Theor Chem Acc (2003) 109:200–205
DOI 10.1007/s00214-002-0408-0

Theoretical Chemistry Accounts

Regular article

Action of HCl on 3-hydroxypyrazolo(iso)quinolines to give 1-chloropyrazoles: evidence for an addition–elimination mechanism by ab initio calculations in gas phase and water

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Received: 27 June 2002 / Accepted: 6 September 2002 / Published online: 14 February 2003

Abstract. Addition–elimination reactions involving a nucleophile and a remote leaving group [$S_N^H(AE)^{tele}$] are well-known under basic conditions, especially amongst electron-poor six-membered heterocycles, but are less commonly encountered for five-membered heterocycles and are rare under acidic conditions. Concentrated HCl converts 1-hydroxy-1*H*-pyrazolo[3,4-*c*] isoquinoline and 1-hydroxy-1*H*-pyrazolo[3,4-*c*]quinoline into 3-chloro-1*H*-pyrazolo[3,4-*c*]isoquinoline and 3-chloro-1*H*-pyrazolo[3,4-*c*]quinoline, respectively. However, apparently neither the isomeric 1-hydroxy-1*H*-pyrazolo[4,3-*c*](iso)-quinolines nor the parent 1-hydroxypyrazole undergo this reaction. Additionally, all these systems are refractory under basic conditions. We present a plausible mechanism for the reaction, involving the 3-addition of Cl^- to the diprotonated heterocycle, followed by the elimination of water. Calculations of the initial transition states and intermediates, using optimisation at B3LYP/6-311 + G(d,p), including thermochemistry [HF/6-31 + G(d)], and single-point Poisson–Boltzmann self-consistent reaction field determination of the free energy of solvation (Jaguar Poisson–Boltzmann self-consistent reaction field), support this mechanism and reproduce the observed order of reactivity, the addition step being 2–4 kcal less favourable for the isomeric 1-hydroxy-1*H*-pyrazolo[4,3-*c*](iso)quinolines and provide a rationalisation for the role of strong acid.

Keywords: 1-Hydroxypyrazole – Addition–elimination – Density functional theory – Poisson–Boltzmann self-consistent reaction field – Continuum solvation model

Contibution to the 8th Electronic Computational Chemistry Conference, 2002

Electronic Supplementary Material to this paper (full text of the lecture in html as given at the ECCC8 conference) can be obtained by using the SpringerLink server located at http://dx.doi.org/10.1007/s00214-002-0408-0.

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Introduction

Addition–elimination reactions involving a nucleophile and a remote leaving group [so-called vicarious formal nucleophilic substitution of hydrogen, $S_N^H(AE)^{tele}$] are well known under basic conditions, especially amongst electron-poor six-membered heterocycles. However, they are less commonly encountered for five-membered heterocycles and are rare under acidic conditions [1]. Recently, Pawlas and coworkers [2, 3] reported the apparent nucleophilic substitution of **1a** and **2a** (and their benzyl ethers, following debenzylation), under acidic conditions (HCl or $MeOH/H_2SO_4$). **1a** reacts rapidly, while **3a**, **4a** and **5a** do not undergo this reaction (Fig. 1). Interestingly, no corresponding reaction was observed under basic conditions (e.g. MeOH/NaOMe).

The reaction may be contrasted with the more facile electrophilic substitution of such species [4]. The authors proposed the mechanism in Fig. 2, in which a chloride ion adds with the concerted elimination of water (hydroxyl) to give **1f**, **2f**, and the product (given as **1g**, **2g**) forms in a subsequent step via tautomerism.

However, the questions of the role of acid and the pattern of reactivity observed among the isomers (**1**–**4**) remain unanswered. The aim of the present work is to put forward a more detailed mechanism that is able to explain the experimental data, and one that is more in keeping with the well-documented $S_N^H(AE)$ mechanism [1]. This mechanism is proposed on the basis of density functional theory calculations, including a continuum solvent model.

Methods

Structures along the reaction path for all five 1-hydroxypyrazoles (**1**–**5**) (Fig. 1, 3) were optimised at HF/6-31 + G(d), and thermochemical analysis was performed at the reaction temperature (353.15 K) using the recommended scaling factor of 0.897. Transition states were checked by perturbation along the imaginary

frequency and reoptimisation to local minima. (Gaussian 98 [5]). Final geometries and gas-phase energies were obtained by optimisation with a density functional theory (B3LYP) and 6-311 + G(d,p) basis set [5] (see electronic supplementary material for geometries). Single-point free energies of solvation were calculated using Jaguar's Poisson–Boltzmann self-consistent reaction field model (PB–SCRF) at B3LYP/6-311 + G(d,p). (Jaguar 4.1 [6]) The total and relative free energies in solution were thus calculated as the sum of the gas-phase energy, thermochemical terms, and the free energy of solvation (including water, hydronium ion, hydrogen chloride and chloride ion to balance the stoichiometry).

Results

A range of possible reaction paths, complexes with water/HCl/Cl^-, protonation states and conformations were considered, especially for the model system **5**. The acid–base behaviour and tautomerism of **1**–**5** were first studied [7]. A plausible reaction path was then established for **5** in the gas phase (Fig. 4). Key features include the necessity of protonation of the pyrazole N-2

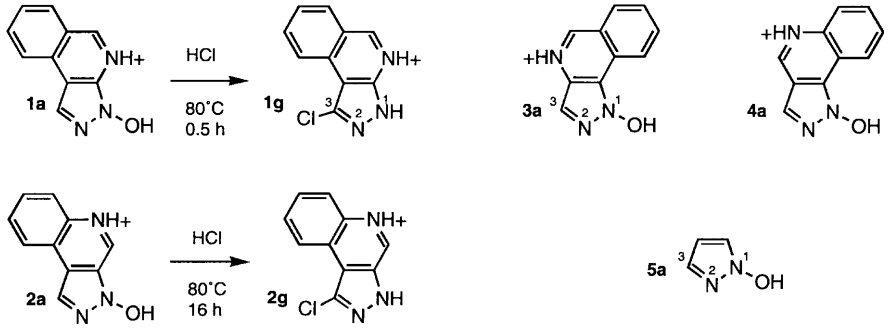

Fig. 1. Reactions of fused 1-hydroxypyrazoles in strong acid

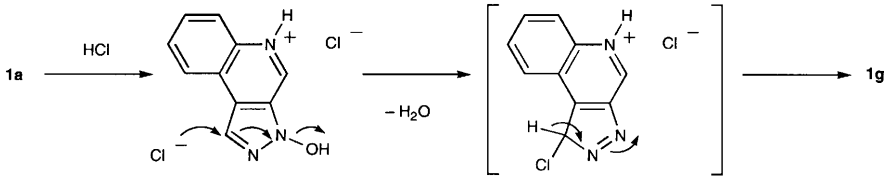

Fig. 2. Previously suggested mechanism

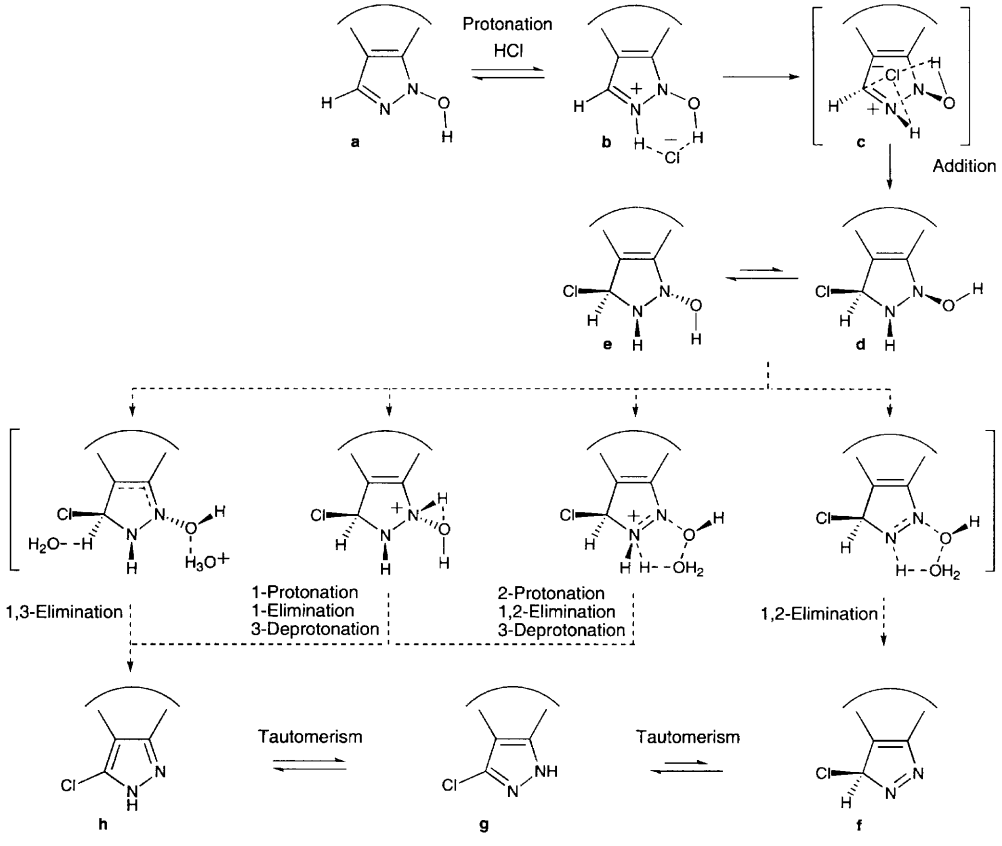

Fig. 3. Mechanism and species calculated along the reaction path

[over and above protonation of the basic (iso)quinoline nitrogen] to facilitate nucleophile addition, and the fact that several pathways are possible for elimination. The elimination step has a lower barrier than the addition step in the gas phase. In solution, it is expected to be lower again, with the explicit participation of solvent.

The addition step and final products were subsequently extrapolated to systems **1**–**4**, including free energy of solvation. In solution, the initial transition states **15c** proved lower in energy than the intermediate minima **15d** at the gas-phase geometries. Optimisation of transition state **5c** in solution led to a structure resembling **5d**, suggesting a barrierless reaction path for anion addition to the pyrazole N-2 protonated starting material, in forming the high-energy intermediates **15d**. Tautomerism is possible for the final chlorinated products, and if **1**–**5f** (3*H*) were to lie on the reaction path they would rapidly tautomerise to the 1*H* and/or 2*H* aromatic forms (**1**–**5g**, **1**–**5h**). Interestingly, in the gas phase, the latter tautomeric pairs were found to be close in energy, except for **1**, where the 2*H* tautomer (**1h**) is clearly favoured over 1*H* (**1g**). In solution, the 1*H* forms are predicted to predominate, except for **1**, where a mixture of **1h** and **1g** is predicted.

The energies of the more important species are given in Table 1, and some of these are depicted in Fig. 5. Parallel paths have been calculated for **1**–**4** in which N-2 is protonated as described previously, but the (iso)quinoline nitrogen remains unprotonated throughout. However these are not likely to be relevant in aqueous acidic solution and have been omitted.

Discussion

S_N^H reactions of azoles

The reaction described here may be formally grouped under the class known as nucleophilic substitution of hydrogen (S_N^H) in as much as chloride is a weak nucleophile, and ultimately replaces the 1-H of **1** and **2**. Unlike better-known examples of S_N^H such as the Chichibabin reaction [8], the formal leaving group here is OH^-. The addition–elimination reaction mechanism is believed to be the most common, with re-aromatisation as part of the elimination step under nonoxidising conditions. Such reactions have been called vicarious nucleophilic substitution and when the leaving group is not adjacent (cine) to the point of substitution, are termed tele [1]. Hence the current reaction may be termed $S_N^H(AE)^{tele}$. What makes this system particularly interesting is that the reaction only appears to occur with relatively mild nucleophiles under strongly acidic conditions. This is extremely rare; one of the few examples is addition–elimination of methanol at the 5-position of 1-hydroxytryptophan derivatives, with dehydration under the influence of H_2SO_4, a case not unlike the present one [9]. Indeed, one could argue that it is misleading to describe the reaction as nucleophilic, given that **1**–**5** are refractory to typical nucleophilic bases. In addition, normally S_N^H reactions are dependent on the heterocycle being electron deficient. Thus, azines are much more reactive than azoles, and five-membered heterocycles must generally be activated by electron-withdrawing groups [1]. A few examples of S_N^H exist for pyrazoles and triazoles under basic conditions. Lopyrev et al. [10] have studied S_N^H amination of 1-methyl-4-nitropyrazole, using ab initio calculations [6-31G(d)]. In the absence of a nitro group, the reaction has also been found to proceed under basic conditions when two nitrogen ring atoms are substituted and the ring thus bears a positive charge. Both 1-O*R*-2-*R*′-triazolium cations and 1-O*R*-2-*R*′-pyrazolium cations undergo $S_N^H(AE)^{cine}$ at the 5-position [11, 12, 13]. This observation leads us directly to postulate that the otherwise electron-rich pyrazole must bear a positive charge in order to accept a nucleophile. In the present case, in the absence of an N-2 alkyl substituent,

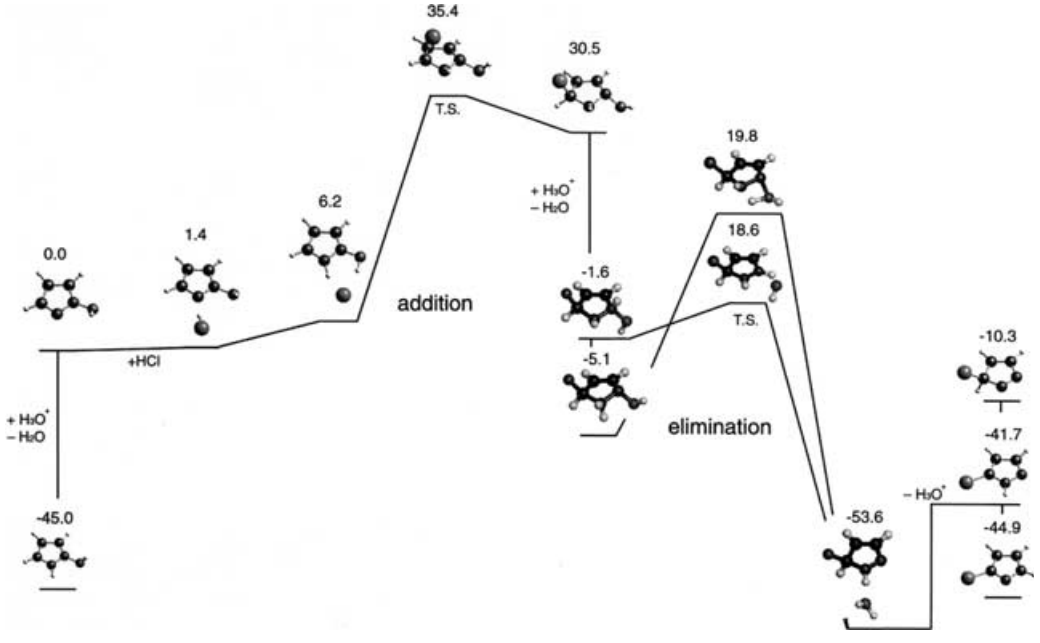

Fig. 4. Model reaction path for addition–elimination of HCl/H_2O to 1-hydroxypyrazole (**5a**) in gas phase (relative free energies at 80 °C, kcal/mol)

Table 1. Energies of **1**–**5** along the addition–elimination reaction path. Gas phase stoichiometry: **a** + H_3O^+ + HCl → **b** + H_2O + HCl → **c**,**d**,**e** + H_3O^+ → **f**,**g**,**h** + H_2O + H_3O^+. Aqueous phase stoichiometry: **a** + H_3O^+ + Cl^- → **b** + H_2O + Cl^- → **c**,**d**,**e** + H_2O → **f**,**g**,**h** + $2H_2O$. Relative free energies of the product of the addition step in solution are given in **bold**

Species	Type	Charge	ZPE	G_{therm}	E	ΔE_{gas}	ΔG_{gas}	ΔG_{solv}	G_{aq}	ΔG_{aq}	ΔG_{aq}
Temperature (K)				353.15		0	353.15		353.15	353.15	353.15
Theory			HF/6-31 + g(d)		B3LYP/6-311 + G(d,p)			B3LYP/6-311 + G(d,p)			
Method			Scaled (0.897)	Scaled (0.897)	Optimised	Relative to **a**	Relative to **a**	Single point	Total	Relative to **a**	Relative to **b**
Units			**h**artree	**H**artree	**H**artree	kcal/mol	kcal/mol	kcal/mol	hartree	kcal/mol	kcal/mol
H_2O	min	0	0.02055	−0.00105	−76.45846			−8.9	−76.47371	254.2	
H_3O^+	min	1	0.03297	0.01079	−76.73107			−99.5	−76.87888		
HCl	mzin	0	0.00650	−0.01532	−460.83385			−1.6	−460.85165	−257.0	
Cl^-	min	−1	0.00000	−0.01827	−460.30373			−75.3	−460.44205		
1a	min	1	0.16467	0.11998	−625.21943	0.0	0.0	−56.9	−625.19015	0.0	5.0
2a	min	1	0.16464	0.12003	−625.22490	0.0	0.0	−57.9	−625.19709	0.0	−1.1
3a	min	1	0.16507	0.12056	−625.22387	0.0	0.0	−58.2	−625.19610	0.0	3.2
4a	min	1	0.16500	0.12051	−625.23276	0.0	0.0	−56.5	−625.20228	0.0	4.7
5a	min	0	0.07270	0.03822	−301.45207	0.0	0.0	−8.2	−301.42697	0.0	12.7
1b	min	2	0.17655	0.13146	−625.43418	36.0	36.1	−188.7	−625.603369	−5.0	0.0
2b	min	2	0.17707	0.13226	−625.43407	39.8	40.0	−187.5	−625.600553	1.1	0.0
3b	min	2	0.17708	0.13224	−625.43844	36.2	36.3	−188.4	−625.60642	−3.2	0.0
4b	min	2	0.17730	0.13253	−625.44347	38.8	39.0	−190.8	−625.61493	−4.7	0.0
5b	min	1	0.08515	0.05046	−301.79800	−46.0	−45.0	−66.5	−301.85354	−12.7	0.0
1c	t.s.	1	0.17746	0.12971	−1086.01461	28.2	40.0	−74.0	−1086.00288	21.6	26.7
2c	t.s.	1	0.17773	0.13016	−1086.01631	30.8	42.6	−76.3	−1086.00779	22.9	21.9
3c	t.s.	1	0.17777	0.12991	−1086.01552	30.4	42.0	−75.0	−1086.00517	23.9	27.2
4c	t.s.	1	0.17777	0.12942	−1086.02359	30.9	42.2	−73.6	−1086.01142	23.9	28.6
5c	t.s.	0	0.08547	0.04664	−762.25326	24.4	35.4	−21.1	−762.240202	22.1	34.8
1d	min	1	0.17836	0.13048	−1086.03237	17.6	29.3	−59.5	−1085.99663	**25.6**	30.6
2d	min	1	0.17824	0.13047	−1086.03294	20.7	32.4	−61.2	−1086.00001	**27.8**	26.7
3d	min	1	0.17836	0.13038	−1086.03126	20.9	32.4	−60.2	−1085.99684	**29.2**	32.4
4d	min	1	0.17812	0.12996	−1086.03821	22.0	33.4	−59.3	−1086.00281	**29.3**	34.0
5d	min	0	0.08632	0.04822	−762.25831	21.8	33.2	−11.3	−762.22805	**29.7**	42.4
1e	min	1	0.17892	0.13055	−1086.04096	12.6	24.0	−58.3	−1086.00340	21.3	26.4
2e	min	1	0.17880	0.13047	−1086.04123	15.8	27.2	−60.0	−1086.00643	23.8	22.7
3e	min	1	0.17893	0.13042	−1086.03800	17.0	28.2	−60.0	−1086.00314	25.2	28.4
4e	min	1	0.17898	0.13073	−1086.04886	15.8	27.2	−58.6	−1086.01147	23.9	28.6
5e	min	0	0.08666	0.04797	−762.26234	19.5	30.5	−11.9	−762.23340	26.4	39.0
1f	min	1	0.15122	0.10563	−1009.60436	−5.6	−6.0	−57.3	−1009.59008	−16.6	−11.5
2f	min	1	0.15107	0.10550	−1009.60458	−2.4	−2.9	−60.4	−1009.59527	−15.5	−16.6
3f	min	1	0.15123	0.10553	−1009.60116	−1.1	−1.7	−57.0	−1009.58647	−10.6	−7.3
4f	min	1	0.15117	0.10551	−1009.60653	1.2	0.6	−57.5	−1009.59271	−10.6	−5.9
5f	min	0	0.05896	0.02340	−685.83325	−3.4	−4.0	−5.2	−685.81813	−10.3	2.4
1 g	min	1	0.15172	0.10640	−1009.64711	−32.1	−32.4	−59.9	−1009.63619	−45.5	−40.5
1 h	min	1	0.15256	0.10741	−1009.65662	−37.6	−37.7	−54.1	−1009.63550	−45.1	−40.0
2 g	min	1	0.15191	0.10672	−1009.65305	−32.3	−32.5	−59.6	−1009.64138	−44.4	−45.5
2 h	min	1	0.15290	0.10784	−1009.65471	−32.7	−32.8	−55.6	−1009.63549	−40.7	−41.8
3 g	min	1	0.15235	0.10708	−1009.65345	−33.2	−33.5	−57.8	−1009.63841	−43.2	−39.9
3 h	min	1	0.15264	0.10740	−1009.65217	−32.2	−32.5	−54.7	−1009.63198	−39.1	−35.9
4 g	min	1	0.15227	0.10702	−1009.66174	−32.8	−33.1	−58.7	−1009.64822	−45.4	−40.8
4 h	min	1	0.15260	0.10741	−1009.65986	−31.4	−31.7	f−55.4	−1009.64080	−40.8	−36.1
5 g	min	0	0.06016	0.02497	−685.88578	−35.6	−36.0	−7.8	−685.873283	−44.9	−32.3
5 h	min	0	0.06016	0.02492	−685.88325	−34.1	−34.4	−6.1	−685.868107	−41.7	−29.0

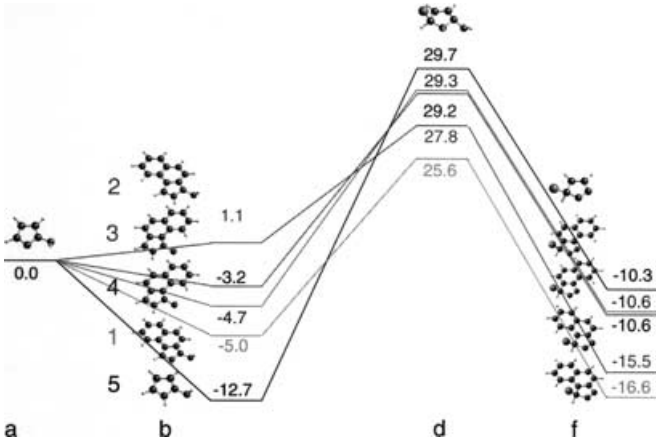

Fig. 5. Comparison of minima on the reaction path, relative free energies (80 °C) in aqueous solution of **1**–**5** (B3LYP/6-311 + G(d,p), PB–SCRF, kcal/mol)

protonation of N-2 in strong acid is able to activate the ring to vicarious nucleophilic substitution. We were unable to locate chloride σ-adducts to C-3 as stable minima without N-2 protonation, further supporting this hypothesis. The protonated fused (iso)quinoline moeities probably also play a role in withdrawing electrons and thus lowering the activation barrier for these pyrazoles. Intrestingly, for 1-substituted pyrazoles activated by nitro groups, reactivity is determined by which pyrazole carbon is substituted, C-4 being more activating than C-3 [10, 14]. One might therefore have anticipated finding reactivity differences among these four fused (iso)quinolines.

Limits of the current computational approach

Using a continuum solvation model, we have demonstrated that the barrier to chloride addition in water for **1**–**2** is lower than for **3**–**4**, which is in turn lower than for **5**, relative to both **1**–**5a** and the pyrazole-protonated **1**–**5b**, which may also be present in strongly acidic solution. However, it is more difficult to determine the absolute barriers, and direct comparison between **1**–**4** and **5** is also problematic. The main difficulty is in directly comparing species carrying different charges; ab initio determination of acid–base equilibria in solution is an unsolved problem, not least because the free energy of solvation of the proton is not experimentally known with accuracy. Simply balancing the stoichiometry (HCl, Cl^-, H_3O^+, H_2O) as done here is a fairly crude means of making the free energies in solution comparable. Nor is it clear that B3LYP density functional theory with a large basis set is adequate for accurately determining protonation states of heteroaromatics in the gas phase [7, 15] even though this is the method of choice for systems of this size. Another quite serious potential source of error is the use of single-point free energies of solvation at the gas-phase geometries. While optimisation in solution is possible, it is time consuming for species of this size, and convergence is difficult to obtain; although the grid-based PB–SCRF method is numerically robust by comparison with alternatives such as the polarisable continuum model, analytic second derivatives are not available and small geometry changes cause energy fluctuations, frustrating optimisation for species of this size. Increases in computer speed and the use of finer reaction field grids will hopefully improve optimisation with the PB–SCRF. Finally, continuum solvation models of the isolated systems are likely to break down when it comes to reaction steps in which explicit solvent molecules take part. While it is apparent that the elimination of the *N*-hydroxy group as water has a low barrier and is strongly exothermic, it has not been possible to demonstrate which of the many conceivable elimination paths is lowest in energy. However, given that it is the formation of the C–C bond in the addition step (σ-adduct) which appears to determine the (relative) reaction barrier height, and that the energies of **1**–**5d** and **1**–**5f** are similar relative to each other, i.e. the energetics are parallel (Fig. 5), it seems unlikely that the elimination step is rate- or selectivity-determining.

Conclusion

The density functional theory study gives a correlation between the relative energy of the HCl adducts of **1**–**5** and the experimentally observed reactivity (**1** > **2** > > **3**, **4**, **5**), lending support for an $S_N{}^H(AE)^{tele}$ addition–elimination mechanism, and provides a framework for predicting this type of reactivity in future. Protonation at N-2 is a necessary component of the reaction. Further work is necessary to elaborate the most favoured elimination pathway, including explicit participation of water.

Acknowledgements. The authors would like to acknowledge the New South Wales Centre for Parallel Computing and the Australian Centre for Advanced Computing and Communications for computing resources, the financial support of the Lundbeck Foundation, and the helpful advice of Per-Ola Norrby and Tommy Liljefors.

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