FTIR Studies of Isomers and Hydrogen-Bonded Associates with the Amidine Moiety in Apolar Solvents*

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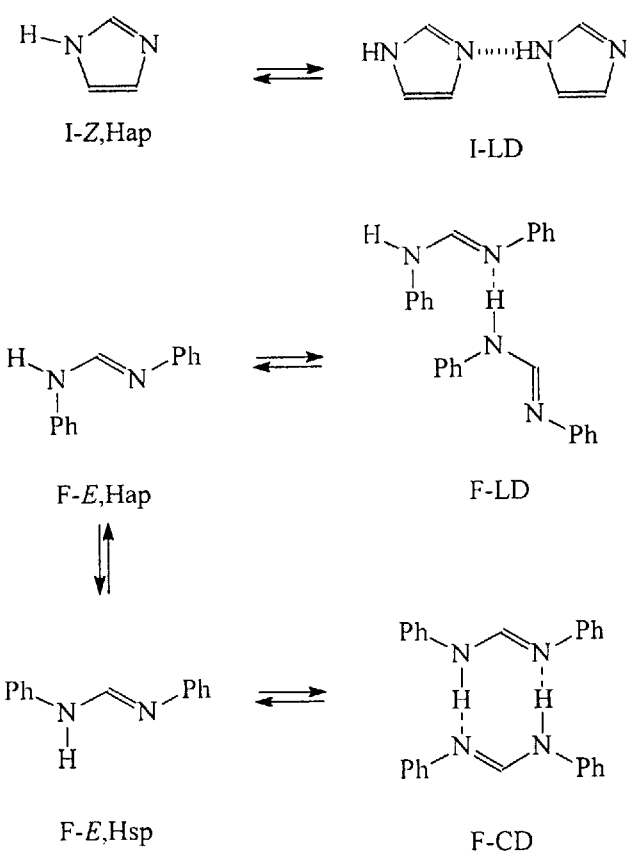
Infrared spectra were recorded in various apolar solvents for two compounds containing the amidine moiety (—NH—CH=N—): cyclic imidazole and acyclic *N*,*N*′-diphenylformamidine (which exists as a mixture of two isomers). Positions of the $\tilde{\nu}$(NH) and/or $\tilde{\nu}$(C=N) bands for monomers and dimers (linear and cyclic) are significantly different and may be used as an indicator of structural properties (rotational and geometrical isomerism as well as association). The free $\tilde{\nu}$(NH) linearly depend on the specific solvent basicity parameter. Isomerization in acyclic formamidine seems to be dependent on the volume of the solvent molecule and its intermolecular interactions with the amidine moiety.

The amidine moiety (—NH—CR=N—) is very common in compounds which play a key role in molecular biology, *e.g.* nucleic acids (adenine, cytosine, guanine) and proteins (histidine, arginine) [1]. It is also incorporated in many synthetic systems of biological importance (sulfaguanidine, madroxin, luminal, dimaprit, cimetidine). To understand physicochemical properties of this moiety, which determines the biological activity of the system, structural studies for model derivatives are important key elements of elucidating the possible intra- and intermolecular interactions, the existence of which is a prerequisite of the life itself.

For our experiments two model compounds, cyclic imidazole (I) and acyclic *N*,*N*′-diphenylformamidine (F) were chosen. Although both derivatives display prototropic tautomerism, their tautomeric forms are identical [2]. They possess the same substituents at the nitrogen atom and the tautomeric equilibrium constant is equal to 1. Imidazole (a model for amino acid histidine, its decarboxylated bioamine histamine and histamine agonists and antagonists) has *Z* configuration on the C=N double bond and the hydrogen atom of the amino group is antiperiplanar to the imino group. Thus, I-*Z*,Hap can only form a linear dimer (I-LD in Scheme 1). Formamidine having *E* configuration (in relation to the C=N double bond) can exist in two rotamers, with the hydrogen atom anti- and synperiplanar to the imino group. Both of these species, F-*E*,Hap and F-*E*,Hsp can autoassociate. The *E*,Hap can form linear associates (*e.g.* F-LD) whereas



Scheme 1. Monomers and associates of imidazole (I) and *N*,*N*′-diphenylformamidine (F).

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F-*E*,Hap F-*E*,Hsp

Fig. 1. The most stable structures of the F-*E*,Hap and F-*E*,Hsp (the phenyl rings twisted out of the amidine plane) found at the HF/6-31G* level.

the *E*,Hsp can form only a cyclic dimer (F-CD) [3—5]. In the solid state formamidine exists in the form of the cyclic dimer only [3]. In solution, two isomers and two associates are possible [4, 5].

The objects of the study were the forms of imidazole and formamidine that exist in solution in relation to the solvent properties. We used apolar solvents which contained neither nitrogen nor oxygen atoms (aside from a few test measurements of the $\tilde{\nu}$(NH) and $\tilde{\nu}$(C=N) spectral regions). These atoms could interfere with the autoassociation in the derivatives studied. For the experiments, we chose FTIR spectroscopy which very well differentiates rotamers and associates [5]. The amidine moiety in imidazole is incorporated into an aromatic system. In formamidine, it is linked to phenyl groups, which being also aromatic and flat constrain the molecule. These structural properties allow easy observation of the N—H and/or C=N group bands in infrared spectra.

In this paper, FTIR spectra were recorded for imidazole and formamidine in 15 apolar solvents, and influence of the solvent on the rotational isomerism and the autoassociation is discussed. Quantum-mechanical (QM) calculations (semiempirical and *ab initio*) were also performed for I-*Z*,Hap, F-*E*,Hap, and F-*E*,Hsp, and thermodynamic and spectral parameters calculated. The $\tilde{\nu}$(NH) and $\tilde{\nu}$(C=N) obtained theoretically were compared with those found experimentally in CCl_4 solutions. Different solvent parameters were taken into account to explain the experimental shift of the $\tilde{\nu}$(NH) bands. Relative stabilities of the F-*E*,Hap and F-*E*,Hsp isomers were estimated in the gas phase (isolated molecules) by QM calculations and in the apolar solvents on the basis of FTIR measurements. Solvent effects on the isomerization constant were discussed.

EXPERIMENTAL

Imidazole and solvents were commercial compounds (Aldrich). Solvents were of anal., HPLC or spectroscopic grade dried over molecular sieves (0.3 nm) before use. *N*,*N*′-Diphenylformamidine was synthesized by reaction of aniline with triethyl orthoformate [6]. After 2 h of heating at boiling temperature the reaction mixture was cooled and formamidine crystals filtered. To increase the purity of the product it was recrystallized from ethanol.

FTIR spectra were recorded for both models on a Fourier transform infrared spectrometer (Perkin—Elmer 2000) for 2—10 different amount of substance concentrations (0.0004—0.1 mol dm^{-3}) using various KBr disc cells with 0.064 mm, 0.627 mm, 1.02 mm, and 2.66 mm path lengths. Two spectral regions, the $\tilde{\nu}$(NH) and $\tilde{\nu}$(C=N) were selected for structural studies. They were decomposed using the mixture of the Gaussian and Lorentzian functions with the help of the Pegrams program (working on the Perkin—Elmer 2000 system). All spectra were recorded at room temperature with 1 cm^{-1} spectral resolution. In each case 16 spectra were accumulated.

COMPUTATION

Quantum-mechanical calculations were applied to isolated molecules of cyclic and acyclic model amidines: I-*Z*,Hap, F-*E*,Hap, and F-*E*,Hsp. For the F-*E*,Hap and F-*E*,Hsp, two structures were considered, one with the phenyl rings situated on the amidine plane, and the other with the phenyl rings twisted out of the N—C=N plane. Geometries were fully optimized without symmetry constraints and the stationary point on the potential energy surface was found. Positive frequencies and lower energies were obtained for the twisted structures (Fig. 1), which were taken for calculations of thermodynamic parameters.

For semiempirical calculations, the Hyper-Chem software package and the Austin Model 1 (AM1) [7] were used as described previously [8]. *Ab initio* calculations were realized using the HF (Hartree—Fock) [9], MP2 (second-order Möller—Plesset perturbation) [10], and DFT (density functional theory) [11] methods and the Gaussian 94 program [12]. Geometries were optimized at the HF/6-31G* level, and harmonic vibrational frequencies (as $\tilde{\nu}$), Gibbs energies ($G°$ at 293.15 K), and dipole moments (μ) calculated. For the F-*E*,Hap and F-*E*,Hsp isomers, single-point energy calculations were additionally performed using the MP2 and DFT(B3LYP) methods and the 6-31G* and 6-311++G** basis sets on geometries optimized at the HF/6-31G* level.

Table 1. Selected Geometrical and Physicochemical Parameters Calculated for Imidazole and *N*,*N*′-Diphenylformamidine (Structures Given in Fig. 1) at the HF/6-31G*//HF/6-31G* Level

Structure	$-G°$	μ	Bond length/nm[a]		Φ_1/°[b]	Φ_2/°[b]	$\tilde{\nu}$(NH)[c]	$\tilde{\nu}$(C=N)[c]
	kJ mol^{-1}	*D*	N—C	C=N			cm^{-1}	cm^{-1}
I-*Z*,Hap	590116.7	3.86	0.1286	0.1344	–	–	3921	1744
F-*E*,Hap	1596228.8	2.71	0.1256	0.1356	−2.9	134.0	3884	1902
F-*E*,Hsp	1596235.4	2.44	0.1256	0.1359	153.1	136.8	3860	1903

a) In the amidine group; *b*) dihedral angle C(phenyl)—C(phenyl)—N—C; *c*) scaling Scott and Radom factor of 0.8953 [13].

Table 2. Relative Stability of the F-*E*,Hap and F-*E*,Hsp (ΔE) Calculated at the Semiempirical (AM1) and *ab initio* (HF, MP2, and DFT)[a] Levels for Structures Given in Fig. 1

Level	$-E$(F-*E*,Hap)[b]	$-E$(F-*E*,Hsp)[b]	$-\Delta E$[b,c]
AM1	216309.7	216314.7	5.1
HF/6-31G*	1596746.4	1596751.0	4.6
MP2/6-31G*	1601885.2	1601885.8	0.6
DFT(B3LYP)/6-31G*	1607082.8	1607084.8	2.0
MP2/6-31++G**	1602243.0	1602244.6	1.6
DFT(B3LYP)/6-31++G**	1607198.9	1607201.6	2.7

a) For geometries optimized at the HF/6-31G*; *b*) in kJ mol^{-1}; *c*) $\Delta E = E$(F-Hsp) − E(F-*E*,Hap) in kJ mol^{-1}.

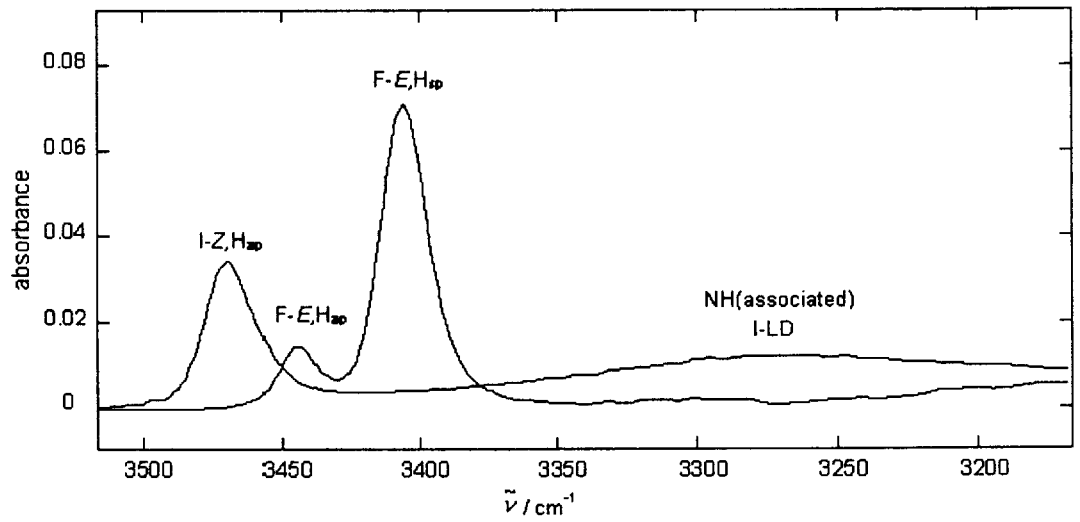


Fig. 2. Free and associated $\tilde{\nu}$(NH) bands for imidazole (I-*Z*,Hap and I-LD) and *N*,*N*′-diphenylformamidine (F-*E*,Hap and F-*E*,Hsp) in $CHCl_3$.

Selected geometrical (the C—N and C=N bond lengths, and the Φ_1 and Φ_2 dihedral angles showing the position of phenyl rings *vis-a-vis* the amidine plane), spectral ($\tilde{\nu}$(NH) and $\tilde{\nu}$(C=N)), and other parameters (μ, $G°$) calculated at the HF/6-31G*//HF/6-31G* level for each amidine isomer are summarized in Table 1. Energies of the F-*E*,Hap and F-*E*,Hsp isomers calculated additionally at the MP2/6-31G*//HF/6-31G*, MP2/6-31++G**//HF/6-31G*, DFT(B3LYP)/6-31G*//HF/6-31G*, and DFT(B3LYP)/6-31++G**//HF/6-31G* levels are given in Table 2.

RESULTS AND DISCUSSION

Among two isomers considered for *N*,*N*′-diphenylformamidine, the *E*,Hsp is more stable than the *E*,Hap at both, the semiempirical (AM1) and the *ab initio* (HF, MP2, and DFT) levels by 0.65—1 kJ mol^{-1}, and therefore it is the preferred one in the case of isolated molecules which are a simulation of the gas phase. The FTIR spectrum of formamidine in CCl_4 solution suggests that in concordance with calculations the dominant isomer is F-*E*,Hsp [5]. The order of the calculated $\tilde{\nu}$(NH) frequencies is similar to that

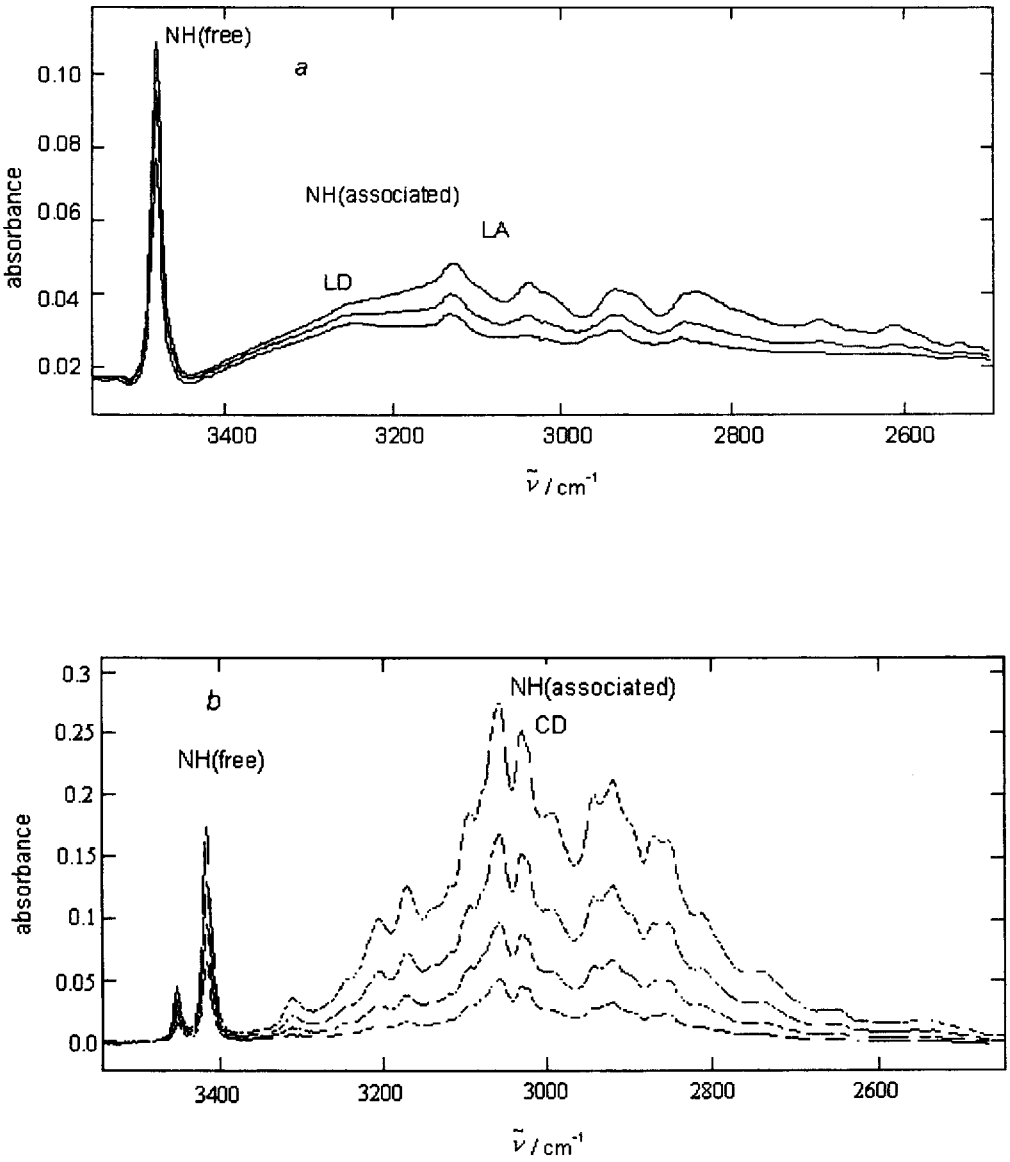


Fig. 3. Free and associated $\tilde{\nu}$(NH) bands for: *a*) imidazole for c = 0.0015—0.05 mol dm^{-3}; *b*) *N*,*N*′-diphenylformamidine in CCl_4 for c = 0.0004—0.01 mol dm^{-3}.

found in CCl_4 (3480 cm^{-1}, 3452 cm^{-1}, and 3415 cm^{-1} for the I-*Z*,Hap, F-*E*,Hap, and F-*E*,Hsp, respectively). The calculated dipole moments for formamidine isomers have a similar pattern to those estimated on the basis of experiment (3.38 *D* and 2.19 *D* for the Hap and Hsp conformer, respectively, 1 *D* = 3.33 × 10^{-30} C m) [14].

Two spectral regions of FTIR bands, the $\tilde{\nu}$(NH) and $\tilde{\nu}$(C=N) were analyzed for both models, imidazole and *N*,*N*′-diphenylformamidine in different apolar solvents. For solvents without oxygen and nitrogen, one free $\tilde{\nu}$(NH) band for imidazole and two free $\tilde{\nu}$(NH) bands for formamidine (corresponding to the isomers *E*,Hap and *E*,Hsp) were found (Fig. 2). Their positions in the IR spectra differ by more than 30 cm^{-1} in $CHCl_3$ solutions. This suggests that it should not be difficult to distinguish the NHap and NHsp groups in the *E* or *Z* configuration of the amidine moiety in more complicated derivatives. The decreasing order of the position of the free $\tilde{\nu}$(NH) bands (I-*Z*,Hap, F-*E*,Hap, F-*Z*,Hsp) is independent of the solvent.

Oxygen- and nitrogen-containing solvents interact with the NH group in more complicated and specific ways than the ones lacking those two atoms. For majority of such solvents, asymmetrical or multiple bands were observed. For example, two bands can be distinguished in the $\tilde{\nu}$(NH) spectral region for imidazole in acetonitrile solutions. These bands correspond to interactions of the NH group with the lone pair of the cyano nitrogen and the π-electrons of the C≡N group. For nitromethane solutions, two bands can also be selected. They correspond to valence and electrostatic interactions, respectively.

Depending on concentration of the compound, lin-

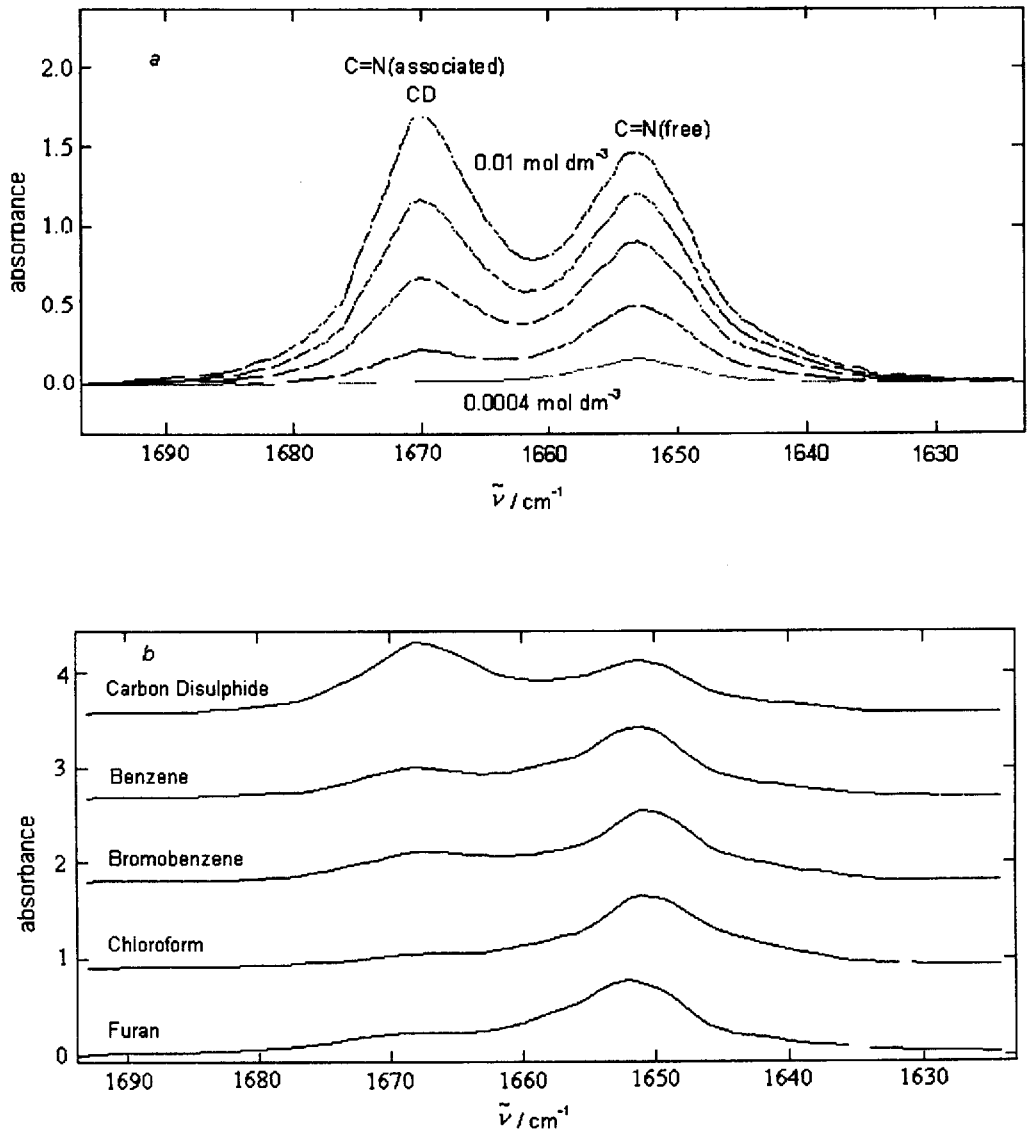


Fig. 4. Free and associated $\tilde{\nu}$(C=N) bands for *N*,*N*′-diphenylformamidine: *a*) in CCl_4 for c = 0.0004—0.01 mol dm^{-3}; *b*) in other solvents for c = 0.01 mol dm^{-3}.

ear (in imidazole) and cyclic associations (in formamidine) are possible in apolar solvents (Fig. 3). The $\tilde{\nu}$(NH) band corresponding to the F-CD has relatively stronger intensity than that of the I-LD due to the higher stability of the cyclic dimer in comparison with the linear one. Associated bands are downshifted by more than 200 cm^{-1}. The significant differences between the $\tilde{\nu}$(NH) bands for monomers (I-*Z*,Hap, F-*E*,Hap, and F-*E*,Hsp) and dimers (I-LD and F-CD) in the FTIR spectra entitle us to conclude that positions of the $\tilde{\nu}$(NH) bands may be used as an indicator of rotational and geometrical isomerism as well as association.

The second frequency region selected for investigation corresponds to the C=N group. For imidazole solutions, the intensity of the $\tilde{\nu}$(C=N) band is very low. For this reason, it was difficult to investigate the free and the associated $\tilde{\nu}$(C=N) bands, because the solubility of imidazole in apolar solvents was not sufficient. A quite different situation was observed for the other model compound. Two bands can be distinguished in this region. They correspond to free and associated $\tilde{\nu}$(C=N) bands (Fig. 4). An increase in dimer proportion was parallel to the increase of formamidine concentration.

Influence of solvent on association is very complex. One can only conclude that neutral, apolar solvents (*e.g.* CS_2 and CCl_4) have almost the same effect on the autoassociation. Other solvents containing heteroatoms and/or π-electrons (*e.g.* CH_iX_{4-i}, C_6H_6, PhX, furan, Et_2O, Et_3N) decrease the autoassociation due to formation of weak H-bonds with the NH or C=N group in the amidine moiety.

The shifts of the $\tilde{\nu}$(NHap) and $\tilde{\nu}$(NHsp) observed in model compounds strongly depend on the solvent basicity. Linear correlation (Fig. 5) was found between

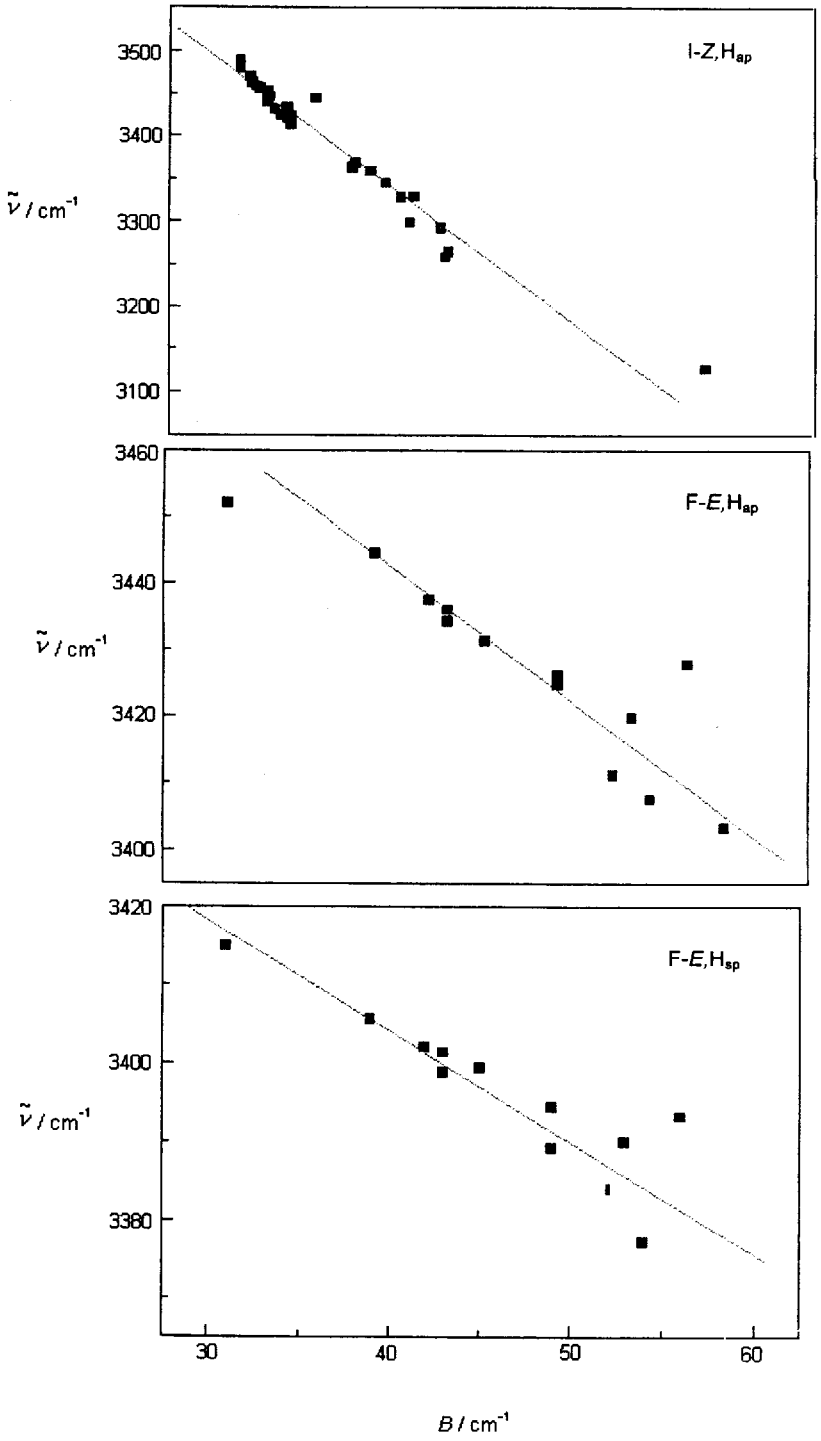


Fig. 5. Correlations between the free $\tilde{\nu}$(NH) and solvent basicity parameter B.

the $\tilde{\nu}$(NH) and specific basicity solvent parameter B [15]. The scale of B parameter (in cm^{-1}) was based on the frequency shift of the OD vibrator of deuterated methanol in various solvents in comparison to the gas phase. In this scale, the larger B value indicates the stronger downshift of the $\tilde{\nu}$(OD) band. The correlations show that generally, interactions of the NH group in the amidine moiety with solvents are similar to those of the OD group in MeOD. The slopes of regression lines are larger than 1 in absolute values. This means that interactions of the NH group with solvent molecules are stronger than those of the OD group in MeOD, and the NH group has stronger H-bond donor properties than the OD group.

Plots between the free $\tilde{\nu}$(NH) and the so-called unspecific solvent parameters [15], such as dipole mo-

Table 3. Isomerization Constant K_I = [F-*E*,Hsp]/[F-*E*,Hap] in Various Apolar Solvents

Solvent	K_I	Solvent	K_I
Carbon disulfide	3.2	Benzene	0.7
Carbon tetrachloride	3.9	Toluene	0.7
Chloroform	5.5	*p*-Xylene	0.5
Dichloromethane	3.3	Chlorobenzene	2.2
1,2-Dichloroethane	2.7	*o*-Dichlorobenzene	2.2
Iodomethane	2.1	*m*-Dichlorobenzene	3.2
Furan	3.1	Bromobenzene	2.1
		Iodobenzene	2.9

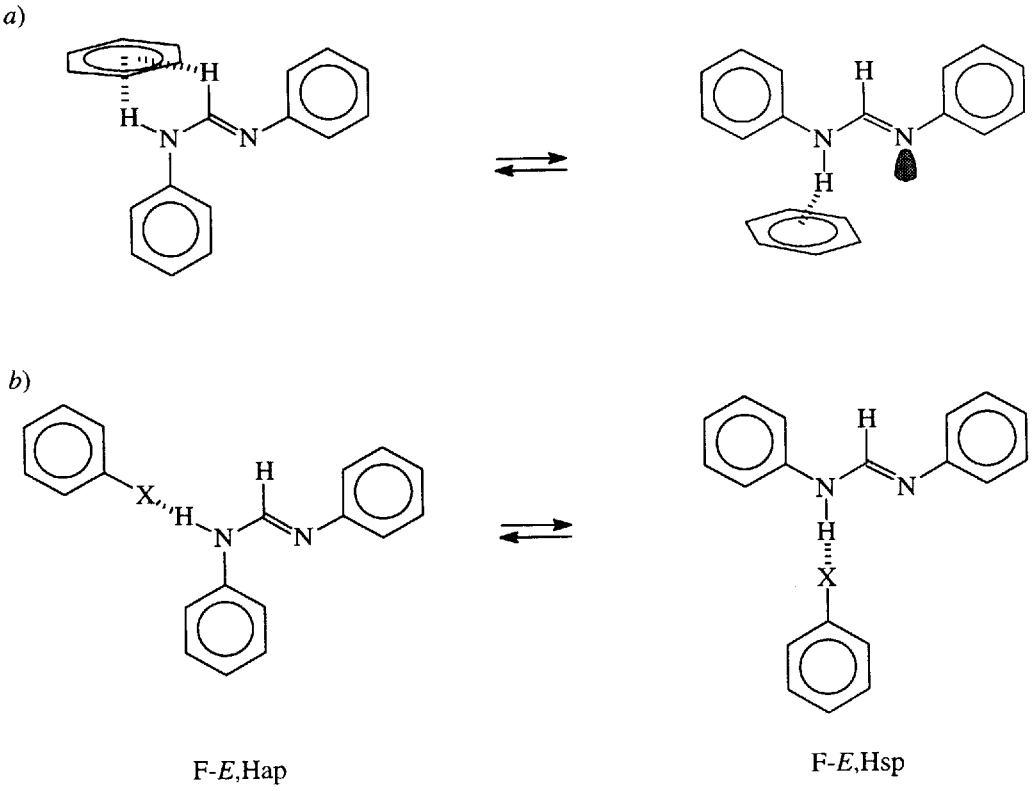
ment (μ) and relative permittivity (ε_T), do not present linear correlations. Such kind of dependences can be selected only for a few solvent families, *i.e.* alkyl and aryl halides and separately π-bases.

The K_I constant for the Hap $\rightleftarrows$ Hsp isomerization in *N*,*N*′-diphenylformamidine has been defined as the ratio of the concentrations of both rotamers: K_I = [F-*E*,Hsp]/[F-*E*,Hap]. Assuming equal absorption coefficients for both NHap and NHsp bands, the isomerization constant is defined as the ratio of the corresponding absorbances: $K_I = A(\text{NHsp})/A(\text{NHap})$. The precise absorbances for the NHap and NHsp bands were obtained from the free $\tilde{\nu}$(NH) contour resolved into two bands.

Perusal of the K_I values summarized in Table 3 indicates that among two isomers considered for formamidine, the *E*,Hsp is more stable than the *E*,Hap in CCl_4, CS_2, $CHCl_3$, CH_2Cl_2, $ClCH_2CH_2Cl$, MeI, PhCl, PhBr, PhI, 1,2-$C_4H_4Cl_2$, 1,3-$C_4H_4Cl_2$, and furan solutions, similarly as it was found for the gas phase by quantum-mechanical methods. Only for benzene, toluene, and *p*-xylene solutions, the *E*,Hap isomer predominates.

The isomerization depends on many solvent parameters, and no linear relation between the K_I and solvent parameters was found, even for structurally similar solvents such as benzene, toluene, *p*-xylene, chloro-, bromo-, and iodobenzene. It can only be concluded on the basis of the K_I values estimated for benzene derivatives that important factors are the volume and the mode of interaction between the solvent and the amidine moiety. Benzene and its alkyl derivatives may interact with the NH group by its π-electrons (Scheme 2) increasing the stability of the F-*E*,Hap isomer ($K_I < 1$), whereas its halogenated derivatives may interact by free pairs of electrons of halogen atom increasing the stability of the F-*E*,Hsp isomer ($K_I > 1$).

The volume factor has also been found to be very important in acyclic acetamidines (RNH—CMe=NR′) and benzamidines (RNH—CPh=NR′) [5*b*]. The bulk Me and Ph groups at the carbon atom of the amidine moiety change the conformational preference in CCl_4 solution from the *E*,Hsp observed in acyclic form-



Scheme 2. Interactions possible for formamidine with *a*) benzene and *b*) its halogenated derivatives.

amidines to the *E*,Hap in acyclic acetamidines and benzamidines. Therefore, formamidines can autoassociate in the cyclic dimer, whereas acetamidines and benzamidines prefer the linear dimer.

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