Abstract. Nucleophilic vinylic substitutions of 4H-pyran-4-one and 2-methyl-4H-pyran-4-one with ammonia were calculated by the B3LYP method using the 6-31G(d,p) basis set. Bulk solvent effects of aqueous solution were estimated by the polarized continuum and Poisson–Boltzmann self-consistent reaction field models using the 6-311+G(d,p) basis set. In the gas phase different mechanisms were found for the two reaction systems calculated. The reaction of 4H-pyran-4-one proceeds through enol, whereas a feasible path for the less reactive 2-methyl-4H-pyran-4-one is the mechanism through a keto intermediate. Addition of ammonia in concert with proton transfer is the rate-determining step of the reaction. The mechanism proceeding either by a bimolecular nucleophilic substitution (S_N2) or by one involving a tetrahedral zwitterionic intermediate is shown to be unlikely in the gas phase or nonpolar solution. The effects of bulk solvent not only consist in a reduction of the various activation barriers by about 25–40 kJ mol\(^{-1}\) but also in a change in the reaction mechanism.

Keywords: 4H-Pyran-4-one – Ammonia – Nucleophilic vinylic substitution – Addition–elimination mechanism – Ab initio

Introduction

Our previous studies [1] dealing with ab initio and density functional theory calculations on the mechanism of nucleophilic vinylic substitution of 4H-1-benzopyran-4-one (chromone) and 4H-pyran-4-one with a hydroxide ion indicated different mechanisms of the reaction in the gas phase and aqueous solution, i.e., addition of hydroxide ion to the C2 carbon of the pyranone is the rate-determining step in aqueous solution, whereas the elimination step can be expected as rate-determining in the gas phase. These calculations confirmed the mechanism proposed by Zsuga and coworkers [2], who studied the kinetics of the reactions of flavone, isoflavones and chromones with a hydroxide ion in aqueous solution. But a more recent kinetics study by Davidson and Kaye [3] demonstrated a different mechanism for this type of the reaction. They established elimination of the leaving group (i.e., ring fission) as the rate-determining step of the reactions of 4-oxo-4H-1-benzopyran-2-carboxamides with ethanolic dimethylamine. In the previously mentioned kinetics studies, two different nucleophiles (anionic oxygen versus neutral nitrogen nucleophile) were used, and thus one might expect different mechanisms for ring-opening reactions of the pyranones depending on the nucleophile as well as the substrate, solvent effects and pH conditions [4]. The kinetics studies with the amine nucleophile [3] were carried out in polar solution, and therefore among other things, the question arises whether the same mechanism can be expected in nonpolar solution. Moreover, owing to the partial aromatic character of the pyranone ring a different mechanism might be expected for the ring-opening reactions of pyranones with amines compared with similar nucleophilic vinylic substitutions, for example, of \(\alpha,\beta\)-unsaturated carbonyl compounds and their analogues with amines [5]. In this paper we investigate the mechanism of nucleophilic vinylic substitution between a pyranone derivative and amine nucleophile, namely, the reactions of 4H-pyran-4-one (2-H) and 2-methyl-4H-pyran-4-one (2-CH\(_3\)) with ammonia assisted...
by a second ammonia molecule using quantum-chemical methods.

**Computational details**

Calculations were performed using the Gaussian 98 [6] and Jaguar 4.1 [7] program packages. The geometries were completely optimized with the aid of Becke’s three-parameter hybrid density functional–Hartree–Fock (HF) method with the Lee–Yang–Parr correlation functional (B3LYP/B3LYP) [8] using the 6-31G(d,p) basis set. Bulk solvent effects (aqueous solution, $\varepsilon = 78.39$) were estimated by single-point calculations using the Poisson–Bolzmann (SCRF) model [9] [PB–SCRF–B3LYP/6-311+G(d,p)//B3LYP/6-31G(d,p)]. In order to elucidate the existence of a zwitterionic intermediate 8 in the mechanism, the addition reaction step (reactants→TS5→8) was also fully optimized at the HF [10] level of theory by employing the polarized continuum model (PCM) [11] [PCM–HF/6-31G(d,p)//PCM–HF/6-31G(d,p), aqueous solution, $\varepsilon = 78.39$]. All stationary points were characterized as minima or transition states by vibrational frequency calculations. In addition, for transition states intrinsic reaction coordinate calculations at the B3LYP/B3LYP and PCM–HF/PCM–HF levels of theory were performed. Thermodynamic quantities were calculated at 298 K and 101.325 kPa using standard rigid-rotor harmonic oscillator partition function expressions. Zero-point energies are unscaled.

**Results and discussion**

On the basis of theoretical [12] and experimental knowledge [3, 4, 5, 13] several possible mechanisms for nucleophilic vinylic substitutions of the pyranones were considered for the calculations (Scheme 1).

The path reactants→TS1→2→2→TS2→9 includes nucleophilic vinylic substitution proceeding by an addition–elimination mechanism [13]. Formation of the initial dipole–dipole complex 1 from substrate + 2 NH$_3$ is exothermic but endergonic (Table 1), and therefore it is not considered further. The attack of ammonia to the C2 carbon (see Scheme 2 for the atom numbering) in the presence of another ammonia molecule proceeds through transition state TS1 forming a tetrahedral keto intermediate 2 (figures for all B3LYP and PCM–HF optimized geometries as well as the corresponding Gaussian input files are provided in the electronic supplementary material). This step presents addition of ammonia in concert with the proton transfer from the ammonia nitrogen onto the C3 carbon assisted by the second ammonia molecule (N8–H9→N10–H11→C3). Although the addition of ammonia to C2 in TS1 is in advance [$d$(C2–N8) = 0.158 nm in TS1(2-H)]