 (**4**)	2.876	2.774	0.102
t-C_4H_9 (**5**)	2.885	2.748	0.137

(b) CH/O Distance (in Å) between One of the Three Hydrogens in C^1H_3 and the C=O Oxygen in Rotamer **a**

	HF [a)]	MP2 [b)]	Δ [c)]
R			
H (**1**)	2.770	2.719	0.051
CH_3 (**2**)	2.661	2.625	0.036
C_2H_5 (**3**)	2.661	2.621	0.040
i-C_3H_7 (**4**)	2.661	2.653	0.008
t-C_4H_9 (**5**)	2.612	2.565	0.047

a) HF/6-31G(d) optimized geometry. b) MP2/6-31G(d) optimized geometry. c) Difference in the distances obtained by the HF and MP2 methods.

Table 4. Relative Gibbs Free Energies ΔZE (in kcal mol^{-1}) at 298 K of the Conformations of Methyl Formate **6**, *N*-Methylformamide **7**, and Propionaldehyde **8** Calculated by the Ab Initio Method [CCSD(T)/6-311++G(d,p)//MP2/6-311++G(d,p)]. Torsion Angles (in degree) CH_3/C=O Are Given in the Parentheses

$CH_3X(CO)H$		
X = O (**6**)	0 (0)	4.30 (180)
X = NH (**7**)	0 (0)	1.07 (180)
X = CH_2 (**8**)	0 (0)	0.63 (120)

markable that every CH/π distance calculated with the use of MP2/6-31G(d) optimized geometry is shorter than that obtained by the HF/6-31G(d) level optimization. For rotamer **a**, difference in the CH/π distance between the two methods (Δ) increases from 0.08 Å (**2**) to 0.10 Å (**3**), 0.12 Å (**4**), and then to 0.20 Å (**5**). For rotamer **b**, this value increases from 0.05 to 0.06, 0.10, and finally to 0.14 Å in the same order. The result is comprehensible on the general principle that, for the CH/π interaction, a large part of the stabilization comes from the correlation (dispersion) energy. Thus, the geometry optimization must be performed at the MP2 level, in order to predict the correct geometry of a molecule where CH/π interactions may play a part.

Table 3(b) lists the CH/O distances for geometries **a** and **b** calculated by the two methods. In rotamer **a**, the CH/O distance becomes shorter in the MP2 optimized structure (Δ ca. 0.01–0.05 Å) while in rotamer **b** such an effect is absent.[10] The magnitude of Δ is smaller than in the case of CH/π interaction; this difference suggests that the effect from the electron correlation is less important in the CH/O interaction[11] than in the CH/π interaction.

Conformation of Simple Carbonyl Compounds. An interesting feature of the above result is that rotamer **a** is the most stable not only in **2**–**5**, but also in **1**. In the latter molecule, we have no alkyl group that can participate in the CH/π interaction with the phenyl group. One may argue that this is because of the tendency of a double bond to eclipse with a C–C or C–H single bond.[12] Our suggestion, however, is that the C^1H_3/C=O eclipsed conformation is stabilized by the CH/O hydrogen bond. In support of this explanation, the distance between a hydrogen in the benzylic methyl and the carbonyl oxygen has been found very short in rotamer **a** (vide supra). The importance of the CH/O interaction in conformational issues was reported in several papers, spectroscopic[13] as well as crystallographic.[14] Tsuzuki et al. recently studied the conformation of a series of compounds CH_2=CH–CH–X–R (X = O or CH_2, R = CH_3, etc.), by MP2/6-311G**//HF/6-311G** calculations. There they found CH/π and CH/O short distances in the preferred geometries; such results indicate the importance of these interactions in determining the conformational equilibrium.[15]

There is ample evidence in the literature that the CH_3/C=O eclipsed conformation prevails in compounds such as CH_3–X–(C=O)H.[16] Examples include methyl formate **6** (X = O),[17] *N*-methylformamide **7** (X = NH),[18] and propionaldehyde **8** (X = CH_2).[19] To examine the possibility that the CH_3/C=O eclipsed conformation is a consequence of the attractive CH/O hydrogen bond, we carried out ab initio calculations of these molecules. Table 4 summarizes the results. The energy profiles are given in Fig. 6.

In all of the above cases, the minimum energy was obtained at CH_3/C=O torsion angle ca. 0°(geometry *Z*, Fig. 7). In the next stable conformation, the CH_3/C=O torsion angle is ca. 180°, 180°, and 120° (*E*), respectively, for **6**, **7**, and **8**. The calculated Gibbs free energy differences ΔZE are in good agreement with the experimental data: 4.30 vs 4.75 kcal mol^{-1} for **6**, 1.07 vs 1.4–1.6 kcal mol^{-1} for **7**, and 0.63 vs 0.7–1.2 kcal mol^{-1} for **8**. The fact that the CH_3/C=O eclipsed geometry *Z* is more favorable than *E* may be interpreted on the bases of the CH/O interaction. In support of this suggestion, the rotameric equilibrium of aldehydes, $R^1R^2R^3C(\gamma)C(\beta)H_2C(\alpha)H$=O, decreases when the number of CH γ to the C=O oxygen decreases. Thus, Karabatsos and Hsi[20] determined the *Z*/*E* ratio of a series of aldehydes, by measurements of NMR coupling constants. The energy difference ΔZE for CH_3CH_2CHO ($R^1 = R^2 = R^3 = H$), $CH_3CH_2CH_2CHO$ ($R^1 = R^2 = H$, $R^3 = CH_3$), *i*-$PrCH_2CHO$ ($R^1 = H$, $R^2 = R^3 = CH_3$), and *t*-$BuCH_2CHO$ ($R^1 = R^2 = R^3 = CH_3$) was reported to be −0.8, −0.7, −0.4, and +0.25 kcal mol^{-1}, respectively. Note that the number of CH which can form a 5-membered CH/π interaction decreases

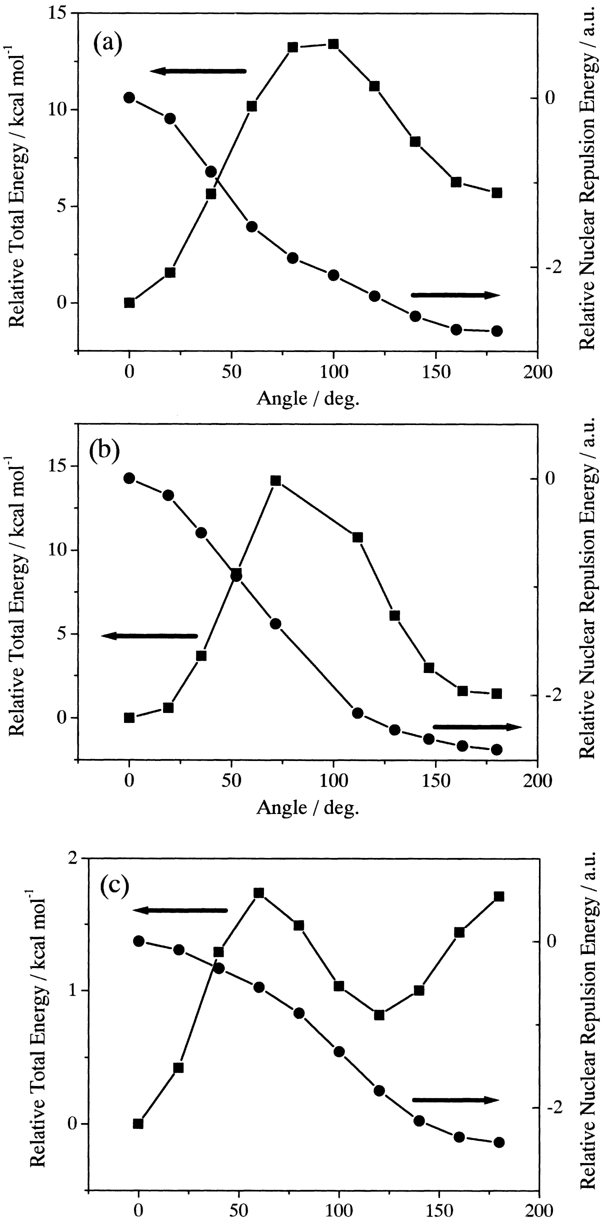

Fig. 6. Interaction energy and relative nuclear repulsion energy. (a) Methyl formate **6**, (b) *N*-methylformamide **7**, and (c) propionaldehyde **8**.

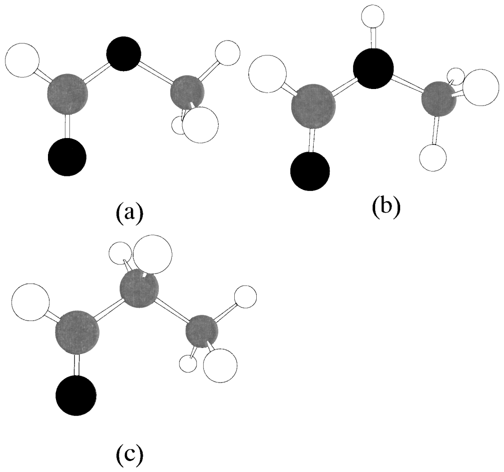

Fig. 7. Most stable geometry of (a) methyl formate **6**, (b) *N*-methylformamide **7**, and (c) propionaldehyde **8**.

Table 5. AIM Atomic Charges of the Conformations of Methyl Formate **6**, *N*-Methylformamide **7**, and Propionaldehyde **8** Calculated by the Ab Initio Method (MP2/6-311++G(d,p)).

	CH_3/C=O torsion angle	C	O	H [a)]
$CH_3X(CO)H$				
X = O (**6**)	0°	+1.571	−1.130	+0.130
	180°	+1.584	−1.111	+0.104
X = NH (**7**)	0°	+1.467	−1.138	+0.096
	180°	+1.484	−1.136	+0.089
X = CH_2 (**8**)	0°	+0.990	−1.074	+0.030
	120°	+0.991	−1.071	+0.022

a) Summation of the atomic charges of three H atoms in methyl group.

from 3 to 2, 1, and then to 0, in the above order. The stabilizing CH/O interaction may decrease in the same order. In geometry *Z*, the shortest distance between a hydrogen in CH_3 and the carbonyl oxygen is 2.65, 2.68, and 2.81 Å, respectively, for **6**, **7**, and **8**; such results suggest the contribution of the CH/O hydrogen bond.

We calculated the electron density at the carbonyl oxygen C=O and CH_3 in the respective conformations. Table 5 shows atomic charges for each conformation calculated by the AIM (atoms in molecule) method.[6] The electron density at the carbonyl oxygen is maximal, whereas that of CH_3 is minimal at geometry *E*. This is consistent with the assumption that an electronic factor is contributing in stabilizing the eclipsed conformation.

In order to estimate the steric repulsion of the CH_3/C=O eclipsed conformation we calculated the relative nuclear repulsion energy at the respective conformations. The relative steric energy of the nuclear repulsion has been found maximal at the CH_3/C=O eclipsed geometry (Fig. 7). Therefore, the electronic structure (CH/O hydrogen bonding) appears to be an important factor in stabilizing this conformation.

Conclusion

The present result that the preferred rotamers in **1**–**5** are **a** and **b** is in accord with the NMR (LSR) data.[1] A similar conclusion was obtained, by experiments, for related aralkyl compounds $CH_3CH(C_6H_5)$–X–R: alcohols (X = CHOH, R = CH_3, C_2H_5, *i*-C_3H_7, *t*-C_4H_9, and C_6H_5; IR, NMR, MS, GLC),[21] sulfides (X = S; indirect evidence),[22] sulfoxides (X = SO; X-ray,[23] ORD/CD,[24] NMR,[25,26] dipole moment measurements[27]), and sulfone (X = SO_2, X-ray[22]). In all of the cases examined so far, conformers corresponding to geometries **a** and **b** have been shown to preponderate. Further, for alcohols with no methyl group at the benzylic position, $C_6H_5CH_2CH(OH)$–R (R = CH_3, C_2H_5, *i*-C_3H_7), were also found the synclinal R/Ph conformations to prevail in solution (NMR).[28] Note that the alkyl group R is close to C_6H_5 in these geometries. This suggests that the CH/π interaction is important in determining the conformation of simple organic molecules.

The implication of the present findings are two-fold. First, ab initio calculations reproduce the conformational equilibrium of simple organic compounds. Developments of computer technology and applications to the molecular orbital method will enable high-level ab initio calculations of various compounds, including supramolecules.[29] Second, the relevance of weak hydrogen bonds, the CH/π and CH/O interactions, to the conformational issue of organic molecules has been demonstrated. There are precedents indicating that CH/π interactions to play an important role in determining the conformation of molecules. Examples include organic compounds,[30,31,32] transition metal complexes,[33,34,35] peptides,[36,37] proteins,[38,39,40] and DNA.[41]

Previous MM2 calculations[3] correctly predicted rotamer **a** as the most stable conformation but suggested erroneously that rotamer **c** would be the next most stable one. Failure of the MM2 method in predicting the correct conformational energy may be attributed to the neglect of favorable CH/π and CH/O interactions and unfavorable electrostatic interactions between C=O and C_6H_5. We conclude that the necessary parameters for such interactions, ignored in the past, should be implemented in the future version of force-field programs.

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