Theoretical Conformational Analysis for Codeinone-6-oximes in Gas Phase and in Solution

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The Z/E isomer ratios for codeinone-6-oxime and 7,8-dihydro-codeinone-6-oxime in chloroform and in a water:acetonitrile 85:15 (volume ratio) mixture have been theoretically calculated using the polarizable continuum method at the B3LYP/6-31G* level. Gas phase optimized geometries and thermal corrections were used for obtaining total relative free energies in solution. For validating the B3LYP/6-31G* calculations, optimized geometries and relative energies for the gas phase formaldoxime have been compared with values from B3LYP/6-311++G** calculations. B3LYP/6-31G* optimized geometric parameters are almost constant for formaldoxime, the C-ring model compound, (methoxy-methyl)vinyl-ketone oxime, and codeinone oximes in the absence of special structural features. Transition states, one for each, have been identified for the syn−anti and anti−anti transformations of formaldoxime. The energy and free energy of the barrier for the syn to anti rotation are 9.4 and 8.5 kcal/mol, respectively; the corresponding barrier values for the anti−anti isomerization were calculated at 55.1 and 53.7 kcal/mol. The Onsager approach of the solvent effect breaks down for such large systems as codeinone oximes. Using the self-consistent ab initio PCM approach, the smallest solvent effect has been calculated just for the molecule with the largest dipole moment. Polarization energies for codeinone-6-oximes are larger than those of the 7,8-dihydro derivatives. The larger polarization energies are accompanied with more negative solute−solvent interaction energies in both solvents. Isomer/conformer compositions have been calculated on the basis of relative internal free energies and free energies of solvation. The frequency-dependent relative thermal correction is negligible for the anti-codeinone oximes, but the value is 0.66 kcal/mol for the Z/syn relative to the Z/anti conformer. In chloroform, the Z:E composition was calculated at 47.5:52.5 as compared to our experimental value of 69:31 from NMR measurements. In the water:acetonitrile mixture, the theoretical ratio is 65.7:34.3 as compared to 73:27 as determined by high-performance liquid chromatography. For 7,8-dihydro-codeinone-6-oxime, the calculated composition in chloroform is 92.4% E and 7.6% Z, and the theoretical values in the water/acetonitrile mixture are 93.9% E and 6.1% Z. Both predictions are close to the experimental finding that the E form is practically the only existing isomer in solution. The different Z/E relative stabilities for the codeinone-6-oxime and the 7,8-dihydro derivative are primarily attributed to a remarkable change in the geometry of the C-ring. Overall, PCM/B3LYP/6-31G* calculations can provide isomer/conformer equilibrium compositions in both nonpolar and aqueous solutions in fair agreement with experimental values.

Introduction

Oximes, R,R′C═N−OR″ type molecules, possess an intrinsic geometric isomerism if the R and R′ groups are different. The different position of the OR″ group relative to the R−C═N moiety allows formation of the Z and E isomers. Furthermore, s-syn (s-cis) and s-anti (s-trans) conformations are possible according to the C═N−O−R″ torsion angle of 0 and 180°, respectively.

The simplest oxime, formaldoxime (H_2C═N−O−H), does not show the Z/E isomerism due to the equivalent substitution of R═R′═H. Yet, this molecule has drawn the most theoretical interest.[1,2] Gas phase geometry optimizations by Long et al.[2] find the planar s-anti structure of lowest energy at both the MP2(full)/6-31G*[3] and the DFT/B3LYP/6-311++G** levels.[4] Bond lengths and bond angles are close to the experimental values determined by microwave spectroscopy.[5] G2 level[6] energy calculations predict relative energies for the transition state for rotation about the N−O bond and the s-syn form of 7.7 and 5.0 kcal/mol, respectively.

Larger oximes, e.g., acetaldoxime,[1,7] chloroacetaldehyde oxime,[8] glyoxalic-acid oxime,[9] acenaphthenequinone monooxime,[10] and 1,2-naphthoquinone monooximes,[11] all show E/Z isomerism due to different groups connecting to the carbon atom of the oxime moiety. Moreover, several conformers are possible for these structures due to rotations about single bonds in the molecules. Rotations of the methyl and OH groups in acetaldoxime[1,7] allow two stable conformers for each of the E and Z forms. The most stable arrangement corresponds to an E isomer. A complicated isomer/conformer equilibrium exists for glyoxalic-acid oxime forming different intramolecular hydrogen bonds in some conformers and allowing 3−4 species within a 1 kcal/mol energy range in the gas phase.[9]

In acenaphthenequinone monooxime and 1,2-naphthoquinone monooximes, there is always a neighboring oxo group making the formation of an intramolecular hydrogen bond feasible. This kind of stabilization has a remarkable effect on the E/Z isomeric

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and the s-syn/s-anti conformational energy differences. For acenaphthenequinone monooxime, the second most stable conformer is a s-syn form with an intramolecular N−O−H···O═ hydrogen bond.[10] This form is less stable only by 1.3 kcal/mol than the most stable s-anti structure as compared to the s-anti energy difference of 4−6 kcal/mol for formaldoxime.[2] For 1,2-naphthoquinones, the s-syn conformer with the above-mentioned intramolecular hydrogen bond becomes the most stable isomer/conformer.[11]

The E−Z interconversion has been the subject of speculation for a long time. Glaser et al.[12] studied the oxime ↔ nitroso compound tautomerism in relation to a possible interconversion path for diazine dioxides. The E oxime ↔ nitroso compound ↔ Z oxime isomerism is always possible theoretically, but the equilibration rate depends on the barrier heights along the path. For formaldoxime, the H_2C═NH−O nitrone and nitrosomethane forms are above the s-anti oxime structure by 11 and 12 kcal/mol, respectively, in the gas phase, and the barrier from nitrone to nitrosomethane is only 2 kcal/mol.[2] Whereas a nitroso structure, in general, can reach a new conformation by a rotation about the formally single C−N bond, thermal isomerization of the oxime and nitrone could take place through rotation about the C═N double bond or by nitrogen inversion. The latter process would require an activation energy of 59.5 kcal/mol for formaldoxime, as obtained by Bach and Wolber from 6-31G calculations.[13] However, Iijima et al.[8] concluded that if a 2-fold potential has been accepted for the rotation about the C═N bond, the potential barrier height is only 12 kcal/mol in the gas phase for chloroacetaldehyde oxime.

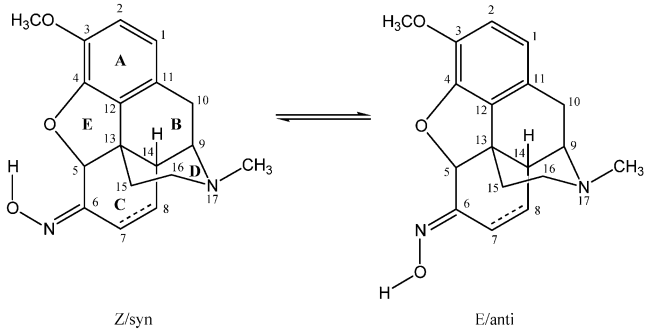
The solvent effect has been calculated theoretically for the oxime ↔ nitroso compound energy difference for formaldoxime and 1,2-naphthoquinone monooximes. Long et al.[2] found that the aqueous environment stabilizes the formaldoxime form relative to the nitrosomethane tautomer by a further 3−4 kcal/mol to a total of 12−16 kcal/mol in aqueous solution. The nitroso forms, thus the *ortho*-nitrosonaphthol structures for 1,2-naphthoquinone monooximes, are less stable than the monooximes by 4−5 kcal/mol at the MP4(SDTQ)/6-31G**//6-31G**+ZPE level and are further destabilized by 1−2 kcal/mol in chloroform and by 2−3 kcal/mol in dimethyl sulfoxide (DMSO).[11] Thus, according to the above two studies, theoretical relative energies for the nitroso isomers in solution are much smaller than the calculated 50−60 kcal/mol activation energy for the thermal isomerization of formaldoxime (in the gas phase).

In the present investigation, theoretical conformation analysis has been performed for codeinone-6-oxime and the 7,8-dihydro codeinone-6-oxime molecules in the gas phase and in solution. Codeinone is an intermediate of the biochemical synthesis of codeine, morphine, and 14-hydroxy-morphine derivatives.[14−17]

Morphine and its derivatives are the most prominent opiate alkaloids. Natural and endogenous opiates represent a widely investigated class of biologically active compounds[18,19] and have a long history in the field of analgesia.[20,21] Structural modification and simplification of the morphine skeleton are of interest even today in order to synthesize subtype selective analgesic pharmacons,[22] which are free of undesired side effects of morphine, such as dependence, tolerance, respiratory depression, and constipation.

A number of semisynthetic codeinone derivatives have potent analgetic and antitussive properties.[23] In addition, during screening cytotoxic agents among morphine alkaloids, codeinone was found to have antitumor activity in human cells with cell death-inducing activity.[24] The results of structure−activity relationships studies among a large number of compounds with a morphine nucleus clearly indicated that changes of functional groups in the C-ring (Scheme 1), particularly at positions 6−8, may be performed without the loss of opioid activity.[25,26] Some modifications in the C-ring of codeinone led to new nitrogen-containing derivatives with improved analgetic potency.[27] Among them, the oxime derivatives possess potent pharmacological activity[28−30] and analytically useful properties.[31]

SCHEME 1: Atom Numbering and Letter Codes for the Rings of Codeine-6-one Oxime and Its 7,8-Dihydro Derivative[a]



[a] The double bond to be saturated in the dihydro derivative has been indicated by a dashed line. In the Z and E oximes, the N−O bond points toward the furan oxygen and away from it, respectively. The structure is syn and anti with HONC torsion angles of 0 and 180°, respectively.

Our NMR and high-performance liquid chromatography (HPLC) experimental results indicate that the Z isomer is more stable than the E form for codeinone-6-oxime both in chloroform and in a water/acetonitrile mixture of 85:15 volume ratio. In contrast, the E isomer is the more stable form in both solutions for the 7,8-dihydro derivative. For exploring this interesting switch of stability, theoretical calculations have been carried out at the DFT/B3LYP/6-31G* level in the gas phase and by using the polarizable continuum dielectric method (PCM) in solution[32] in order to explore the structural reasons for the above experimental finding. A detailed review on codeinone oximes, emphasizing pharmacological and analytical aspects for this family of compounds, has been published recently.[31]

Methods and Calculations

Experiment. Experimental results were described in detail previously.[31] The oximes were prepared by the standard reaction of the corresponding oxo compound and hydroxylamine[33] leading to a mixture of the Z and E isomers. The isomeric ratio of the samples was determined by ^{1}H NMR spectroscopy. Spectra were recorded by a 200 MHz Varian Gemini spectrometer in $CDCl_3$, deuterated methanol, 2-propanol/acetonitrile mixture, and DMSO-d_6. The analytical HPLC system was composed of a Jasco PU-987 pump equipped with a Rheodyne 7725i injector unit (Cotati, CA) (20 mL loop) and a Jasco MD-910 diode array UV detector (Tokyo, Japan). The temperature was kept at 25 °C using a Jones Chromatography M 7955 (Hengoed, U.K.) column thermostat. The mobile phase containing 15% (v/v) of acetonitrile in 0.1 M ammonium acetate buffer of pH 7.0 was used. A constant flow rate of 1 mL/min was maintained during all experiments. Samples were dissolved in methanol or in the eluent. Preparative HPLC was carried out on a Chiralcel OD (250 mm × 10 mm i.d.) column (Daicel, Tokyo, Japan) using *n*-hexane-2-propanol-triethylamine 70:30:0.01% (v/v) as the mobile phase with a flow rate of 3 mL/min. The mixture of morphinane oxime isomers was dissolved in methanol. The sample concentration was 2 mg/mL. The injection volume of 1 mL was used in all cases.

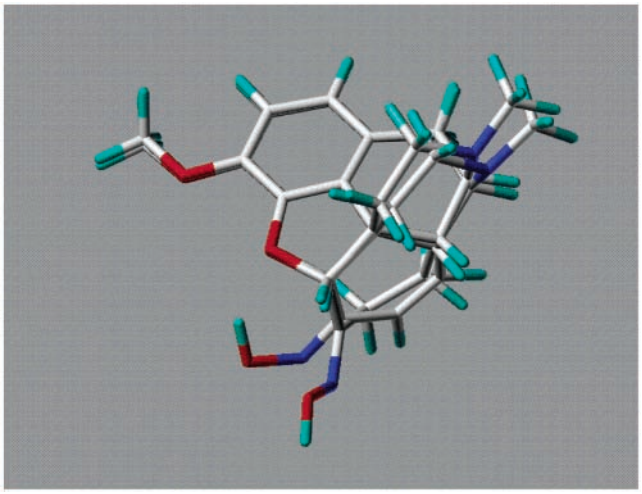


Figure 1. Superimposed **3a** and **4a** structures. Color code: C, white; H, green; O, red; N, blue. Because of a geometry change in the C-ring upon the saturation of the $C_7{=}C_8$ double bond, the $C_6{=}N$ double bonds point in remarkably different directions. In **3a**, the Z/syn conformer can be formed without steric repulsion. For the **4a** structure, the $H{-}C_5$ bond lies practically in the CNO plane of the oxime moiety and would exert a strong repulsion to a syn oxime−hydrogen.

Calculations. The final goal in the present study is to provide theoretical rationale for the experimentally found Z/E isomer ratios for the codeinone-6-oxime and the 7,8-dihydro-codeinone-6-oxime in different solvents. As in any conformational analyses, determination of the relevant geometry is a central problem. This is more profound for morphine analogues where strained rings are also expected (Scheme 1). This scheme also indicates the notation used in the present article. The isomer is called Z when the oxime hydroxyl is toward the ether oxygen of the model compound (see below) or toward the furan oxygen in codeinone derivatives. In E conformers, this OH group is away from the ether or furan oxygen and is closer to the 7,8-$CH{=}CH_2$ moiety or its dihydro derivative of codeinone oxime. The conformation is s-syn (or cis) with torsion angle HONC = 0° for the oxime moiety, whereas this angle is equal to 180° in the s-anti (or trans) form.

DFT/B3LYP/6-31G* geometry optimizations have been performed for the Z and E conformers of both oximes, using the Gaussian 98 package[34] implemented in the SV1ex supercomputer at the Ohio Supercomputer Center. Preliminary geometry optimization by utilization of the Sybyl 6.6 modeling package[35] and the Tripos force field indicated that the geometry may be favorable for an intramolecular hydrogen bond between the oxime OH group and the furan oxygen atom if the Z oxime takes the s-syn conformations. It was unfavorable for the 7,8-dihydro derivative, since the hydrogen atom connecting to C5 is almost in the $=N{-}O{-}H$ plane (Figure 1) and would exert a large H···H repulsion in a Z/syn conformation. Thus, we performed geometry optimization for both the s-syn and the s-anti conformers of the Z isomer of codeinone-6-oxime, but only the s-anti form was considered for its E isomer and for the Z and E isomers of the 7,8-dihydro derivative. In an E/syn conformation, the hydroxyl-hydrogen would get too close to a C-ring hydrogen for this molecule. The importance of the possible intramolecular O−H···O (furan) hydrogen bond was studied on the model compound (methoxy-methyl)vinyl-ketone oxime, $CH_3{-}O{-}CH_2{-}C(=N{-}OH){-}CH{=}CH_2$. This molecule is a cutout of the relevant part of the E- and C-rings and so is devoid of geometry constraint by the ring structure. If the intramolecular hydrogen bond has a large structure stabilization effect, then a more favorable bond could be formed in this case than in the Z/s-syn structure of the codeinone-6-oxime. All optimized codeinone derivates were confirmed as local energy minima on the basis of frequency analysis. Thermal corrections to free energy were calculated in the rigid rotator, harmonic oscillator approximation.[36]

Although the B3LYP/6-31G* geometry optimization and frequency analysis is a routine procedure, it is computationally very intense for such a large molecule as $C_{18}H_{20}N_2O_3$ (H_{22} for the dihydro derivative). Our computational resources do not facilitate the geometry optimization in solution that would be our ultimate goal. Thus, we optimized the structure with an unprotonated piperidine nitrogen atom in the gas phase and performed single point energy calculations in solution. The methyl-substituted nitrogen in the piperidine ring must be unprotonated in a nonprotic solvent as chloroform. It can be, however, protonated in a water/acetonitrile mixture. The pK_a of codeine is 7.95, and our experiments were carried out in a solution of 0.1 molar ammonium acetate buffer at pH 7.0. Taking the codeine pK_a as relevant for the codeinone oximes, the majority of oxime molecules must be protonated under the present experimental conditions.

Proper assignation of the protonation state of amines is prerequisite for a successful conformational analysis in aqueous solution. For histamine[37] and norepinephrine,[38] as 2-substituted ethylamine derivatives, consideration of a protonated amino group is necessary for obtaining relevant results. Because intramolecular hydrogen bonds can be formed in some conformations of these molecules, roles of the H-donor and H-acceptor atoms switch if neutral, instead of a protonated amino group, are considered.

For substituted ethylamines, the amino group is a rotatable end group of an aliphatic chain. In contrast, the piperidine nitrogen of codeine analogues is stably located in the D-ring. Although the ring can take different conformations, the flexibility is limited in a fused system. Distances of the piperidine nitrogen and the oxime oxygen remain fairly large, about 6.5 and 7.2−7.3 Å for the 7,8 dihydro and unsaturated codeinone oximes, respectively, in any studied conformations. Because experiments revealed similar Z/E ratios for the 7,8-dihydro derivative in chloroform and water/acetonitrile mixtures, we concluded that the oxime is either primarily unprotonated even in the water/acetonitrile mixture, implying a pK_a value of about 6 or smaller or (we considered this option more likely) the protonation taking place in the aqueous solvent in fact does not remarkably affect the Z/E ratio. Then, even in this latter case, the unprotonated model could work.

PCM calculations were performed in chloroform with a dielectric constant, ϵ, of 4.71 at $T = 298°$. The value was calculated from the temperature dependence of ϵ for chloroform.[39] Such an empirical equation was not available for the water:acetonitrile = 85:15 (volume ratio) mixture containing 0.1 molar ammonium acetate. In 1 M aqueous solution of strong electrolytes, the dielectric constant is reduced by about 10 ϵ units at $T = 293°$.[40] Assuming a proportionality, for our 0.1 M solution, a 1 ϵ unit decrease was accepted. Also assuming an ideal mixture for the water/acetonitrile system (which corresponds to about 11.5 wt % solution), an ϵ value was estimated on the basis of proportional dielectric constant contribution from both components. The final estimated ϵ value was 75, close to that derivable from the graph by Avdeef et al.[41]

In appreciation of the experimental information regarding the composition of the E/Z isomers, one has to keep in mind the experience that the E/Z ratio may depend on the way of the preparation of the oxime;[7] thus, the experimental E/Z ratio for

TABLE 1: Geometric Parameters Optimized at the B3LYP/6-31G* Level[a]

	C═N	N−O	O−H	CNO	NOH	HONC
			CH_2NOH			
exp[b]	1.276	1.408	0.956	110.2	102.7	180.0
s-anti	1.274	1.402	0.970	111.2	102.4	180.0
	(1.268)	(1.402)	(0.964)	(111.5)	(103.2)	(180.0)
s-syn	1.274	1.377	0.983	116.9	109.0	0.0
	(1.269)	(1.379)	(0.975)	(116.8)	(109.5)	(0.0)
TS1	1.271	1.437	0.973	111.9	104.8	73.1
	(1.266)	(1.434)	(0.967)	(112.6)	(105.9)	(71.2)
TS2	1.244	1.316	0.987	∼180.0	108.0	∼180.0
	(1.244)	(1.315)	(0.977)	(179.0)	(108.0)	(178.8)
			$CH_3-O-CH_2-C(=N-OH)-CH=CH_2$			
Z/syn (**2a**)	1.296	1.375	0.985	118.3	108.4	16.4
Z/anti (**2b**)	1.292	1.402	0.970	113.3	101.8	178.4
E/anti (**2c**)	1.288	1.405	0.969	112.5	101.6	180.0
			codeinone-6-oxime			
Z/syn (**3a**)	1.295	1.383	0.983	117.2	108.2	25.4
Z/anti (**3b**)	1.291	1.398	0.970	112.1	102.2	-179.9
E/anti (**3c**)	1.289	1.404	0.970	112.4	101.8	-177.8
			7,8-dihydro-codeinone-6-oxime			
Z/anti (**4a**)	1.292	1.410	0.969	112.8	101.7	-179.5
E/anti (**4b**)	1.282	1.408	0.970	112.6	101.8	-179.8

[a] Bond lengths in Å, angles in degrees. Values in parentheses for CH_2NOH from B3LYP/6-311++G** geometry optimizations. [b] Ref 5b.

the crude product may not reflect the equilibrium composition. Indeed, the neat liquid of *Z*-acetaldoxime provided 40% E isomer in an equilibration process.[42] In our recent study,[31] we found that after heating the isolated pure Z isomer on a water bath for an hour, the amount of the sterically less favorable E form slightly increased. On the basis of CH-5 group signals, the Z/E ratio was found to be 92:8 in DMSO-d_6. All of these findings raise the question about the possible isomerization path of the E/Z isomers to be discussed below.

Results and Discussion

Gas Phase Geometries and Energies. Optimized geometric parameters of the oxime moiety are compared in Table 1 for different molecules. Formaldoxime is a good starting point for studying the s-anti and s-syn conformational differences, since the Z and E isomers are equivalent for this small molecule.

Experimentally, the s-anti structure was identified.[5] Calculated geometric parameters with the 6-31G* basis set are close to the experimental values. Not indicated in Table 1 that the experimental HCN angles deviate by 6.2°. The HCN angle is 121.8°, when the H-atom is cis to the oxygen, and is 115.6° for the trans HCNO arrangement. The trend was well-reproduced theoretically: the corresponding values are 123.1 and 116.7°. Altogether, the theoretical estimate is close to the experimental structure for formaldoxime.

The s-syn structure (HONC = 0°) has a characteristically shorter N−O bond length as compared to the anti conformation. The CNO angle increases by about 6°, and the O−H bond length is also remarkably stretched. These geometric changes are consequences of the unfavorable H(C)···(O)H interaction existing in the s-syn form. The molecule is planar, and the H−C═N−O−H moiety forms a five-membered ring structure where the two end hydrogens would be too close to each other without a longer O−H bond and a larger CNO angle with respect to the anti conformer.

Two transition state structures have been identified in the present study. TS1 corresponds to the rotation of the hydroxyl-hydrogen about the N−O bond, connecting the syn and the anti forms. The rest of the molecule remains nearly planar while the H-atom is out of the molecular plane by 73.1° in the transition state. The most important geometric change in this state is related to the large increase for the N−O bond length, which is a nonsurprising increase for the rotation axis. Such an increase of the central bond was also found for the torsion of the structurally slightly similar O═N−O−O^- system in B3LYP calculations.[43]

The TS2 structure was intended to characterize the "rotation" of the OH group about the C═N bond. For not imposing a symmetry restriction on the transition state, the N−O−H plane was set near to 90° with respect to the H_2CN plane in the initial geometry, thus slightly destroying the mirror image symmetry. Strictly speaking, the molecule had a C_1 symmetry close, however, to C_s with two perpendicular atom planes. The optimization led to a molecular geometry with all atoms practically in a single plane. Thus, the results suggest a path for the anti to anti structural change without a rotation of the OH group about the C═N double bond. Instead, the OH group stays in the H_2CN plane and the O atom moves along a curve defined by the N−O distance. In the TS2 state, the CNO angle is 180° and the NOH bond angle is 108°. The hydroxyl-hydrogen eclipses one of the H(C) atoms. Both the C−N and the N−O bond lengths shorten conspicuously, mainly the N−O bond. A similarly linear C−N−O moiety was found by Bach and Wolber,[13] but their N−O bond length calculated probably at the HF/6-31G level (only the basis set was specified in that article) is 1.331 Å as compared to our value of 1.316 Å.

All of the above results have been obtained with the relatively small 6-31G* basis set. This set may not properly handle the transition state structures. For validating our 6-31G* values, the geometries of the formaldoxim conformers were reoptimized at the B3LYP/6-311++G** level. Changes are small even for the TS1 and TS2 structures (Table 1). The C═N distances are shorter by up to 0.006 Å. Deviations in the N−O bond length are negligible. The largest basis set effect was found for the O−H bond length. This value is consistently smaller by up to 0.01 Å with the larger basis set. Changes in bond angles are up to 1.1°. The optimized HOCN torsion angle value changes by 1−2° for the TS structures. The basis set effect is very moderate for this oxime prototype, and the comparable results are in good agreement with those from MP2(full)/6-31G* calculations.[2] Overall, the findings are promising that geometry determination for larger systems can be performed at the B3LYP/6-31G* level with confidence.

TABLE 2: Energy and Thermal Correction Values Relative to the Anti Conformer of CH_2NOH[a]

	ΔE(int)	ΔZPE	$\Delta(H_{vibr}(T) -$ ZPE)	$-T\Delta S(T)$	ΔG_{th}	ΔG(int)
			B3LYP/6-31G*			
s-syn	4.60	−0.28	−0.05	0.07	−0.25	4.34
TS1	9.37	−0.92	−0.17	0.22	−0.87	8.50
TS2	55.09	−1.55	−0.08	0.28	−1.35	53.74
			B3LYP/6-311++G**			
s-syn	5.77	−0.34	−0.03	0.04	−0.33	5.44
TS1	9.65	−0.92	−0.17	0.22	−0.87	8.78
TS2	56.79	−1.55	−0.07	0.25	−1.37	53.74
anti[b]		0.14	−0.01	0.00		

[a] Values in kcal/mol. [b] The X(B3LYP/6-31G*) − X(B3LYP/6-311++G**) differences for the anti form. X = ZPE, ($H_{vibr}(T)$ − ZPE), $TS(T)$.

Relative energies and free energies for H_2C═N−OH are compared in Table 2. The s-syn conformer is above the anti form by 4.60 and 5.77 kcal/mol at the B3LYP/6-31G* and

B3LYP/6-311++G** levels, respectively. The G2 relative energy by Long et al.[2] is 5.0 kcal/mol. The TS1 value was also determined by these authors as 7.7 kcal/mol. In this case, our B3LYP calculations predict a value of about 1.7−2.0 kcal/mol higher. The TS2 relative energy has been calculated in the present study as 55.09 and 56.79 kcal/mol with the two basis sets. The 6-311++G** basis set predicts a value higher by 1.7 kcal/mol than the one calculated with the 6-31G* set. The increase of the conformational energy is similar to that for the s-syn conformer, but the basis set effect for the TS2 structure is relatively much smaller. The large activation energy value is close to that of Bach and Wolber[13] and suggests that if estimation of Iijima et al.[8] for the barrier height of about 12 kcal/mol for a 2-fold potential is correct, then the anti to anti isomerization for oximes does not proceed along the route characterized by TS2 in the gas phase. This route can be involved in solution if solvent effects considerably reduce the activation energy. Otherwise, the isomerization probably takes place with another mechanism. Among them, tautomerization via the nitrone or the nitroso compound seems to be feasible, as supported by several studies including solvent effect calculations.[1,2,10−12]

In a physicochemical equilibrium, however, the free energy, instead of the energy difference, is decisive. Relative free energies do not differ very much from the corresponding energy values in Table 2, thus leaving the above conclusions primarily valid. The relative zero point energy (ZPE) is small for the s-syn conformer, in line with the thermal corrections for the vibration, $H_v(T)$ − ZPE. Here, $H_v(T)$ is the vibrational energy at temperature $T = 298°$. Entropy changes are also small. This term provided the largest free energy contribution, of about 0.5−1.0 kcal/mol, in several previous studies.[37,38,44] The explanation was that in systems with vibrational frequencies below 200 cm^{-1} the vibrational entropy contribution is large. Even small changes in these frequencies for the different conformers result in remarkable relative $TS_{vibr}(T)$ values. For formaldoxime, however, the lowest frequencies are in the 335−546 cm^{-1} range for the different conformers with the two basis sets considered. (The imaginary frequencies for the transition state structures have been disregarded in the relative free energy calculations.) Relative vibrational entropies are not very sensitive to small changes in these values; thus, the vibrational entropy contributions are small. (Translational entropy is constant for isomers, and the change in the rotational entropy is also small due to nearly constant moments of inertia.)

Relative free energies are smaller than energies by about 0.9 and 1.4 kcal/mol for the TS1 and TS2 structures, respectively. The correction is about 10% for TS1 but is only about 2% for TS2. Thus, TS2 free energies are still too high for thermal isomerization of formaldoxim along this route in the gas phase.

The model compound, $CH_3-O-CH_2-C(=N-OH)-CH=CH_2$ shows Z/E isomerism, in contrast to formaldoxime. Upon replacement of the formaldoxime hydrogens with carbons, the C=N bond lengths elongate by 0.01−0.02 Å, as calculated from B3LYP/6-31G* optimizations for the anti and syn conformations (Table 1). N−O and O−H distances change only by up to 0.003 Å. Bond angles differ by about 1°. The HONC torsion angles are still close to 180° both in the Z and in the E anti conformations despite the nonplanarity of the rest of the molecule. (See below the analysis for the Z/syn structure.) The corresponding values for the codeinone oximes are similar to those of the model compound. The basic conclusion from the comparison of the three groups of geometries is that the characteristic parameters of the anti and syn oximes are largely retained. The only remarkable difference was found in the C=N bond length, when the two C−H bonds are replaced by C−C bonds. This difference is not surprising and leaves unaltered the conclusion that oximes of −C−C(=N−OH)−C− types can be reasonably modeled at the B3LYP/6-31G* level.

The HONC torsion angle is 0° for the planar s-syn formaldoxime but deviates from this value by 16−25° in the model compound and in the Z/syn codeinone-6-oxime. One of the goals for studying the model compound was just to explore the effect of a spatially close ether oxygen on the HONC torsion angle. The furan oxygen can form, in principle, an intramolecular hydrogen bond with the oxime hydroxyl group. The O(furan)···HO distance was calculated as 1.844 Å for Z/syn codeinone oxyme (structure **3a** in Table 1). The corresponding value for the model conformer (**2a**) is 1.796 Å. Thus, in the more flexible **2a** structure, the hydrogen bond is remarkably 0.05 Å shorter and indicates structure stabilization effect due to this intramolecular bond formation. The nonzero HONC torsion angle, however, may not be taken as a direct evidence for the endeavor of the system for forming an intramolecular hydrogen bond. In calculations for both the anti and the syn formaldoxime, planar (C_s) molecular symmetry was maintained throughout the optimization. It may not cause a problem for the anti form but could result in a strained structure for the syn conformer, despite its local energy minimum structure as confirmed by frequency analysis. In the planar syn form, the hydroxyl hydrogen eclipses a CH hydrogen in formaldoxime. Although the C=N distances are longer by about 0.02 Å in **2a** and **3a**, still the eclipsing C−C and O−H bonds could be unfavorable. Thus, the nonzero HONC torsion angles for **2a** and **3a** may be indications of the energy lowering of systems in cases when the HONC planarity is not forced. An oxygen atom at a possible hydrogen bond distance favors this out-of-plane rotation of the oxime hydrogen.

For the model compound, the most stable conformation is Z/anti (**2b**). This structure is more stable by 1.63 and 2.50 kcal/mol than the Z/syn and E/anti (**2c**) structures, respectively. It is very surprising that the two anti conformers differ by 2.50 kcal/mol. The syn−anti energy difference is reduced from 4.60 kcal/mol in formaldoxime to 1.63 kcal/mol. The explanation lies in a rotation of the methoxy group of the model compound. In E/anti, the optimized CC(oxime)CO(ether) torsion angle is 180°. The value is 140 and 56° for Z/syn and Z/anti, respectively. In E, the two oxygens of the model compound are far from each other. In Z/syn, the oxygens are closer to each other but the oxime hydrogen mediates a hydrogen bond to the ether oxygen. In Z/anti, the oxime hydrogen is not located between the oxygens; instead, the lone pairs of the oxime oxygen point toward the lone pairs of the ether oxygen. With an unchanged CCCO torsion angle of 140°, this arrangement must be largely unfavored. The system relieves of this strain by a rotation of the CH_3O group to a gauche position, far away from the oxime moiety. This is possible for the model compound but is impossible for the ring systems of compounds **3** and **4**. The local effects are combined more complicatedly, however, when analyzing the relative energies for the **3** conformers (Table 3).

For codeinone-6-oxime, the most stable conformer/isomer is Z/anti (**3b**). The E/anti structure (**3c**) is less stable only by 0.25 kcal/mol at the B3LYP/6-31G* level. The relative energy of the Z/syn (**3a**) is 0.51 kcal/mol. Thus, this energy sequence, E (**3b**) < E (**3c**) < E (**3a**) differs from that for the model compound, E (**2b**) ≪ E (**2a**) ≪ E (**2c**). The small energy difference of the **3** anti conformers indicates that the O···O repulsion is not as expressed for **3b** as for **2b**. The explanation may be that the furan oxygen is out of the oxime plane, and

TABLE 3: Relative Energies and Thermal Corrections for Codeinone Oximes[a]

	ΔE(int)	ΔZPE	$\Delta(H_{vibr}(T) -$ ZPE)	$-T\Delta S(T)$	ΔG_{th}	ΔG(int)
codeinone-6-oxime						
Z/syn (**3a**)	0.51	0.36	−0.20	0.51	0.66	1.17
Z/anti (**3b**)	0.0	0.0	0.0	0.0	0.0	0.0
E/anti (**3c**)	0.25	0.10	0.01	−0.14	−0.03	0.22
7,8-dihydro-codeinone-6-oxime						
Z/anti (**4a**)	1.15					
E/anti (**4b**)	0.0					

[a] Values in kcal/mol.

TABLE 4: Dipole Moments in the Gas Phase and in Solution[a]

	gas phase	chloroform	water/acetonitrile (85:15)
codeinone-6-oxime			
Z/syn (**3a**)	5.21	6.24	7.59
Z/anti (**3b**)	1.84	2.47	3.61
E/anti (**3c**)	2.23	2.93	4.02
7,8-dihydro-codeinone-6-oxime			
Z/anti (**4a**)	2.20	2.80	3.98
E/anti (**4b**)	2.24	2.79	3.72

[a] Values in D.

the lone pairs can primarily avoid each other. For a further strain relief, however, not such a rotation, which was feasible for the model compound, is possible here about the C−C(oxime) bond. The repulsion must still exist and reduces the advantage of an anti conformation, as concluded from the relatively small Z/syn − Z/anti energy difference of only 0.51 kcal/mol. As mentioned above, the syn−anti energy difference for planar formaldoxime structures is 4.60 kcal/mol. On the other hand, the Z/anti structure, with possible O···O repulsion, is more stable by 0.25 kcal/mol than the E/anti structure without this sort of repulsion. Thus, we conclude that the relative energies for the **3** structures cannot be derived on the basis of simple, local geometry considerations for the oxime group, and other factors must play important roles, too.

Relative frequency-dependent corrections are small for the E/anti conformer (Table 3). Because of the compensation effect of the ΔZPE and $-T\Delta S(T)$ terms, the total free energy correction, $\Delta G_{th} = \Delta\text{ZPE} + \Delta(H_v(T) - \text{ZPE}) - T\Delta S(T)$, is −0.03 kcal/mol. No such compensation has been found for the Z/syn form, where ΔG_{th} is 0.66 kcal/mol. This latter free energy correction is remarkable, mainly keeping in mind that only about 1 kcal/mol differential solvent effect has been calculated for this conformer (see next section).

For the 7,8-dihydro derivative (**4**), only gas phase energies have been computed (Table 3). Both isomers were considered in the anti oxime conformation. The E isomer is more stable by 1.15 kcal/mol than the Z/anti form. This large stabilization of the E/anti form for **4**, in contrast to the destabilization of the E isomer by 0.25 kcal/mol for the **3** molecule, confirms our above idea that the Z/E energy difference in the anti conformation is sensitive to other geometry factors basically related to the geometry of the ring system. Differences in the geometries of the Z/syn codeinone oxime and the Z/anti form of the 7,8-dihydro derivative are revealed from the superimposed structures in Figure 1. Saturation of the C-ring results in a remarkable modification of the local geometry. The C═N bonds point in fairly different directions for the two structures, leading to a relocation of the oxime group. This effect has been considered as the primary reason for the switch in stability for the Z and E isomers for the oximes of the two molecules.

Solvent Effects. In Table 4, dipole moments calculated in the gas phase and in solution are compared. All conformers are in anti position except **3a** with a syn C═N−O−H arrangement. In a syn conformation, the lone pairs of the N and O atoms in the oxime moiety are on the same side of the N−O bond. This arrangement allows a large dipole moment, 5.21 D for **3a**. Lone pairs are on opposite sides of the N−O bond in the anti form with correspondingly reduced dipole moment. The primary role of the lone pair orientation in determining the molecular dipole moment, even for codeinone derivatives with different ring geometries, was revealed from the finding that all four anti structures in Table 4 have their dipole moments in a relatively narrow range of 1.84−2.24 D.

Dipole moments increase in solution by polarization of the solute. The increase is considerable even in the low dielectric constant ($\epsilon = 4.71$) solvent chloroform. The dipole moments increase by 0.5−0.7 D for the anti conformers, and it increases to 6.24 for **3a**. Even larger dipoles were calculated in the water/acetonitrile mixture: dipole moments for the anti form are in the 3.61−4.02 D range; the value of 7.59 D for **3a** shows an increase of 2.4 D as compared to the gas phase.

Comparison of the in solution dipole moments and the calculated solvent effect in Tables 5 and 6 indicates the breakdown of the Onsager approximation[45] for such large systems. In this approach, a nonpolarizable point dipole is placed into a cavity within the solvent, and the reaction field of the polarized solvent interacts with the dipole in the cavity. The interaction energy representing the stabilizing solvent effect in this approach is proportional to the square of the solute's dipole moment. From Table 4, the Onsager solvent effect should be the most negative for the **3a** structure of this molecule. In contrast, PCM calculations revealed the least negative solvent effect for **3a**. This leads to the nonsurprising conclusion that the point dipole approximation does not provide reliable values for such large systems in a cavity carved approximately around the van der Waals surface of the solute.

The solvent effect in the PCM approach is the difference of the free energy of the gas phase molecule and that of the solute in the polarizable continuum. Because the geometry distortion has been neglected upon solvation in the present study, the solvent effect has been calculated here as

$$G(\text{solv}) = E_{\text{supol}} + 1/2\ E_{\text{ss}} + G_{\text{dr}} + G_{\text{c}} \qquad (1)$$

and the total in solution relative free energy is

$$\Delta G_{\text{tot}} = \Delta E(\text{int}) + \Delta G_{\text{th}} + \Delta G(\text{solv}) \qquad (2)$$

ΔE(int) + ΔG_{th} values were taken from Table 3, and the same ΔG_{th} was accepted for **3b**,**c**, as well as for the **4a** and **4b** difference. Terms in eq 1 have been calculated by PCM at the B3LYP/6-31G* level. E_{supol} and E_{ss} stand for the solute polarization energy corresponding to the internal energy increase for the solute polarized by the solvent and for the solute−solvent interaction energy, respectively. The solvation electrostatic free energy is $E_{supol} + 1/2\ E_{ss}$.[32] The $G_{dr} + G_c$ terms stand for the dispersion−repulsion and the cavity formation free energy, respectively.

E_{supol} values in chloroform (Table 5) are 0.3−0.6 kcal/mol for all studied structures. (Absolute, instead of relative, values are indicated in Tables 5 and 6 for E_{supol} and 1/2 E_{ss} in order to show the order of magnitude of the individual terms.) Relative values are almost zero except for **3a** where ΔE_{supol} is 0.18 kcal/

TABLE 5: Solvation Energy Components in Chloroform[a]

	ΔE(int)	ΔG_{th}	E_{supol}	1/2 E_{ss}	G_{dr}	G_c	G_{drc}	G(solv)	ΔG_{tot}
				codeinone-6-oxime					
Z/syn (**3a**)	0.51	0.66	0.56	−5.14	−24.13	25.31	1.18	−3.40	1.82
Z/anti (**3b**)	0.0	0.0	0.38	−5.38	−24.38	25.33	0.95	−4.05	0.0
E/anti (**3c**)	0.25	−0.03	0.35	−5.55	−24.55	25.39	0.84	−4.36	−0.09
				7,8-dihydro-codeinone-6-oxime					
Z/anti (**4a**)	1.15		0.32	−4.73	−25.01	25.59	0.58	−3.83	1.45[b]
E/anti (**4b**)	0.0		0.31	−4.86	−25.06	25.48	0.42	−4.13	0.0

[a] Values in kcal/mol. [b] The value was calculated without considering ΔG_{th} for codeinone-6-oxime.

TABLE 6: Solvation Energy Components in Water/Acetronitrile 85:15 Mixture[a]

	ΔE(int)	ΔG_{th}	E_{supol}	1/2 E_{ss}	G_{dr}	G_c	G_{drc}	G(solv)	ΔG_{tot}
				codeinone-6-oxime					
Z/syn (**3a**)	0.51	0.66	3.82	−20.95	−30.53	34.86	4.33	−12.80	2.99
Z/anti (**3b**)	0.0	0.0	3.45	−22.09	−30.85	34.87	4.02	−14.62	0.0
E/anti (**3c**)	0.25	−0.03	3.59	−22.08	−30.92	34.96	4.04	−14.45	0.38
				7,8-dihydro-codeinone-6-oxime					
Z/anti (**4a**)	1.15		2.88	−19.23	−31.93	35.25	3.32	−13.03	1.59[b]
E/anti (**4b**)	0.0		2.82	−19.53	−31.85	35.10	3.25	−13.46	0.0

[a] Values in kcal/mol. [b] The value was calculated without considering ΔG_{th} for codeinone-6-oxime.

mol. The 1/2 E_{ss} values are similar for isomers/conformers of a molecule but are slightly more negative for **3** than for **4**. This deviation indicates that the conjugated codeinone-6-oxime is more readily polarizable than its 7,8-dihydro derivative. The more polarized solute induces larger reaction charges in the solvent, and the final effect is a stronger solute−solvent electrostatic interaction. Induction of larger reaction charges in the solvent requires, however, a more polarized solute that is reflected by the more positive E_{supol} values for the **3** as compared to **4** anti conformers in chloroform. Nonelectrostatic terms, G_{dr} and G_c, are fairly constant, and despite their large individual values, their sum is about only 1 kcal/mol due to the different signs. Relative terms are even smaller, up to 0.2 kcal/mol.

Similar qualitative conclusions can be derived for the solvation in the water/acetonitrile mixture. In this solvent, however, E_{supol} is about 3 kcal/mol and the 1/2 E_{ss} term is as negative as −20 to −22 kcal/mol. This much more negative value relative to that in the chloroform is due to the large increase of the dielectric constant from 4.71 to 75 (accepted for our mixed solvent including 0.1 mol/dm^3 ammonium acetate). It is to be mentioned here that the electrostatic part of the solvation free energy, E_{supol} + 1/2 E_{ss}, is −18.64 kcal/mol for **3b**, whereas this value is only −16.34 for the corresponding Z/anti structure of the dihydro derivative, **4a**. The electrostatic solvent effect is reversed as compared to that expected on the basis of dipole moments, 3.61 and 3.98 D, respectively (Table 4). This finding is another example against using dipole moments as the orienting quantity in estimating electrostatic solvent effects. A similar reversal, at a smaller scale, can be seen for **4a**,**b** with respective dipole moments of 3.98 and 3.72 D and with electrostatic solvation free energies of −16.34 and −16.71 kcal/mol, respectively.

Equilibrium in Solution. Our NMR experiments in chloroform found a Z/E ratio of 69:31 for codeinone-6-oxime, and the ratio was determined as 73:27 by HPLC in the water/acetonitrile mixture. In contrast, for 7,8-dihydro-codeinone-6-oximes, the E isomer exists in 100%, according to the experimental ratio determination.

On the basis of values in Tables 3, 5, and 6, the equilibrium mixture for codeinone-6-oxime is 45.3% Z/anti, 2.2% Z/syn, and 52.5% E/anti, corresponding to a calculated Z/E ratio of 47.5:52.5. The experimental ratio corresponds to a Z−E relative free energy of −0.47 kcal/mol as compared to our calculated value of +0.09 kcal/mol. Although our model with a nonprotonated piperidine nitrogen atom should be a good approximation in this solution, there have been several approximations applied in the present calculations. Geometries were optimized in the gas phase, and thermal corrections were calculated for these structures. Relative energies were calculated at the B3LYP/6-31G* level. This level showed a deviation of 0.4 kcal/mol energy for the syn conformational energy of formaldoxime, as compared to G2 energies.[2] Despite these possible error sources, the calculated composition in the water/acetonitrile mixture, 65.3% Z/anti, 0.4% Z/syn, and 34.3% E/anti, giving a ratio of 65.7:34.3, is close to the experimental one of 73:27.

For 7,8-dihydro-codeinone-6-oxime, the theoretical compositions are 92.4% E/7.6% Z and 93.9% E/6.1% Z in chloroform and in water/acetonitrile, respectively. Both predictions are close to the experimental finding that the E isomer exists practically exclusively in solution. In summary, our PCM/B3LYP/6-31G* calculations could distinguish the two compounds by finding high populations for both the Z and the E isomers of codeinone-6-oxime, whereas the E isomer was found as the almost exclusive form for the 7,8 dihydro-codeinone-6-oxime, in fair agreement with the experimental results.

Conclusion

In solution compositions for codeinone-6-oxime and 7,8-dihydro-codeinone-6-oxime have been theoretically calculated using the polarizable continuum method at the B3LYP/6-31G* level. For validating calculations at this level, optimized geometries and relative energies for the gas phase formaldoxime have been compared with values from B3LYP/6-311++G** calculations and with those of Long et al.[2] obtained from MP2(full)/6-31G* geometry optimizations and G2 level relative energies. B3LYP/6-31G* values, both geometric parameters and relative energies, are close to higher level values.

B3LYP/6-31G* optimized and reasonably comparable geometric parameters are almost constant for formaldoxime, $CH_3-O-CH_2-C(=N-OH)-CH=CH_2$ and codeinone oximes in the absence of special structural features. Two transition states have been identified for formaldoxime and were expected to be involved in the syn−anti and anti−anti isomerizations. The energy and free energy barriers to the thermal anti−anti isomerization were calculated at 55.1 and 53.7 kcal/mol,

respectively. Both values seem to be too high, however, for providing a practically possible isomerization path, and the present authors are inclined to believe that the in solution Z/E isomerization takes place via solvent-assisted tautomerization to a nitrone or nitroso compound structure.

The gas phase molecular dipoles increase by 0.5−0.7 D in chloroform and by 1.5−1.8 D in water:acetonitrile mixture (volume ratio 85:15) for the anti codeinone oxime isomers. An even larger increase has been calculated for a Z/syn oxime. The Onsager approach of the solvent effect breaks down for such large systems. Using the self-consistent ab initio PCM approach, the smallest solvent effect has been calculated just for the molecule with the largest dipole moment. Polarization energies for codeinone-6-oximes are larger (more positive) than those of the 7,8-dihydro derivatives. The larger polarization energies are accompanied by more negative solute−solvent interaction energies in both solvents.

Isomer/conformer compositions have been calculated on the basis of relative internal free energies and free energies of solvation. The frequency-dependent relative thermal correction is negligible for Z and E anti-codeinone oximes, but the value is 0.66 kcal/mol for the Z/syn relative to the Z/anti conformer.

In chloroform, the Z:E composition was calculated as 47.5:52.5 as compared to our experimental value of 69:31 from NMR measurements. The theoretical ratio in the water:acetonitrile mixture is 65.7:34.3 as compared to the experimental value of 73:27 determined by HPLC. For 7,8-dihydro-codeinone-6-oxime, the theoretical composition in chloroform is 92.4% E and 7.6% Z, similar to that in the water/acetonitrile mixture as 93.9% E and 6.1% Z. Both predictions are close to the experimental finding that only the E isomer exists in solution. The different Z/E relative stabilities for the codeinone-6-oxime and the 7,8-dihydro derivative are primarily attributed to changes in the relative internal energy due to a remarkable modification of the C-ring geometry. Overall, PCM/B3LYP/6-31G* calculations can provide equilibrium isomer compositions in both nonpolar and aqueous solutions in fair agreement with experimental values.

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