

Complexation reactions in pyridine and 2,6-dimethylpyridine-water system: The quantum-chemical description and the path to liquid phase separation

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Phase separation in substituted pyridines in water is usually described as an interplay between temperature-driven breakage of hydrogen bonds and the associating interaction of the van der Waals force. In previous quantum-chemical studies, the strength of hydrogen bonding between one water and one pyridine molecules (the 1:1 complex) was assigned a pivotal role. It was accepted that the disassembly of the 1:1 complex at a critical temperature leads to phase separation and formation of the miscibility gap. Yet, for over two decades, notable empirical data and theoretical arguments were presented against that view, thus revealing the need in a revised quantum-mechanical description. In the present study, pyridine-water and 2,6-dimethylpyridine-water systems at different complexation stages are calculated using high level Kohn-Sham theory. The hydrophobic-hydrophilic properties are accounted for by the polarizable continuum solvation model. Inclusion of solvation in free energy of formation calculations reveals that 1:1 complexes are abundant in the organically rich solvents but higher level oligomers (i.e., 2:1 dimers with two pyridines and one water molecule) are the only feasible stable products in the more polar media. At the critical temperature, the dissolution of the external hydrogen bonds between the 2:1 dimer and the surrounding water molecules induces the demixing process. The 1:1 complex acts as a precursor in the formation of the dimers but is not directly involved in the demixing mechanism. The existence of the miscibility gap in one pyridine-water system and the lack of it in another is explained by the ability of the former to maintain stable dimerization. Free energy of formation of several reaction paths producing the 2:1 dimers is calculated and critically analyzed. *Published by AIP Publishing.* <https://doi.org/10.1063/1.5010177>

I. INTRODUCTION

Partial miscibility of many pyridine derivatives in water is a common phenomenon known for over a century.^{1,2} Closed-loop solubility curves in the temperature-composition plane of the phase diagram were obtained for each of the liquid systems of water-dimethylpyridine (lutidine) homologues.³⁻⁵ A short summary of the relative miscibility of water and pyridine derivatives can be found in Ref. 6. Immiscibility only weakly depends on the position (para, ortho, meta) of the substituent CH₃ groups and strongly on their quantity and size. In the water-pyridine derived systems, it can be assessed by the relative size of the region enclosed in the closed-loop coexistence curve. 2,6- and 2,5-lutidine-water systems have similar extended close-loop region, while the remaining dimethyl homologues, with the adjacent methyl groups, have a slightly smaller immiscibility region.^{3,4,6} Pyridine derivatives augmented by one methyl group are much more miscible in water. All methylpyridines are completely miscible at normal pressure^{5,7} but are partially miscible at elevated pressures.⁸

The transition of a homogeneous liquid phase at Lower and Upper Consolute Solution Temperatures (LCST

and UCST, respectively) into two phases is attributed to temperature-induced demixing effect triggered by the breaking of hydrogen bonding (HB) between water and pyridine derived molecules. Three energy components are involved in this process: (a) the dispersion energy that preferentially binds a molecule with its own kind, thus favoring demixing, (b) hydrogen bonding, favoring mixing between the donors and the acceptors, and (c) translational entropy favoring mixing. Above the UCST, mixing occurs normally due to the dominance of entropy. As temperature is lowered, mixing entropy is smaller and dispersion forces lead to partial separation. But as the temperature decreases below the LCST, hydrogen bonding dominates over the dispersive force, leading again to mixing. These theoretical considerations were backed by lattice-based simulations by Kumar *et al.*⁹ In their model, the “donor” and the “acceptor” molecules at lattice sites exhibit nonspecific dispersive and directional (i.e., HB) interactions. The thermodynamic rules were obeyed by statistical simulation in the Monte Carlo code and the qualitative features of the closed loop diagram were obtained. Other theoretical formulations incorporating similar interaction components essential to all multiple reentrant solubility systems have been constructed previously by Andersen and Wheeler,¹⁰ Barker and Fock,¹¹ and Goldstein and Walker,¹² who also implemented a statistical model for a pyridine-water system.¹³

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An important factor in the viability of the above model is its ability to predict the effect of the substituents on the size of the immiscibility gap. Basic guidelines were given by Cox⁴ in 1954, who divided a pyridine into two parts: the nitrogen-hydrophilic group, promoting solubility in water, and the hydrophobic hydrocarbon part, that facilitates demixing. When a hydrogen atom of the pyridine is substituted by an alkyl group, the hydrocarbon character of the molecule is amplified, resulting in reduced solubility. In addition, an increase in electron density occurs, especially at the vicinity of the nitrogen, and the size of this effect slightly varies in accord with the position of the substituent. Theoretically, the increase in water-pyridine interaction should lead to stronger mixing and to shrinkage of the immiscibility region. This contradicts experimental results, as pointed by Brovchenko and Oleinikova,⁶ who proposed a different description. In their model, the demixing phenomenon of methyl-substituted pyridine in water was described solely by means of HB in three bonding schemes of varying strengths and conformations. According to that theory, dispersion energy, while accounted for by classic potential, had no special importance in the formation of a binary phase. An additional weak bonding between π orbitals of the aromatic ring and water hydrogen was suggested and designated as one of the essential parts in the demixing scheme. However, the alleged empirical evidence provided for such bonding was that of weak interaction between the aromatic ring of a pyridine molecule and of hydrogen, covalently bonded to a nitrogen atom of a pyrrole in CCl_4 .¹⁴ In our opinion, this is not enough to postulate significant HB between the perpendicularly oriented pyridine aromatic ring and H_2O molecule in water. This view is strengthened by quantum-mechanical calculations showing that at normal conditions (i.e., without imposing restrictions in geometry optimization), the $\text{OH} \cdots \pi$ interaction scheme in pyridine will always converge at a nitrogen lone-pair bonding position in the H_2O -pyridine system.^{15,16}

Despite the inconsistencies mentioned above in different statistical approaches, most of them gave reasonable description of major physical properties of binary mixtures that includes HB. Only recently, a full molecular-dynamic based calculation with classical potentials clearly simulated hydrogen bonding and dispersion interactions in the 2,6-lutidine-water system and reproduced liquid-liquid demixing including LCST and some other physical properties of the binary system.¹⁷ Despite these achievements, currently there is no theory of the phase separation employing both quantum-chemical calculations and thermodynamics in a satisfactory manner.

There was a considerable effort in the past to find a viable chemical picture. Traditional models have focused on a quantum-chemical analysis of a core H_2O -pyridine structure (the 1:1 complex) and its methyl substituted derivatives. Pápai and Jancsó¹⁶ studied the relative stability and interaction energies of various pyridine and five methyl-derived (2-,3-,4-mono and the 2,6- and 3,5-di methyl) pyridine-water complexes and compared them to the experimental miscibility. The study implemented the B3LYP hybrid functional with Dunning-augmented correlation consistent polarized valence (aug-cc-pVDZ) basis set for the geometry calculation and Møller-Plesset perturbation (MP2) theory of a similar basis set at single point. It showed that the association energies

in the methyl-substituted complexes (5.07 kcal/mol for the largest interaction in 2,6-lutidine- H_2O complex) are slightly larger than those in the pyridine-water (4.42 kcal/mol) complex. The association energy of the HB in the pyridine-monomethylpyridine-dimethylpyridine series followed the increasing immiscibility order only generally. Small energy difference between the dimethyl and monomethyl substituted homologues (0.1-0.2 kcal/mol) had no strict hierarchy that might be expected from proton affinities in different pyridine derivatives. The conclusion that strong hydrogen bonding facilitates demixing contradicts the assumption of all but Brovchenko and Oleinikova model.⁶ The authors suggested that the differences in the miscibility order of the methyl-substituted pyridines are not simply related to the strength of the HB with the water molecule and that other factors must be included. It should be noted that in their calculations of the association energy, entropy loss was not accounted for (entropy loss is expected to be higher in larger 1:1 pyridine substituted complex). In later studies, pyridine/lutidine-water clusters larger than 1:1 were examined. This included calculation of a possible protonation path for one pyridine molecule with up to five water molecules¹⁸ and the PFG diffusion NMR study¹⁹ conducted on 2,6-lutidine-water samples. The latter study has been supported by quantum mechanical calculations that proposed several theoretical structures. Based on results from NMR and FTIR measurements, the authors deduced that lutidine-water clusters contain 2-4 organic and 2-3 water molecules. The assumption that clustering accompanies the formation of the immiscibility gap in methyl substituted pyridine in H_2O was also supported by recent small-angle neutron scattering measurements.²⁰

In respect to other members of the methyl-substituted pyridine-in-water group, the 2,6-lutidine-water liquid system has been studied extensively^{3-5,17,19-22} mainly because its LCST is slightly above room temperature and shows one of the widest miscibility gaps reported. Contrary, pyridine is the only member of its family that does not have immiscibility gap with water at any physical settings.

In this paper, we present a quantum-mechanical comparative study of the methyl-substituted pyridine-water system, based on these two members of the pyridine family. Our aim is to derive a complete quantum-chemical description of the binding properties in the pyridine/lutidine-water systems, at differing complexation levels, and then to propose a new chemical model of the phase separation phenomenon backed by thermodynamic arguments. Since the interaction energy of a structure is expected to be affected by its hydrophilic/hydrophobic character, solvation simulation is carried out.

II. CALCULATION METHODS

The calculation scheme of the present work is simple. All the geometry and single point calculations are done by Kohn-Sham methods. Additionally, second order Møller-Plesset Perturbation (MP2) calculations were added in vacuum derivations. Geometry structures are fully optimized and all internal coordinates are converged at strict convergence criteria. Only real vibrational frequencies are allowed. This

is conducted at a Dunning correlation-consistent, polarized valence, double-zeta basis set (Aug-cc-pVDZ), following single point calculations at the Aug-cc-pVTZ basis set level.^{23,24} Two Kohn-Sham methods are employed: (1) Truhlar's main group thermochemistry and noncovalent interactions M06-class hybrid functional: **M06-2X**²⁵ and (2) The **wB97xD** functional from Chai and Head-Gordon,²⁶ which includes long-range dispersion corrections of Grimme's D2 dispersion model.²⁷ Although the M06-2X already incorporates some medium range dispersion interactions, herein, following recommendation,^{28–30} it is augmented by the D3³¹ long range term (M06-2X/D3). The two DFT functionals were among the 19 functionals included in a systematic comparative study by Sherrill and co-workers,²⁸ of non-covalently interacting systems with hydrogen bonding and dispersion interactions. The examined functionals employ the dispersion terms DFT-D2²⁷ and DFT-D3³¹ or have dispersion included inherently. The M06-2X/D3 and the wB97xD, while not the best, were chosen among several other well-performing DFT functionals mainly due to their superior performance in the solubility calculations of pyridine and 2,6-lutidine molecules in water and their respective organic media (see the [supplementary material](#) for comparison).

Solvation is simulated by the polarizable continuum model (PCM³²) implemented in the Gaussian 09,³³ where the radii and non-electrostatic terms are taken from the Truhlar SMD solvation model.³⁴ The PCM/SMD is a popular implicit solvation model for regular solvents capable of reproducing correctly free energies of solvation for solutes, for which it was parameterized.³² Directional solute-solvent interaction, e.g., hydrogen bonding is averaged out by this implicit solvent model. In order to use it correctly, vital water molecules must

be included explicitly. However, organic-water complexes are interconnected into a network of hydrogen bonded water molecules that constitute the bulk of the solvent. By choosing a specific cluster, one may discard of a large number of other states where energetic degeneracy and very tiny differences in interaction energy with water can lead to notable differences in calculation of the formation energy. Below (above) the LCST, where hydrogen bonds are supposedly present (dissolve), this choice might be of special importance. In all calculations with SMD models, results of free energy of solvation are given in gas phase reference state of 1M.

The free energy of solvation, obtained in M06-2X/D3/Aug-cc-pVTZ, wB97xD/Aug-cc-pVTZ calculations for water-pyridine and water-2,6-lutidine, are presented in Table I. Corresponding empirical data are also given.^{34–37} In general, there is a good correlation between the empirical and calculated figures of the free energy of solvation. Very good results are obtained for free energy of solvation of lutidine in lutidine and pyridine in H₂O. Relatively high discrepancy of ~1.0 kcal/mol is found for solvation of water molecules in water. Above average error of ~0.9 kcal/mol is found for 2,6-lutidine solvation in water and a similar error of ~0.8 kcal/mol is found in calculation of pyridine in pyridine. It should be noted, though, that in all but exceptional cases, errors in calculation of the solvation energy of the monomers should cancel-out in the solvation energies of the complexes that encompass these monomers.

In the last two columns of Table I, gas/solution calculated vs. empirical dipole moments are given. The calculated and the experimental values agree in both DFT implementations. The major differences between the gas and solution calculations are due to the relative polarization strength of

TABLE I. Comparison between Kohn-Sham algorithms in derivation of the solvation properties of the composites of the water-pyridine/lutidine systems. Solvation energies are in kcal/mol, and dipoles are in Debye units.

Molecule/Method	Solvent	Calc. ΔG_{sol}	Exp. ΔG_{sol} ^a	Calc. dipole (gas/solvent)	Exp. dipole (gas/solvent)
H ₂ O/M06-2X/D3 H ₂ O/wB97xD	H ₂ O	-7.43 -7.20	-6.31	1.92/2.47 1.90/2.44	1.85 ^b / 2.58÷2.95 ^c
H ₂ O/M06-2X/D3 H ₂ O/wB97xD	<i>PYRIDINE</i>	-4.38 -4.28		1.92/2.14 1.87/2.10	1.85 ^b /...
H ₂ O/M06-2X/D3 H ₂ O/wB97xD	<i>2,6-LUTIDINE</i>	-4.23 -4.14		1.92/2.11 1.87/2.08	1.85 ^b /...
PYR/M06-2X/D3 PYR/wB97xD	H ₂ O	-4.77 -4.75	-4.70	2.28/3.33 2.30/3.39	2.22 ^d /...
PYR/M06-2X/D3 PYR/wB97xD	<i>PYRIDINE</i>	-6.32 -6.29	-5.47	2.26/3.18 2.29/3.23	2.22 ^d /...
LUT/M06-2X/D3 LUT/wB97xD	H ₂ O	-3.84 -3.76	-4.60	1.55/2.55 1.56/2.53	.../...
LUT/M06-2X/D3 LUT/wB97xD	<i>2,6-LUTIDINE</i>	-6.22 -6.16	-6.04	1.53/2.26 1.54/2.23	.../...

^aReference 34.

^bReference 36.

^cReference 37.

^dReference 35.

TABLE II. Structure and association energy of the 1:1 complexes in vacuum—The effect of the BSSE correction.

1:1-System/Method	Structure ^a	N-H ₂ O distance (Å)	∠C ₄ N ₁ H (deg)	-ΔE (kcal/mol)	BSSE corr. -ΔE (kcal/mol)
<i>LUT/wB97xD</i>	L1(⊥)	1.891	171.9	8.68/8.52 ^b	8.33 ^b
<i>LUT/M062x-D3</i>	L1(⊥)	1.896	169.7	8.43/8.27 ^b	8.10 ^b
<i>LUT/B3LYP</i>	L1(⊥)	1.919	167.5	6.68	6.51
<i>PYR/wB97xD</i>	P1(⊥)	1.912	177.7	7.29	7.15
<i>PYR/M062x-D3</i>	P2(∥)	1.951	157.1	7.17	7.05
<i>PYR/B3LYP</i>	P1(⊥)	1.920	176.9	6.41	6.29
<i>LUT/MP2</i>	L1(⊥)	1.898	167.1	8.80	7.85
<i>PYR/MP2</i>	P2(∥)	1.937	159.8	7.69	6.97
<i>PYR/MP2</i>	P1(⊥)	1.914	176.9	7.69	6.94

^aRelative positions (⊥/∥) of the H₂O plane in respect to the aromatic plane.

^bRevised total/BSSE corrected interaction energy in the eclipsed position of the CH₃'s in the 1:1 complex. Corrected because of the erroneous configuration of the lutidine monomer in vacuum, in the automatic counterpoise calculation.

the embedding solvents. The strength of the molecular dipole increases in correlation with the solvent polarity. The following order of increasing polarity is retained: vacuum < 2,6-lutidine < pyridine < water.

Since this DFT study employs fully optimized geometries with non-negative vibrational frequencies obtained at a rather high level of theory (geometry: Aug-cc-pVDZ, energy: Aug-cc-pVTZ), the Basis Set Superposition Errors (BSSEs) are expected to be low. The results of the uncorrected *vs.* corrected association energies for 1:1 lutidine/pyridine-H₂O complexes in vacuum and the geometric data of the optimized structures are given in Table II.

The definition of the interaction energy, ΔE^{1:1}, is given in Eq. (1), where E_g^{1:1}, E_g^{1:0}, and E_g^{0:1} are the electronic ground state energies of the 1:1 lutidine/pyridine-H₂O complex, the single organic, and water molecules, respectively,

$$\Delta E^{1:1} = E_g^{1:1} - (E_g^{1:0} + E_g^{0:1}). \quad (1)$$

In Table II, the old B3LYP (at similar Aug-cc-pVDZ/pVTZ, basis set) dispersionless algorithm and the second order Møller-Plesset Perturbation (MP2) method were added for comparison with the modern two Grimme-augmented DFT algorithms. Notably, for the MP2 and both the DFT methods, the BSSE-corrected energies are very close (though the *M062x-D3* shows a slightly better match). Markedly, for all DFT methods, the BSSE errors, as estimated by

the counterpoise method, were lower than 0.2 kcal/mol. Consequently, BSSE corrections were omitted in the following DFT calculations.

The geometries of the structures are presented in Fig. 1. For pyridine in vacuum, calculations made with wB97xD/B3LYP and M062x show notable structural differences, designated in P1 (H₂O is perpendicular to the aromatic plane) and P2 (H₂O is parallel to the aromatic plane) configurations, respectively. Although seemingly different, there is a small energy gap between the two configurations. The interaction energy in P1 is only 0.07 kcal/mol stronger than in P2 for wB97xD, while P2 is only 0.25 kcal/mol stronger than in P1 for M062x. In the MP2-based benchmark calculations, the pyridine 1:1 complexes were derived at slightly weakened convergence criteria. The two almost iso-energetic structures (the P1 and the P2) enabled geometry comparison with the DFT methods.

There is an important difference between the interaction energy of the pyridine (P1) and the 2,6-lutidine (L1) structures. Difference of ~1.10 kcal/mol for wB97xD and M062x algorithms is attributed to the Grimme dispersion term and to some increase in the electron density of the aromatic ring in the lutidine molecule. Conversely, only 0.27 kcal/mol difference between pyridine and lutidine is calculated by B3LYP. The change is ascribed to the electron-donor properties of the substituents. The overall increase

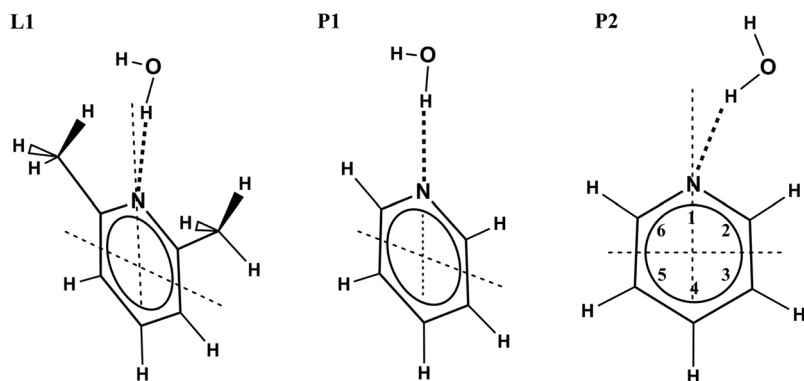


FIG. 1. Structures of 1:1 complexes of 2,6-lutidine and pyridine in vacuum optimized geometry.

in the interaction energy in dispersion-corrected algorithms is higher than the derived figure of ~ 0.9 kcal/mol, estimated by the MP2 method, but within a reasonable margin. The energy difference between the empirical dispersion augmented methods and the B3LYP is also demonstrated in the $N \cdots H$ bond distance (column 3) in 2,6-lutidine, which is shorter by 0.023-0.028 Å in the formers. In pyridine, the respective difference is of 0.008 Å only (for similar P1 structures).

III. RESULTS AND DISCUSSION

A. The pyridine and the 2,6-lutidine, 1:1 complexes—Solvation properties and structural differences

At the LCST of the 2,6-lutidine-water coexistence curve (34 °C), most of the mass fraction is of water (62.3%) and the molar ratio H_2O /lutidine is ~ 10 . At the lowest water content at ~ 120 °C, this fraction diminishes to $\sim 20\%$,³ corresponding to a molar H_2O /lutidine ratio of 1.5. Hence, the “rich organic fraction” formed after demixing is composed mainly from H_2O molecules but at a higher than average organic content. Thus, in analyzing solvent effects in aqueous media, one needs to assess the influence of organic presence on the complexes. In this study, calculations were conducted in both water and the respective organic solvent (pyridine or 2,6-lutidine). The lutidine- H_2O 1:1 complex is presented in two possible isomeric structures in Fig. 2: L2(I) and L3(II) of which the latter is of stronger bonding.

Results of calculations are presented in Table III. Solvation terms in the amphiphilic 1:1 pyridine/lutidine- H_2O complex are important in calculations of the interaction energy, and in Table III they deserve particular attention. The relative net contribution of the free energy of solvation, $\Delta\Delta G_{sol}^{1:1}$, is calculated with Eq. (2),

$$\Delta\Delta G_{sol}^{1:1} = \Delta G_{sol}^{1:1} - \Delta G_{sol}^{1:0} - \Delta G_{sol}^{0:1}, \quad (2)$$

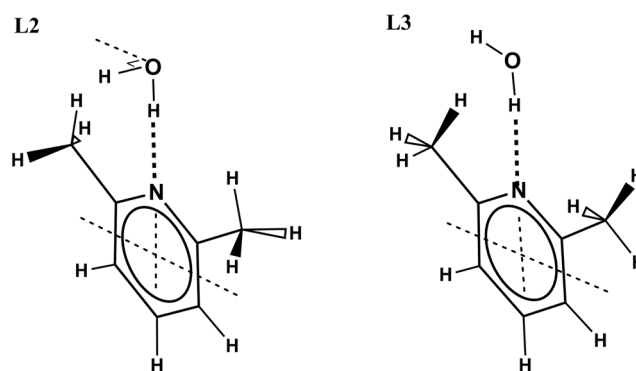


FIG. 2. Structures of 1:1 complexes for 2,6-lutidine in solvent optimized geometry.

where $\Delta G_{sol}^{1:1}$, $\Delta G_{sol}^{0:1}$, and $\Delta G_{sol}^{1:0}$ are the free energies of solvation of the 1:1 complex, the H_2O , and the pyridine/lutidine molecules, respectively. Therefore, a positive $\Delta\Delta G_{sol}^{1:1}$ term (i.e., the ingredients are better dissolved than the complex) weakens the total interaction energy in the 1:1 complex, while a negative value makes it stronger. In Table III, $\Delta\Delta G_{sol}^{1:1}$ is presented in column 7 after factorization into the electrostatic and the non-electrostatic (CDS) parts. Solvation constituents of the 1:1 complexation [see Eq. (2)], $\Delta G_{sol}^{1:1}$, are presented similarly, as the electrostatic and the non-electrostatic energy terms in columns 5 and 6, respectively. Electron interaction energy, ΔE , which in the case of solvents includes solvation free energy contribution, is given in column 8.

In the following analysis, it is argued that the data express the hydrophilic-hydrophobic interplay between different parts of the complex. Hydrophilic attraction can be seen as the manifestation of the dipole interactions between the mutually oriented solute-solvent molecules, which in PCM description are represented by a continuous media. The overall strength of this effect is given by the electrostatic energy in column 5 of Table III. In accord to the respective strength, solvents of stronger polarization lead to stronger electrostatic attraction

TABLE III. Structure and solvation properties, association energies, gas phase entropy loss, and Gibbs energy for 1:1 complexes in water and in respective organic solvents. The electron interaction energy term, ΔE , includes solvation contribution. Energy terms are in kcal/mol.

1:1-System/Solvent/Method		N- H_2O distance (Å)	Dipole (D) vac./solv.	$\Delta G_{El,Static}^{1:1}$	$\Delta G_{CDS}^{1:1}$	$\frac{\Delta\Delta G_{El,Static}^{1:1}}{\Delta\Delta G_{CDS}^{1:1}}$	ΔE_{Solv}	$\Delta H_{T=298.15}$	$\Delta TS_{298.15}^{1M}$	Gibbs energy + conf. & rot. symmetry
PYR/ H_2O /wB97xD	P1(⊥)	1.802	4.96/6.21	-12.79	3.45	+1.87/+0.75	-4.23	-2.89	-6.23	+2.52
	P1(⊥)	1.802	4.93/6.15	-13.03	3.45	+1.87/+0.75	-3.84	-2.54	-6.12	+2.76
	P1(⊥)	1.854	4.91/5.81	-7.31	-2.47	+1.26/-0.47	-6.24	-4.56	-5.80	+0.42
	P1(⊥)	1.860	4.88/5.77	-7.43	-2.46	+1.26/-0.46	-5.87	-4.22	-5.87	+0.83
LUT/ H_2O /wB97xD	L3(⊥)	1.797	4.24/5.54	-12.98	3.59	+1.72/-0.14	-6.00	-4.55	-7.01	+1.64
	L2(⊥)	1.839	4.07/5.47	-11.62	3.87	+3.08/+0.14	-4.61	-3.11	-6.28	+2.35
LUT/ H_2O /M062x-D3	L3(⊥)	1.787	4.26/5.57	-13.31	3.60	+1.70/-0.14	-5.69	-4.51	-7.28	+1.95
	L2(⊥)	1.835	4.01/5.38	-11.89	3.87	+3.12/+0.13	-4.32	-2.94	-6.37	+2.61
LUT/LUT/wB97xD	L3(⊥)	1.872	4.07/4.87	-6.48	-3.02	+1.11/-0.31	-7.14	-5.46	-6.88	+0.60
	L2(⊥)	1.872	3.99/4.87	-5.64	-2.80	+1.95/-0.09	-6.19	-4.38	-6.41	+1.21
LUT/LUT/M062x-D3	L3(⊥)	1.877	4.05/4.85	-6.62	-3.01	+1.13/-0.32	-6.90	-5.32	-6.24	+0.10
	L2(⊥)	1.869	3.99/4.87	-5.82	-2.80	+1.93/-0.11	-5.79	-4.15	-7.17	+2.20

for similar solutes, while solutes of stronger polarization display stronger electrostatic energy for similar solvents. Thus, lutidine in water has lower electrostatic strength than the more polar pyridine in water but has higher electrostatic energy than the less polar lutidine in lutidine. A related effect is manifested in the differing figures of the dipole strength in column 4 for vacuum *vs.* solvated species, where increase in dipole strengths upon transition from vacuum to water-pyridine (or water-lutidine) solvated complexes is accompanied by a corresponding increase in the respective electrostatic term.

Although still debated, hydrophobicity is often described as an entropic effect originating from the disruption of highly dynamic hydrogen bonds between molecules of water by the nonpolar solute. The cohesive forces between the solvent molecules cause non-polar molecules or clusters to clump together thereby reducing the surface area exposed to water. The SMD method implemented in Gaussian 09 calculates the non-electrostatic dispersion-repulsion and cavitation energy terms based on the atomic surface tensions descriptor. Horvath *et al.*³⁸ and later Truhlar and Cramer³⁹ showed the ability of the atomic surface tension descriptor to account for the hydrophobic effect. Accordingly, the non-electrostatic term in column 6 is especially suited for defining hydrophobicity. This is readily observed for the hydrophobic lutidine 1:1 complex in aqueous media, as a highly positive (hydrophobic) solvation term (+3.59 kcal/mol). The energy difference between the non-electrostatic terms of the lutidine complex in water and in lutidine solvents is 6.6 kcal/mol, which is higher than the respective figure of 5.9 kcal/mol, for the less hydrophobic pyridine complex. There is a very small difference between the energies obtained by the M062x-D3 and wB97xD functionals, and in the following discussions, in all but distinct cases, only calculations based on the wB97xD functional will be addressed.

Minimization of the external surface of the hydrophobic part in a polar solvent, together with polarization effects that maximize the electrostatic bonding, leads to following structures: The L1 structure that is obtained in vacuum, the L3 structure that is similar to the L1 but with H₂O and lutidine molecules in in-plane orientation in aqueous and lutidine solutions, and the L2 structure that is similar to the L1 but with both CH₃ groups positioned in flipped down configuration. In aqueous medium, L2 is less hydrophilic (more positive electrostatic part) than the corresponding L3. Therefore the interaction energy is weaker than in L3. A small dispersion term between the H₂O and the in-line positioned substituent methyl probably contributes to the energy difference.

In all cases, L2 structure presents a defined local minimum which, depending on the solvation media, is energetically higher (weaker binding) by 1.0-1.4 kcal/mol in comparison to the L3. The lack of analogous second local minimum in the 1:1 pyridine complex is due to the relative smallness of the energy difference between the \perp and II positions. This leads to rapid convergence of the search algorithm to a single-structured isomer, P1(\perp), as presented in Table III. This may also point to the origin of a second minimum in the 1:1 lutidine complex, *i.e.*, the dispersion term, which can be relevant in L3 but not in the L2 structure. Recall, though, that the energies of both structures

strongly depend on the choice of continuous model for simulation of hydrogen bonding media. In fact, the hydrogen bonded 1:1 complex is surrounded by additional H₂O molecules whose directional bonding might have a non-negligible impact on the geometry and the surface potential of the L2 and the L3 schemes. We have tested the impact of a close directional bonding on the implicit continuous media approach. When the 1:1 complex is augmented by two additional water molecules that are hydrogen bonded to the oxygen atom of the original H₂O, the parallelism of the L3 structure can be extended up-to 40° out-of-axis angle (between the planes of the H₂O and the lutidine molecules) in a shallow potential minimum. Herein, the lutidine-water complex for both the L2 and the L3 structures has been limited to the original 1:1 stoichiometry by practical reasons. For clarity, both structures, here and in following discussions, are marked by different gray shading schemes [light-gray for L2(\perp); dark-gray for L3(II)].

The small formational changes visible at different P1(\perp) structures are described mainly by the \sim 0.05 Å shortening of the O–H \cdots N hydrogen bond of the 1:1 pyridine complex, observed in the more polar solvent. We assume this is the result of strong polarization effect in complexes in polar environment. Dipole-dipole interaction energy, E_{μ} , of two parallel polar molecules **A** and **B**, having in-line oriented dipole moments, μ_A and μ_B , is proportional to $-\mu_A\mu_B/R^3$, where R is the distance between the acting dipoles, at the equilibrated structure of the 1:1 complex. Stronger dipoles induced in a polar solvent will increase the negative polarization energy in the 1:1 complex, shortening the interaction coordinate distance down to a point where the increase in the negative polarization energy, ΔE_{μ} , is balanced by the increase at the slope of the potential surface energy. Therefore, a newly equilibrated structure with shorter O–H \cdots N distances is formed. The increase of polarization can be analyzed by examination of dipole strength in Tables I and III. Sizeable 7% and 15% increase in dipole moments of the water-solvated pyridine complex and pyridine molecule in comparison to those obtained in pyridine solvent is shown. Similarly, 0.03-0.08 Å shortening in the O–H \cdots N bond length is found in the 2,6-lutidine 1:1 complex. For the 1:1 lutidine complex and lutidine molecule, changes in the molecular dipole strength going from water to lutidine solvent are even more pronounced, displaying \sim 13% enhancement in dipole moment of the more polar solvent. Hence, the complicated behavior of amphiphilic molecules, when complexed in a polar solvent, leads to a non-intuitive result absent from calculations conducted in vacuum: reduction of the total interaction strength in water-solvated 1:1 complexes (see in Table III) while at the same time polarization-induced shortening in the interaction coordinate distance.

But what is the reason for the lower interaction energy in polar solvents? The net free energy of solvation, $\Delta\Delta G_{sol}^{1:1}$, incorporating all the above-mentioned hydrophobic-hydrophilic contributions, bears the main difference in the interaction energy of solutes in different environments. For example, the net interaction energies of 1:1 2,6-lutidine complex, as calculated by the wB97xD functional in vacuum, lutidine, and water for L3/L2 structures, are: -8.52 , -7.14 – -6.19 , and -6.00 – -4.61 kcal/mol, respectively. However, the total

interaction energies (before the subtraction of the solvation energy term) are quite similar: -8.52 , $-7.94/-8.05$, and $-7.58/-7.83$ kcal/mol, respectively. Similarly, the net interaction energies of the 1:1 pyridine complex in vacuum, pyridine, and water are -7.29 , -6.24 , and -4.23 kcal/mol, while their respective total interaction energies are -7.29 , -7.03 , and -6.85 kcal/mol.

Why does the net free solvation energy, $\Delta\Delta G_{sol}^{1:1}$, is less favorable (more positive) in water in comparison to the less polar solvents? The reason for this is that in an aqueous solution, the H₂O molecule and the polar part of the pyridine have higher electrostatic interaction with the surrounding media as separated entities than as integral parts of the 1:1 complex. The positive energy difference of $+1.87$ kcal/mol in the electrostatic part of $\Delta\Delta G_{sol}^{1:1}$ contains almost 75% of the total energy difference in water. This is so because when separated, water and pyridine molecules have the potential ability to form up to five hydrogen bonds with the surrounding medium, but only three bonds are available when bonded in the 1:1 complex. Consequently, in comparison to separated constituents, the net electrostatic solvation energy of the 1:1 complex decreases. Since the strength of the electrostatic solvation energy depends on the polarity of the surrounding media, the net (relative) electrostatic solvation term, $\Delta\Delta G_{El.Static}^{1:1}$, is reduced in the less polar solvent. Hence, the decrease of the solvation electrostatic energy in the pyridine 1:1 complexes, from -12.79 kcal/mol in water to -7.31 kcal/mol in pyridine, is accompanied by a similar 33% reduction in the net electrostatic solvation energy, from $+1.87$ kcal/mol to $+1.26$ kcal/mol.

The general inclination of the polarization effect in lutidine 1:1 complexes is similar to that of the pyridine. There is a high electrostatic energy difference between the water and lutidine solvated 1:1 complexes (-12.98 vs. -6.48 kcal/mol for the L3, -11.62 vs. -5.64 kcal/mol for the L2 structures, respectively) and similar difference in the respective relative electrostatic solvation terms, $\Delta\Delta G_{El.Static}^{1:1}$ ($+1.72$ vs. $+1.11$ kcal/mol in the L3, $+3.08$ vs. $+1.95$ kcal/mol for the L2 structures, respectively).

The difference in the non-electrostatic terms of the 1:1 complexes between water and pyridine reflects the hydrophobic nature of the P1(\perp) structure in water ($\Delta G_{CDS}^{1:1} = +3.45$ kcal/mol), in comparison to the one solvated in pyridine ($\Delta G_{CDS}^{1:1} = -2.46$ kcal/mol). For lutidine complexes, a similar difference in the hydrophobic nature of the water and lutidine-solvated structures shows the $+3.59$ -(-3.02) kcal/mol energy gap for the L3 structure and an identical, $+3.87$ -(-2.80) kcal/mol, change for the L2 structure. The relative non-electrostatic energy contributions, $\Delta\Delta G_{CDS}^{1:1}$, are $+0.75$ and -0.46 kcal/mol for water and pyridine solvents, respectively. No distinct difference in $\Delta\Delta G_{CDS}^{1:1}$ is calculated in lutidine complexes.

B. The pyridine and the 2,6-lutidine, 1:1 complexes—The formation energy

In the last three columns of Table III, the change of enthalpy, ΔH , the entropy loss (vibrational, rotational, and translational), ΔTS , and the Gibbs free energy of the reaction are shown. The latter term, i.e., the change in Gibbs free

energy in complexation reaction, is given by

$$\Delta G^{1:1} = \{(\Delta E^{1:1} + \Delta\Delta G_{sol}^{1:1}) + \Delta ZPE^{1:1} + \Delta E_T^{1:1}\} - \Delta TS_{assoc}^{1:1} \quad (3)$$

The sum in round brackets is the change in electronic energy with the addition of the solvation net free energy, ΔE_{Solv} , optimized at the solvated geometry structure. The $\Delta ZPE^{1:1}$ and the $\Delta E_T^{1:1}$ are the changes due to complexation in the Zero Point Energy (ZPE) and in the thermal energy. The thermal energy change is a combination of vibrational, translational, rotational, and “work” terms. In the case of association reaction where a product is made from two components, the three rotational and the three translational degrees of freedom add $-0.5RT$ each, and with additional $-RT$ of the “enthalpic work” term they sum to a total of $-4RT$. In our case, at room-temperature, this negative energy is almost balanced by the positive vibrational thermal energy, leading to a small total thermal change smaller than ± 0.31 kcal/mol. Together with the ΔE_{Solv} and $\Delta ZPE^{1:1}$ terms, this defines the enthalpy change, ΔH .

As discussed by Steinberg and Scheraga⁴⁰ and others,^{41–43} the association entropy change term in gas phase, $\Delta S_{assoc}^{1:1}$, which consists of vibrational, translational, and rotational parts, accounts for the loss of ordering in the association reaction. The total entropy change in the system is the sum of $\Delta S_{assoc}^{1:1}$ and the solvation entropy change (included in $\Delta\Delta G_{sol}^{1:1}$). Since the geometries of the gas and solvated phases are rather different, the association entropy was derived for the liquid, but in accord with the usual gas phase entropy formalism.⁴⁰ The “gas phase” entropy in Table III (column 10) is calculated at minimal rotational group symmetry, $\sigma = 1$, and addresses a standard reference state of 1M concentration (i.e., after renormalization of the translational entropy term from 1 atm). All the rotational-vibrational terms are obtained at the wB97xD/Aug-cc-pVDZ and M062x/D3/Aug-cc-pVDZ theory level without correction for the harmonic approximation of the low energy normal modes.

The free energy of the reaction is displayed in the last column of Table III. It accounts for the rotational-conformational entropy change by introducing a correct rotational symmetry number, σ . This is quantified in Eq. (4) (see Ref. 44), where $S_{(\sigma=J)}$ is the entropy of a molecule for which the rotational symmetry number is not accounted for (i.e., the entropy written in column 10)

$$S_{(\sigma)} = S_{(\sigma=1)} - RT^* \ln(\sigma). \quad (4)$$

Here we include the rotational symmetry of the H₂O (D_{2h} , $\sigma = 2$) and that of the organic molecules (C_2 , $\sigma = 2$) in calculating the free energy of the reaction. In the following calculations for higher structures, molecular rotational symmetry is treated by similar rules. In addition, conformational ordering of a pair of similar molecules/complexes is accounted too, but rotational-symmetry entropy change in flexible, non-covalent complexes, is omitted.

The results of the free formation energy calculations for the pyridine and lutidine 1:1 complexes express the basic solvation property in both structures: due to the above arguments, complexation is more stable in organic than in aqueous media. As expected, in the current solvation formalism, the lutidine 1:1 parallel complex has a lower free energy of formation than

in the perpendicular scheme (0.1÷0.6 and 1.2÷2.2 kcal/mol in organic solvents for the L3 and the L2 structures, respectively). Smaller differences but at higher absolute values are found in aqueous medium. Solvation properties in pyridine complexation are very similar to that of the lutidine 1:1 structures (0.4÷0.8 and ~2.6 kcal/mol in organic and water solvents, respectively).

We now discuss three issues. First, what is the accuracy of the calculations of the free energy of formation? The numerical accuracy in the multipart derivation of the free energy of formation in Eq. (3) is affected by two terms: the solvation free energy and the entropy loss. The error due to the difficulty in utilization of the implicit solvation model was argued above. The second major error source results from the inherent instability posed by the six low energy rotations and vibrations accounting for the association vibration energy in the complex. They are known as the major contributors to the errors in association entropy. Another notable error in entropy calculation is attributed to the numerical instability acquired during the solvation modeling. Because of those errors, the results of the free energy of formation in Table III and elsewhere should be used with caution and mostly as showing a general trend across several calculations.

Second, we address the issue that all values of the free energy of formation in Table III correspond to lower than 50% formation probability (in organic solvents, the probability of a stable 1:1 complexation is close to null). This requires a review of the empirical evidence in favor of the pyridine/lutidine-water complexation process. Indeed, the assumption of the formation of the water-organic complexes at room temperature in water is based on many experimental confirmations.^{19,20,45–51} Raman isotropic scattering validated stable water-pyridine hydrogen bonding.^{45,46} Presence of higher than 1:1 structures was inferred from polarized Raman measurements.⁴⁷ Raman technique was also implemented in studying the picosecond vibrational dynamics of the hydrogen-bonded pyridine complexes.⁴⁸ Small-angle neutron scattering technique showed the existence of hydrogen bonded 2,6-lutidine and pyridine structures.^{20,49} Hydrogen-bond-driven room temperature complexation was demonstrated in PFG-NMR and FTIR measurements.^{19,50,51} Monte-Carlo based MD simulation proved that at least 63% of the pyridine molecules was at constant hydrogen bonding with H₂O molecule at room temperature.⁵² But although the majority of the cited studies confirm the existence of hydrogen bonding at differing levels of water-organic complexation, the particular 1:1 complexation is not quantified nor is it explicitly identified. However, in a recent PFG-NMR study,¹⁹ calculations of self-diffusion have showed that strongly diffusing water-organic species, which, according to Einstein-Stokes formula, match the diffusion profile of a minimal lutidine-water complex, exist mainly in the organic-rich solvent content (~90% of lutidine in water). This assumption is confirmed now in this study.

The third issue is the similarity in the values of the free energy of formation of the lutidine and the pyridine complexes, differing by only 0.25 kcal/mol in organic solvents. This undermines the assumption (discussed previously) of a much stronger H₂O binding in the methyl-derived pyridine. Here, an energy difference of 0.8÷1.0 kcal/mol between the pyridine

and the lutidine complexes is found in direct electronic energy binding (column 8 but without the solvation terms). This value is much closer to the 0.7 kcal/mol difference found in a previous work at the MP2/aug-cc-pVDZ level of theory.¹⁶ Careful examination reveals that the energy difference upon solvation depends on the structure of the lutidine complex. For L2, which is similar to the P1 in pyridine complexation, the energy difference decreases but for the L3 complex, the energy differences with the pyridine 1:1 structure increases to 1 kcal/mol and even above. However, stronger binding prompts larger entropy loss; hence, much of the energy difference between the P1 and the L3 structures is lost when free energy of formation is calculated. Experimentally, the 2,6-lutidine (wide binary coexistence loop) and the pyridine (full mixing) show the largest deviation in demixing behavior that in most statistical models is ascribed to difference in the free energy of formation of the 1:1 complex (though in substituted pyridines, different models predict opposite effect). However, here we demonstrate that in organic solvents, after accounting for the solvation energy and the entropy loss, the free energy of formation for the L2 structure is too positive to be of major importance and the change in free energy between the L3 and the P1 structures is too small to be regarded in a theoretical explanation on differences in the mixing behavior. Additionally, in aqueous medium, free energy of formation in 1:1 is too positive to be considered as a viable path to liquid phase separation. Therefore, the mixing-demixing phenomenon in water-substituted pyridine systems cannot be described by 1:1 complexation. In Secs. III C–III E, the possibility of dimerization processes is analyzed.

C. The pyridine-H₂O and the 2,6-lutidine-H₂O, 2:1 complexes—Structural properties

Dimer formation is the next stage in pyridine/lutidine-H₂O complexation. The most efficient way to achieve dimerization is by adding an additional organic molecule to the pre-existing 1:1 complex. We call it the 2:1 dimer. The partial free energy of formation, $\Delta G_{prt1}^{2:1}$, and the equilibrium rate constant, $K_{prt1}^{2:1}$, is given in Eqs. (5) and (6), respectively,

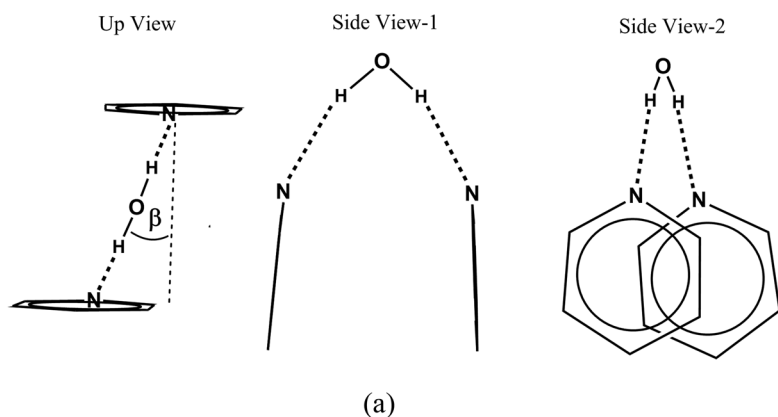
$$\Delta G_{prt1}^{2:1} = G^{2:1} - G^{1:1} - G^{1:0}, \quad (5)$$

$$K_{prt1}^{2:1} = \exp(-\Delta G_{prt1}^{2:1}/RT). \quad (6)$$

Formation of the 2:1 dimer depends on the availability of a second hydrogen bond in the 1:1 complex for the additional organic molecule to interact with. This is so since spontaneous bonding of three separated components: two organic and one water molecules is less probable (we address this question below). The formation predominance of such a dimer over the 1:1 complex is due to an additional binding term, the dispersion interaction that is able to bind the two organic molecules together. However, the loss of entropy during the dimerization is larger than the loss of entropy in 1:1 complexation, so this process is not trivial and needs to be examined.

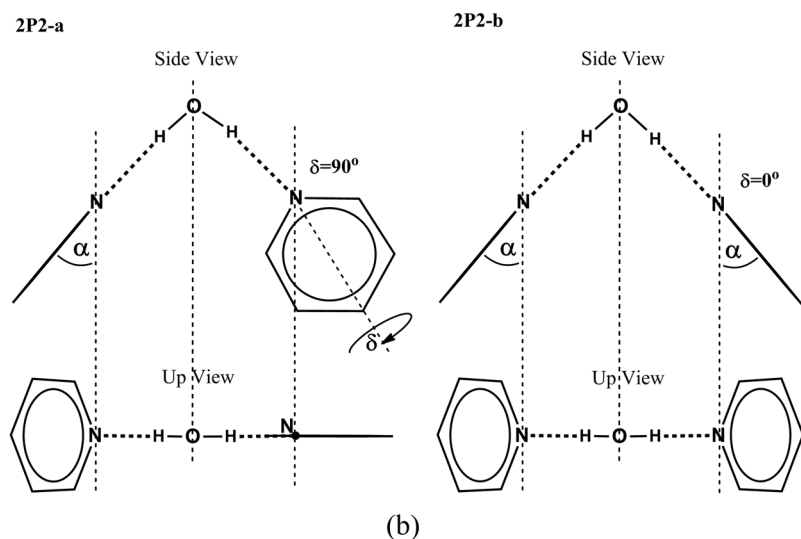
Figures 3(a) and 3(b) show the two calculated structures, 2P1 and 2P2 (the 2P2 is split between the 2P2a and the 2P2b conformations), of the 2:1 complexes of a pyridine in aqueous medium and in pyridine solvent. The two basic conformations show a common feature of a hydrogen-bonded organic pair,

2P1



(a)

FIG. 3. Structures of 2:1 pyridine dimer. (a) The 2P1 compact structure. (b) The 2P2-a and 2P2-b loose structures.



(b)

tied together via the H_2O molecule in a bridge-like structure. The main difference between the two is the degree of compactness of the respective 2P1 or 2P2 structures.

The data for the two DFT algorithms (wB97xD, M062x/D3) and the two solvents (water, pyridine) are presented in Table IV. This includes the structure nomenclature that is tabulated in the second column, the inter-atomic distances: nitrogen-aqueous hydrogen, nitrogen-nitrogen, and angles: β (dimer tilt), δ (ring rotation), and α (ring inclination) in columns 3 to 7. The angles are defined in a way to enable standardization (see table's notes) although in different structures they might not have the same geometrical meaning. Dipole intensity in solvent and the hydrophilic/hydrophobic-related solvation terms (electrostatic/non-electrostatic) are shown in columns 8 and 9. The net contribution of the solvation free energy term in column 10 is in accord with the following equation:

$$\Delta\Delta G_{sol}^{2:1} = \Delta G_{sol}^{2:1} - \Delta G_{sol}^{1:0} - \Delta G_{sol}^{1:1}. \quad (7)$$

Columns 11 to 14 of Table IV present the "partial" complexation energy [the partiality is defined by Eq. (5)], enthalpy change, room-temperature entropy loss, and the change in free energy in the partial formation of the 2:1 dimer. Those terms

are in accord with previous definitions discussed in the case of the 1:1 complexation.

Figure 3 and Table IV present the two basic structures of the pyridine 2:1 dimer: the *compact* (2P1) and the *loose* (2P2a, 2P2b). The 2P1 structure can be readily calculated with all methods and solvents, but calculation of the 2P2 structure is not viable for the M062x-D3 algorithm in aqueous medium. There are also geometrical differences between the wB97xD and the M062x-D3 methods in derivation of the 2P1 structure. A slight distinction between the two functionals is found in the inclination angle α : it is larger for the M062x-D3 ($4.0^\circ/5.8^\circ$) than for wB97xD ($2.6^\circ/3.7^\circ$) in both solvents (i.e., H_2O or pyridine, respectively). The inclination angle shows the parallelism of the organic molecules. Larger deviation angle might stand for weaker dispersion attraction between the organic molecules. A large difference occurs for the tilt angle of the 2P1 dimer: it is much larger in M062x-D3 ($34^\circ/31^\circ$) than in wB97xD ($23^\circ/21^\circ$) in both solvents (i.e., in H_2O or pyridine, respectively). The tilt angle in the 2:1 pyridine complex is a stabilizing feature. It facilitates optimization of the attractive bonding due to dispersion related effects and the repulsion due to the π -electron aggregation of the interacting aromatic rings (repulsive quadrupole-quadrupole interaction). For many years, it has received a substantial attention in studies of the

TABLE IV. Structure and solvation properties, association energies, gas phase entropy loss, and Gibbs energy for the 2:1 pyridine dimer in water and in pyridine. The electron interaction energy term, ΔE , includes solvation contribution.

2:1-Pyridine-H ₂ O /...Solvent/Method	N-H ₂ O dist. (Å)	N-N dist. (Å)	Dimer tilt- β^a (deg)	Ring rot.- δ^a (deg)	Rings incl.- α (deg)	Dipole (D)	$\Delta G_{El,Static}^{2:1} / \Delta G_{CDS}^{2:1}$	ΔE_{Solv}	$\Delta H_{T=298.15}$	$\Delta TS_{298.15}^{IM}$	Gibbs energy + conf. & rot. symmetry	
H ₂ O/wB97xD	2P1 2P2-a	1.914 1.862/75	3.533 4.200	23 44	0 34	2.6 35	10.54 9.18	-18.28/+3.78 -19.10/+4.77	-6.63 -5.01	-5.20 -3.38	-9.34 -8.92	+3.72 +5.13
H ₂ O/M062x-D3	2P1	1.943/70	3.570	34	0	4.0	10.27	-17.64/+3.65	-6.67	-5.30	-9.25	+3.54
PYR/wB97xD	2P1 2P2-b	1.980 1.927	3.534 4.452	21 5	0 5	3.7 45	9.70 7.73	-12.24/-3.64 -12.49/-3.88	-6.43 -5.10	-4.90 -3.37	-9.55 -7.31	+4.24 +3.53
PYR/M062x-D3	2P1 2P2-a	2.020/1.98 9.1.945	3.524 4.237	31 0	0 0	5.8 35	9.54 8.38	-11.92/-3.51 -12.45/-3.85	-6.40 -5.07	-4.96 -3.36	-9.42 -7.88	+4.05 +4.11

^aGeneralization in angle calculations for differing structures results in following designations: The tilt angle, β , is a complementary angle between the molecular planes of the H₂O and the pyridine ring of closest to orthogonality conformation. In the case of a parallel dimer structure as in **2P1**, this is the exact tilt angle found between dimer's composites. The rotational angle δ is the difference between the angles defined by the planes of H₂O and each of the arenes. For the symmetrical **2P2-a**, **2P2-b** structures, this impose the $\delta = 90^\circ$ and $\delta = 0^\circ$ rotations, respectively.

so-called “sandwich” of parallel displaced benzene dimers, with various tilt angles in the range: 21° – 27° (calculated in vacuum).^{53–56} The resemblance between our 2:1 pyridine/lutidine dimers and the “displaced parallel and substituted benzene dimers” is further addressed below.

The difference between the M062x-D3 and the wB97xD algorithms in the *loose* 2P2 formations is larger especially for aqueous media: in contrast to the 2P2-a structure obtained by the wB97xD algorithm, there is a lack of a definite local minimum for the 2P2 in the M062x-D3 algorithm in water. Since the interaction energies in the 2P1 structures for the two DFT methods are similar, the discrepancy can be attributed mainly to the absence of a potential barrier on the potential surface of the M062x-D3 functional in water. Negligible potential difference (5.07 vs. 5.10 kcal/mol) in the closely related 2P2-a and 2P2-b structures as found by M062x-D3 and wB97xD, respectively, indicates the energetic equivalence of the two 2P2 structures on the surface potential. From the cumulative calculations, it is apparent that the two structures 2P1 and 2P2 are in shallow local potential wells with a probable transition state separating them. From different optimization calculations, it is implied that the stationary point is at a perfect 2P2-a structure symmetry ($\delta = 90^\circ$ for one pyridine) but with a very low inclination angle ($\alpha = \sim 0^\circ$) on the second pyridine.

Table V present results for the 2:1 lutidine dimer in a way analogous to that of Table IV and with a similar nomenclature. The only difference is in the numbering scheme of the columns (column 2 of Table IV has been deleted in Table V). The structure is presented in Fig. 4. In contrast to the pyridine, the 2,6-lutidine formation shows a single minimum in any calculation setup. This relative rigidity in the structures is due to the existence of the potential barriers prompted by the CH₃ orientational confinement and by the dispersion interaction term incorporated in the wB97xD and the M062x-D3 algorithms. The utilization of Grimme dispersion correction is vital to the 2:1 formation. When examined by the well-tested B3LYP Kohn-Sham algorithm (not presented here), lacking the dispersion terms, the lutidine 2:1 configuration loses the conformational rigidity of the parallel dimer and shows a very low binding energy.

Similar to the 2P1 nomenclature, we call the *compact*, parallel-tilted 2:1 lutidine structure obtained by both the wB97xD and the M062x-D3 algorithms, 2L1 dimer. The structural difference in calculations made by the two algorithms is the tilt angle β which is larger in structures obtained by the M062x-D3 compared to the one obtained by wB97xD. Evidently, its origin should be attributed to the shallowness of the dispersion interaction potential acting between the two lutidines. In columns 9 to 13 in Table V, the energy data are marked by two gray shades indicating two different energy setups and should be read in conjunction with corresponding data with similar gray shading markings of Table III. The reason for the duplicate energies is due to the possibility of duplicate 1:1 precursor structures: L2(\perp), L3(II) with different solvation free energy, $\Delta G_{sol}^{1:1}$, electronic, $E^{1:1}$, enthalpy, $H^{1:1}$, room-temperature entropy, TS and the free Gibbs energy, $G^{1:1}$ terms. Consequently, this will lead to different energy terms for the 2:1 lutidine dimer. We emphasize that the

TABLE V. Structure, solvation properties, association energies, gas phase entropy loss, and Gibbs energy for the 2:1 2,6-lutidine dimer in water and in 2,6-lutidine. Gray shading markings in columns addressing changes in the net solvation/energy properties need to be read in conjunction with corresponding data with similar gray shading markings of Table III. All calculations follow the 2L1 geometry scheme. The electron interaction energy term, ΔE , includes solvation contribution.

2:1- Lutidine-H ₂ O I...Solvent/Method	N-H ₂ O dist. (Å)	N-N dist. (Å)	Dimer tilt- β^a (deg)	Ring rot.- δ^a (deg)	Rings incl.- α (deg)	Dipole (D)	$\Delta G_{EIS}^{2:1} \dots /$ $\Delta G_{CDS}^{2:1}$	$\Delta \Delta G_{sol}^{2:1}$	ΔE_{Solv}	$\Delta H_{T=298.15}$	$\Delta TS_{298.15}^{IM}$	Gibbs energy + conf. & rot. symmetry
H ₂ O/wB97xD	1.921	3.566	14	0	0.2	8.73	-16.44/+4.63	+1.34 -0.30	-10.36 -11.75	-9.18 -10.61	-9.18 -9.91	-0.41 -1.11
H ₂ O/M062x-D3	1.907	3.752	29	0	2.6	8.38	-16.68/+5.21	+1.97 +0.28	-9.39 -10.76	-8.35 -9.92	-9.84 -10.75	+1.08 +0.41
LUT/wB97xD	1.986	3.558	15	0	1.3	7.59	-9.34/-3.62	+2.70 +1.64	-8.86 -9.81	-7.15 -8.23	-10.04 -9.91	+2.48 +1.27
LUT/M062x-D3	1.994	3.801	31	0	3.3	7.29	-9.36/-3.75	+2.72 +1.70	-8.71 -9.82	-7.37 -8.54	-11.11 -10.18	+3.33 +1.23

^a Angles β and δ are defined as in Table IV.

differences between the two energy terms of each structure in Table V are completely defined by the differences in the interaction enthalpy, $\Delta H^{1:1}$, and room-temperature entropy loss, $\Delta TS^{1:1}$, for the analogous pair of the L2(\perp), L3(II) structures. This is so because the differences in the “partial-1” free formation energy, $\Delta G_{prt1}^{2:1}$ (and all of its constituents, separately), can be directly defined by the $\Delta G^{1:1}$ via Eq. (8), where $\Delta G_{Tot}^{2:1}$ is a constant which defines a measure of a free “total” energy of formation, independent of the free energy of formation in 1:1 complexation (basically, $\Delta G_{Tot}^{2:1}$ is the free energy of formation when the 2:1 dimer product is made from three separate reactants: the two organic and one H₂O molecules)

$$\Delta G_{prt1}^{2:1} = \Delta G_{Tot}^{2:1} - \Delta G^{1:1}. \quad (8)$$

Therefore, since the association of the L3(II) structure is 1.0-1.4 kcal/mol stronger than in L2(\perp), the interaction energy in the related 2L1 structure will be similarly weaker.

D. The pyridine and the 2,6-lutidine, 2:1 complexes—Energy and solvation properties

The results in Table IV show that entropy loss leads to highly positive values of the free energy of formation for pyridine dimers. One can see that in the case of pyridine as a solvent, the energetic preference of the *compact* over the *loose* structure disappears. This is because higher ordering in the less flexible structure dictates a higher entropy loss. Although, in water there is a definite thermodynamic predominance of the *compact* over the *loose* conformers. However, this 2P1 conformer still has a highly positive free energy of formation, which remains high even in comparison to the positive formation energy of the P1 complex. Hence, the only feasible conclusion from the calculation of the pyridine 2:1 dimer is that dimerization is not workable.

Contrary to this conclusion, lutidine 2:1 dimers in aqueous medium have practical formation rates, as demonstrated by the low positive or negative figures of the free energy of formation (Table V). This is true for both conformational paths of the 2L1 structure, though, as might be expected from the dimer formation path of Eq. (8), the one originated in L2 has a clear rate advantage over the L3 counterpart. Conversely, in calculations in the organic solvent, the free energy of formation was highly positive in both conformational paths of the 2L1 structure. The complementary solvation behavior in the organic and polar solvents of the lutidine 1:1 and the 2:1 structures is intriguing. Since both structures are mutually connected with an opposite reaction energy sign via Eq. (8), their solvation behavior might be addressed with similar correspondence.

All lutidine dimers share a single stable structure of a similar geometry, called 2L1, in all solutions. The large differences in free energies of the 2L1 dimers in various solutions are addressed to their respective solvation energies. The symmetry group of 2L1 is similar to the one of 2P1 (C₂). Although the 2P1 is more polar than the 2L1, both dimers should have comparable solvation behavior. We discuss the effect of the solvation on the interaction energy in 2L1 first by examining the 2P1, then by analyzing the effect of the addition of the substituents on the solvation energy in 2P1.

2L1

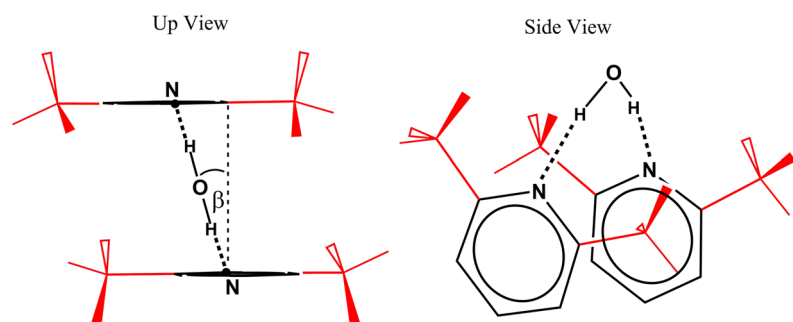


FIG. 4. The 2L1 compact structure of the 2:1 lutidine dimer.

In H_2O , the electrostatic and non-electrostatic solvation terms of 2P1 are -18.28 and $+3.78$ kcal/mol, (e.g., in wB97xD), respectively. In comparison, the pyridine molecule/1:1 complex has $-6.00/-12.79$ and $+1.25/+3.45$ kcal/mol, respectively. The similarity in “hydrophobic” terms in the P1 and the 2P1 structures is due to a match in the external surface of the organic parts (though the tilted dimer is slightly larger) obtained by contracting four external faces in two separate monomers to two in one dimer. In total, the non-electrostatic term contributes -0.92 kcal/mol ($3.78 - 1.25 - 3.45$). Correspondingly, the electrostatic term adds $+0.51$ kcal/mol ($-18.28 + 6.00 + 12.79$) to the net energy of solvation for the 2P1 in water. The positive figure is attributed to the reduction in number of potential hydrogen bonds in the dimer in comparison to the constituents (e.g., 1:1 complex and pyridine molecule). Similar analysis for solvation of the 2P1 dimer in pyridine leads to $-0.21/+0.40$ kcal/mol contribution to the non-electrostatic/electrostatic term of the net energy of solvation. The reduction in the negative net non-electrostatic energy is clearly attributed to lack of hydrophobic effect. The small reduction in the positive electrostatic net solvation energy is explained by polarization weakening effect in less polar solvents.

The balancing effect between the electrostatic and the non-electrostatic variations in the solvation energy of 2P1 can be stated now in terms of the net free energy of solvation, $\Delta\Delta G_{sol}^{2:1}$, where upon complexation, the relative decrease in net hydrophobic repulsion in dimers in water is accompanied by similar decrease in the net electrostatic energy. In the less polar organic solvent, the absence of hydrophobic repulsion is accompanied by a similar lack of change in the net electrostatic energy. Markedly, in terms of the net free energy of solvation, $\Delta\Delta G_{sol}^{2:1}$, the energy contribution to the overall binding in the 2P1 dimer is smaller than $|\pm 0.5|$ kcal/mol in all solvents (Table IV).

In the case of the 2L1, the addition of four CH_3 groups enlarges the positive free energy of solvation in the interaction energy. This is presented in Table V. The organic substituents reduce the solubility of the lutidine dimer. In aqueous media, the free energy of solvation is -11.81 kcal/mol ($-16.44/+4.63$) for the 2L1 in comparison to -14.50 kcal/mol ($-18.28/+3.78$) for the 2P1. Similarly, in organic solvents, we have -12.96 kcal/mol ($-9.34/-3.62$) for the 2L1 in comparison to -15.88 kcal/mol ($-12.24/-3.64$) in the 2P1. The examination of the electrostatic and the non-electrostatic parts of the net free energy of solvation, $\Delta\Delta G_{sol}^{2:1}$, shows that the major change in

solvation energy in the 2:1 lutidine structure over the pyridine dimer must be attributed to the variations in the net electrostatic part rather than to the non-electrostatic one. The reason is the internal change in the delocalized charge distribution in the arenes (specifically, the enhancement in nitrogen electronegativity), as reflected in the solvation energy of the methylated pyridine dimer.

The following question arises: how do the substituent groups affect the interaction energy of the dimer? We propose two explanations:

(A) a popular assumption suggested previously that the increase in interaction in the water-lutidine 1:1 complex is caused by the increase in electron density of the aromatic ring upon methylation.^{16,54} For the alkyl substituent in π -stacked benzene dimers, an opposite effect was argued by Cozzi *et al.*,^{57,58} i.e., Coulombic repulsion should maximize in a pair of electron-rich rings. Combining those views, it might be expected that nitrogen-driven depletion of electron density in the aromatic ring would reduce Coulombic repulsion, while a parallel increase in extra electron density of nitrogen would mostly be drawn in hydrogen bonding with the H_2O molecule.

(B) The second explanation we “borrow” from multiple studies on benzene dimers is that the strong binding in lutidine dimers is a result of intense but local direct interaction effect of the substituents on the closest part of the adjacent aromatic ring. These interactions in stacking arenes have been extensively studied in systems of the so-called “tilted” or “displaced” parallel benzene dimers for many years by several research groups.^{56–62} The present view describes the general effect of the substituents in stacking interactions mostly as the effect of the substituent-induced dipole in local C–H bonds at the nearest end of the other arene.⁶² Calculations revealed that in vacuum, each methyl substituent in a benzene dimer adds ~ 0.6 kcal/mol to the total interaction energy.⁵⁶ In the case of solvation, the local (“direct”) effect of the substituents needs to be discussed separately because of the additional effect of solute polarization on the electron density of the aromatic dimer system. Pure hydrophobic dimers based on simple benzene dimers are expected to be beneficial for future study of the dispersion (or other) binding effects of pyridine/lutidine dimers in solvents.

E. The 2,6-lutidine dimer—The path to phase separation

Calculations show that pyridine and 2,6-lutidine 1:1 complexes share very close formation energies (in the case of

the L3 conformer) that might even favor pyridine (in the case of the L2 conformer) in their respective organic solvents. In an aqueous medium, both pyridine and 2,6 lutidine 1:1 complexes show constant positive free energy of formation precluding stable complexation at considerable rates. A recent PFG-NMR study¹⁹ confirms this prediction in the case of the 2,6 lutidine 1:1 complexes. But positive free formation energy below LCST disagrees with the standard description of the phase separation phenomenon based on a temperature-driven disassembly of the 1:1 hydrogen bonded complexes at LCST. In organic solvents, the similarity in the free energy of the formation of the 1:1 complexes of the two pyridines, one with the widest phase separation region and another lacking it completely, denoted an additional gap in the 1:1 complexation theory. A different phase separation model was needed. The pivoting role of the 2:1 dimer and higher level pyridine-water and lutidine-water complexing reactions in phase separation phenomena was absent in previous theories. We argue that the negligible dimerization rate in the case of the pyridine is the reason for the difference in phase separation properties of the pyridine in comparison to the 2,6 lutidine. The existence of the dimer structure for the 2,6 lutidine in water is implied in the PFG-NMR study that demonstrated the presence of a minimal organic molecule complex in the low water content and of higher complexing structures of two or more organic molecules, in high water content.¹⁹ This complementary solvation behavior in both structures is in accord with our calculations strategy of the “*partial-1*” dimerization process [see Eqs. (5) and (8)].

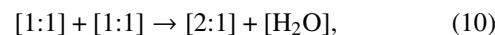
Dispersion interaction between the organic molecules contributes positively to the mixing enthalpy. Therefore, as compared to the 1:1 complex, in the 2:1 dimer, only half of the molar amount of the organic entities needs to be demixed in order to reach the phase separated state. In other words, the 2:1 dimer is preferential over the 1:1 complex in terms of the mixing entropy loss and phase separation potential. In addition, the main drawback in the standard description of a phase separation, namely that an increase in hydrogen bonding strength in substituted pyridine 1:1 complexes should enhance miscibility where the opposite has been observed, is corrected in 2:1 dimerization theory. Stronger dispersion interaction in substituted pyridine 2:1 dimers facilitates liquid phase

separation because stronger dispersion between pairs of organic molecules promotes demixing.

Examination of Table V reveals considerable deviations in estimation of the formation energy by the wB97xD (higher than in 1:1 formation stability) and the M062x-D3 (lower than in 1:1 formation stability) algorithms. The low value of the formation stability of the 1:1 structure in water leads to similar conclusion about the formation stability of the “*partial-1*” dimerization scheme. Consequently, a different dimerization scheme that we call “*partial-2*” is considered in Eq. (9)

$$\Delta G_{prt2}^{2:1} = \Delta G_{Tot}^{2:1} - 2 * \Delta G^{1:1}. \quad (9)$$

It can be readily shown that Eq. (9) relates to the non-covalent hydrogen-bonding reaction in Eq. (10), where, [2:1], [1:1], and [H₂O] are the molar concentrations of the 2:1 dimer, 1:1 complex, and the H₂O molecule, respectively. Therefore, the thermodynamic formation constants in equilibrium, $K_{prt1}^{2:1}$ and $K_{prt2}^{2:1}$, can be related to the respective equilibrium constants of the $\Delta G_{Tot}^{2:1}$ and the $\Delta G^{1:1}$, $K_{Tot}^{2:1}$ and $K^{1:1}$, by Eqs. (11) and (12), correspondingly



$$K_{prt1}^{2:1} = K_{Tot}^{2:1}/K^{1:1}, \quad (11)$$

$$K_{prt2}^{2:1} = K_{Tot}^{2:1}/(K^{1:1})^2. \quad (12)$$

The results of all the energy and entropy terms for the “*partial-2*” and the “*Total*” schemes are introduced in Table VI.

As could have been expected, when the 2L1 dimer is formed in accord with Eq. (9), in water it has high negative energy of formation in all cases but has lower formation stability in the organic solvent. The figures show more negative free energies than in the case of the previous scheme. Therefore, it could be said that in water, only the 2L1 dimers and the free 2,6-lutidine are available. But the impact of reaction 10 in the phase separation process is not limited to appearance of more favorable formation energies. The addition of the H₂O at the right side of Eq. (10) reduces the entropy of translation and makes the reaction virtually independent of temperature. In comparison to all other formation reactions ($\Delta G^{1:1}$, $\Delta G_{prt1}^{2:1}$, $\Delta G_{Tot}^{2:1}$), $\Delta G_{prt2}^{2:1}$ has larger share at elevated temperatures. Moreover, the release of one water molecule as part of the dimer formation reaction has an important implication in the mixing

TABLE VI. Enthalpy, entropy loss, and Gibbs free energy in the 2:1 lutidine dimer formation derived by the “*partial-2*” and the “*Total*” schemes. Gray shading scheme is the same as in Tables V and III. Energy is given in kcal/mol.

	Gibbs energy + conf.			Gibbs energy + conf.		
	$\Delta H_{(T=298.15)}$	$ATS_{298.15}^{1M}$	& rot. symmetry	$\Delta H_{(T=298.15)}$	$ATS_{298.15}^{1M}$	& rot. symmetry
	M062-x+D3			wB97xD		
$\Delta G_{prt2}^{2:1}/H_2O$	-4.62	-2.17	-2.86	-3.84	-2.56	-1.28
$\Delta G_{prt2}^{2:1}/LUT$	-1.69	-3.16	+1.06	-2.05	-4.87	+2.82
$\Delta G_{prt2}^{2:1}/H_2O$	-7.50	-3.63	-4.28	-6.99	-4.38	-2.61
$\Delta G_{prt2}^{2:1}/LUT$	-3.85	-2.90	-1.36	-4.39	-3.01	-1.38
$\Delta G_{tot}^{2:1}/H_2O$	-13.73	-16.19	+0.83	-12.86	-17.12	+2.63
$\Delta G_{tot}^{2:1}/LUT$	-12.62	-16.92	+2.67	-12.70	-17.35	+3.02

process. In the standard phase separation formulation, water molecules release at the LCST is an entropy dependent process and the direct outcome of 1:1 complex disassembly. In this work, part of water release that facilitates demixing is the outcome of 2:1 dimer assembly.

Errors in entropy calculation, limitations in the implementation of the PCM solvation, and neglect of possible conformers (especially 2,6-lutidine molecule where two stable but slightly less negative structures were found) probably have slightly reduced the values of free energies of formation. Careful weighting of those factors should lead to stronger interaction energies in all dimerization reactions. Still, a larger portion of the organic molecules are retained in a single form. But in previous discussion, we argued that disassembly of the 1:1 complexes is not the major factor in phase separation dynamics. Evidently, intermolecular dispersion between *separated* organic molecules is not the major cause that promotes spontaneous demixing.

But how do the organic molecules constituting the dimers affect phase separation? Additional question need to be discussed: temperature has a negative impact on the free formation energy in complexation reactions; hence, in equilibrium with monomer species, dimerization is reduced at elevated temperatures. But if strongest dimerization occurs at the lowest possible temperature (i.e., immediately after dimer formation) why phase separation does not follow? First, dimer formation reduces the molar content of separated monomers that need to be demixed. Second, recall that below the LCST, the 2:1 dimers are interconnected into a network of hydrogen bonded water molecules. At the LCST, most of the $O \cdots H$ hydrogen bonds are disrupted (i.e., the dimer loses its hydrogen bonds with the outside water molecules), but the compact structure of the dimer is not. This is so because the water molecule at the “bridging” position is more tightly hydrogen bonded to the nitrogen atoms of the lutidine dimer than to the external H_2O molecules (in fact, H_2O has stronger HB in pyridine 1:1 or in ammonia-water complex than in the water dimer^{16,64}). Accelerated dimer diffusion then takes place and phase separation dynamics begins.

As a result, the organic dimer structures aggregate into large hydrophobic clusters of rich organic content that expel water. In the large organically rich clusters, dimers are disassembled whereas in the water-rich region, dimer formation is accelerated. At LCST, high diffusion rate enables transport of the newly formed 2:1 structures. Therefore, the dimer concentration in the water-rich regions decreases until equilibrium is reestablished when new dimers are formed. This constant dimer transport toward the organically rich region where they disassemble proceeds until two-phase coexistence is established. In this description, phase separation requires the formation of the 2:1 dimers, but it is the *cleavage of the external hydrogen bonds* at LCST that stimulates the phase separation dynamics.

IV. CONCLUSIONS

Based on the above results, we argue that the dimerization of amphiphilic molecules in a polar solvent is facilitated by hydrogen bonding at the hydrophilic part of the molecule and

by the dispersion forces acting between the hydrophobic counterparts. The solvation contribution to the interaction energy is an essential part in the total binding. In this study, we employ implicit PCM/SMD solvation schemes that provide valuable information on the pyridine/lutidine- H_2O 1:1 complexation and 2:1 dimerization. The implementation of the PCM/SMD in a polar solvent resulted in reduced values of the interaction energy for all 1:1 complexes, but for 2:1 lutidine dimers, an opposite effect was shown. In the case of the 1:1 complexation, this is a result of a reduced hydrophilic response. For the 2:1 dimers, interaction energy can be described by sum of several contributions, including the balancing reduction of the hydrophobic and the hydrophilic solvation terms and (as in case of the 2,6-lutidine dimer) by the local induction effect of the substituent on the charge distribution scheme in other arene.

The difference in interaction energy between pyridine and 2,6-lutidine based dimers is a combination of following factors: (A) The increase in electron density in the aromatic ring, facilitating bonding of nitrogens to the bridging water molecule. (B) Interaction enhancement due to a local, direct effect of the substituents on the nearest part of the adjacent arene. The substituent effect on the interaction energy of the displaced benzene dimer was discussed in several studies.^{57–62}

In the future, it would be beneficial to extend studies of the local direct effect of substituents in benzene dimers in vacuum, to polar solvents and to compare the results to those of the 2:1 pyridine and the 2,6-lutidine dimers. The seeming similarity between the pyridine and benzene dimers presents an opportunity to utilize the rigorous quantum-mechanical analysis on benzene for a more precise description of complexation in other organic-aqueous binary systems.

The present work corrects the known deficiencies of the conventional molecular chemistry description of the phase separation phenomenon in water-pyridine derived systems, based on the 1:1 complexation.^{9–13} Our model objects the dominant role of the 1:1 complex in the direct demixing mechanism. Instead, it is shown that the 1:1 structure acts as a precursor in formation of the 2:1 dimers. The pivotal role is attributed to the formation of the highly complexing organic structures, facilitating the reduction of the mixing entropy loss in the demixing process. The phase separation dynamics at the LCST is triggered by the cleavage of external hydrogen bonds in dimers. The ensuing diffusion of the dimers leads to a partially demixed state. The differences in the demixing of the pyridine and the 2,6-lutidine are described by the ability of the latter to maintain stable dimerization.

Some aspects in the present study are hard to answer in the quantum-mechanical methodology. The shallow potential wells in the current study need to be verified by a full statistical approach. These include the dispersion interaction between the pyridines and hydrogen bonding which undergoes averaging in the standard PCM description. Specialized MD studies are welcome and may help to examine those questions in future studies.

SUPPLEMENTARY MATERIAL

See [supplementary material](#) for comparison between the best performing dispersion corrected Kohn-Sham algorithms,

which also includes derivation of the free energy of solvation of the composites of the water-pyridine/lutidine (1:1) systems.

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