The Formamidine–Formic Acid Dimer: A Theoretical Examination of its Equilibrium Structure and of the Double-proton-transfer Process

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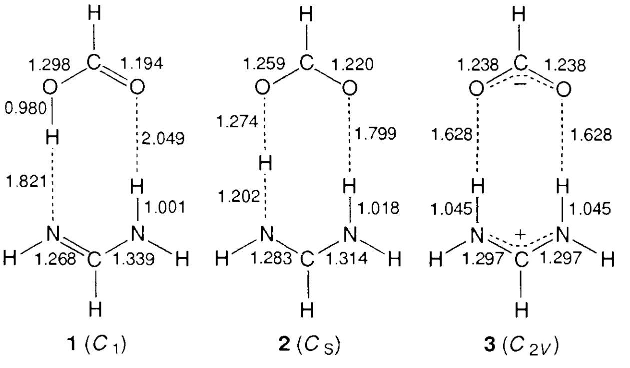
Ab initio molecular-orbital calculations with moderately-sized basis sets and incorporating electron correlation predict that the formamidine–formic acid dimer has a doubly-hydrogen-bonded equilibrium structure of C_1 symmetry and that double-proton transfer takes place *via* an ion-pair structure of C_{2v} symmetry in a stepwise process.

The interaction of amidines with carboxylic acids is of significant biological importance[1] as a consequence of the presence of the amidine (more specifically, guanidine) moiety in arginine, and the demonstration that enzymic arginine residues may serve as binding sites for carboxylic acids. Arginine is important in molecular recognition[2] and in determining the tertiary structure of proteins.[1] The amidinium ion has been claimed to be an ideal complement for a carboxylate ion through the formation of a cyclic, doubly hydrogen-bonded structure.[2a,3] Difficulties in detailed experimental characterization of the species involved provide an opportunity for theory to contribute usefully. A number of theoretical studies have attempted to model such interactions through calculations on the guanidine–formic acid system.[4,5] However, the size of this system has meant that the studies reported to date have involved only simple levels of theory and sometimes rather drastic geometric constraints. We have found that results for this and related systems are very sensitive to the level of theory employed and that calculations at low levels may be misleading. In this Communication, we present results for the prototypical formamidine–formic acid system, including for the first time full geometry optimization and incorporation of the effects of electron correlation are presented.

Standard *ab initio* molecular-orbital calculations[6] were carried out with modified versions[7] of the GAUSSIAN 86,[8] GAUSSIAN 88[9] and GAUSSIAN 90[10] systems of programs. Geometry optimizations were performed at the Hartree–Fock level with the 3-21G, 3-21+G and 6-31G* basis sets, and additional energy calculations were carried out on the HF/6-31G* structures at the HF/6-31+G*, 6-31G**, MP2/6-31G*, MP2/6-31+G* and MP2/6-31G** levels. Stationary points on the surface were characterized as equilibrium or transition structures by calculation of harmonic vibrational frequencies at the 3-21G or 6-31G* levels as appropriate. Selected geometrical parameters are displayed in Fig. 1 and schematic energy profiles at a selection of levels of theory are shown in Fig. 2.

The preferred structure of the formamidine–formic acid dimer (**1**, Fig. 1) may be regarded as a doubly-hydrogen-bonded combination of the *neutral* component molecules, formamidine and formic acid, only slightly perturbed from their normal structures, with long bridging N · · · H (1.821 Å) and O · · · H (2.049 Å) hydrogen bonds. It is non-planar (C_1 symmetry) largely as a result of slight pyramidality at the amino nitrogen atom. Double-proton transfer may take place *via* the transition structure **2** and the C_{2v} intermediate **3**, the latter of which resembles a formamidinium-formate ion pair; it has N–H bonds of length 1.045 Å, only slightly longer than those in the formamidinium cation 1.000 Å, and O · · · H hydrogen bonds (1.628 Å).

Our calculations suggest that the double-proton transfer takes place by a stepwise mechanism, *i.e.* transfer of the hydroxy hydrogen in **1** is virtually complete (to yield the ion pair **3**) before transfer of the amino hydrogen (to give **1′**) begins. In this respect, our findings parallel those recently reported[5d] for the formamidine dimer but differ from those for the formic acid dimer.[5c,5e]



1 (C_1) **2** (C_S) **3** (C_{2V})

Fig. 1 Selected geometrical parameters for optimized structures (HF/6-31G*) of stationary points associated with the formamidine–formic acid dimer

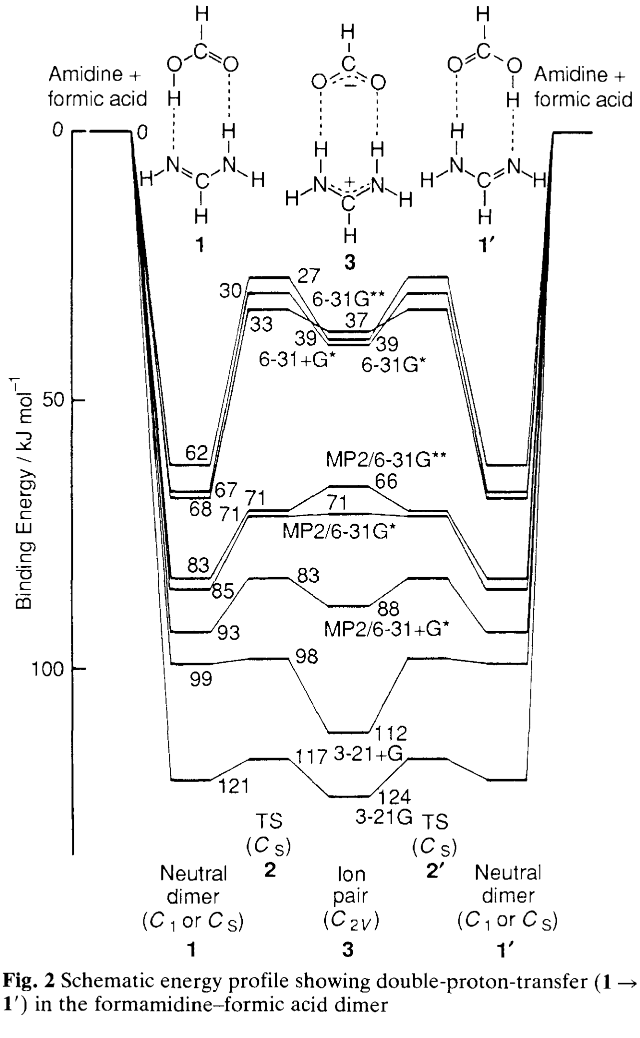


Fig. 2 Schematic energy profile showing double-proton-transfer (**1** → **1′**) in the formamidine–formic acid dimer

Our calculated energy profiles (Fig. 2) demonstrate the sensitivity of the results to the level of theory used. Simpler levels of theory (3-21G, 3-21+G) incorrectly predict the ion pair **3** to lie lower in energy than the neutral dimer **1**. On the other hand, all our higher level calculations (6-31G*, 6-31+G*, MP2/6-31G*, MP2/6-31+G* and MP2/6-31G**) favour the neutral dimer structure **1**. By combining our best results (MP2/6-31G*, MP2/6-31 + G* and MP2/6-31G**), we conclude that **1** lies about 10 kJ mol^{-1} lower in energy than **3** and that there is little or no barrier separating **3** from **1**. Motion along the potential surface from **1** to **1′** should occur fairly easily.

As all previous studies[4] of guanidine-formic acid complexes were carried out at levels of theory that give qualitatively incorrect results for the formamidine–formic acid system, we are currently investigating the guanidine–formic acid system at levels of theory comparable to those used here.

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