S_N2 Substitution on sp^2 Nitrogen of Protonated Oxime

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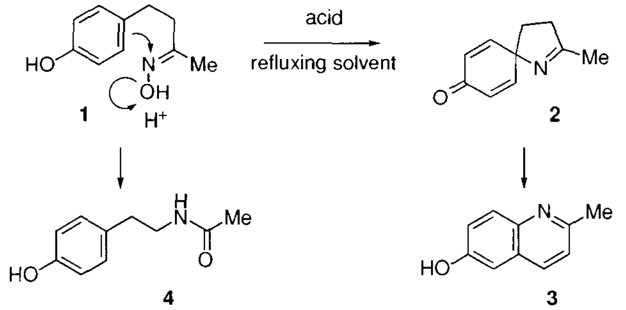
Theoretical studies on intramolecular nucleophilic displacement of the protonated oxime oxygen with an aryl ring revealed that the substitution reaction on the sp^2 nitrogen atom is a low energy process. This seemingly anomalous substitution is due to the low-lying σ^*-orbital of the *O*-protonated oxime. The theoretical conclusion received experimental support.

The $CF_3SO_3H/(n\text{-}Bu)_4NReO_4$-mediated ring forming reaction of a ketone oxime bearing an electron-rich aryl group in the β-position (e.g., **1**) is a unique synthetic transformation.[1] The acid/rhenium catalyst mixture acts on **1** to first produce the spiro compound **2** in high yield, which then rearranges to quinoline **3** under forcing conditions. Its synthetic utility notwithstanding, the reaction poses two puzzling mechanistic questions: the (nearly total) lack of Beckmann rearrangement product **4** and an implication that the reaction involves substitution upon an sp^2-hybridized nitrogen atom (cf. **1**). It has been commonly accepted that direct nucleophilic substition on an sp^2 carbon atom does not take place[2] and so may be expected for nitrogen analogs. To examine the feasibility of such a process and to compare it with the Beckmann rearrangement pathway to **4**,[3] we have carried out the post-Hartree-Fock *ab initio* calculations on the two reactions pathways of the oxime **1** in the presence of a proton to find that the pathways leading to **2** and **4** are of comparable energy, and hence that the sp^2 nitrogen substition is a facile process taking place with inversion of stereochemistry. Experimental studies confirmed that the two pathways do compete under the conditions using a non-nucleophilic acid.



The stationary points determined for **1** by full geometry optimization at the MP2(FC)/6-31G* level[4,5] are shown in Figure 1. A 3D picture of the crucial transition structure (**TS2**) is shown in Figure 2. Starting with oxygen-protonated oxime **INT**, the Beckmann rearrangement takes place with a low activation energy of 8.0 kcal mol^{-1}. **TS1** indicates 1,2-migration of the alkyl group with concomitant elimination of a water molecule. These energetic and structural features are essentially the same as those determined in a previous study,[6] which reported that the nitrogen protonation is a non-productive process and nitrogen-to-oxygen migration of proton is a rate determining step of the reaction. In the gas phase, the cationic product **PD1** forms as a discrete intermediate, serving as a precursor of the amide **4**.

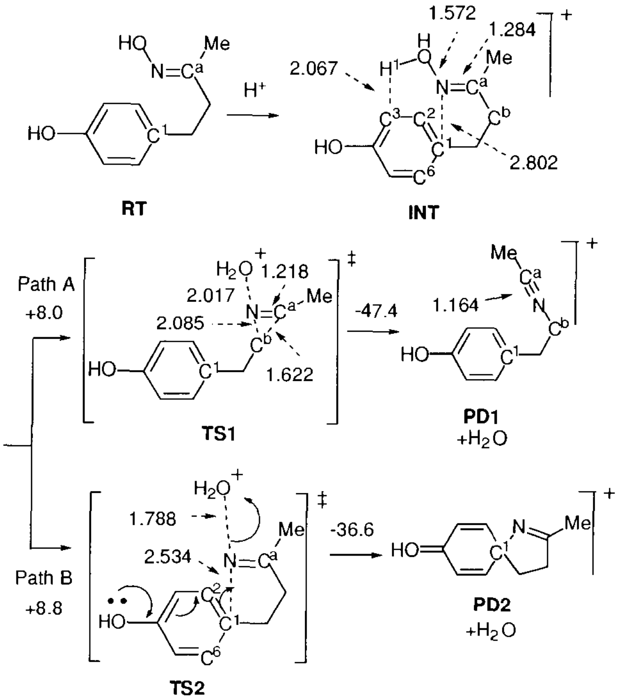


Figure 1. Representative stationary points in the reaction of (*E*)-4-(4-hydroxyphenyl)butan-2-one oxime (MP2/6-31G*). Bond lengths are in Å, and the energy changes above arrows in kcal mol^{-1}.

It was noted that, in **INT**, which, among numerous possible conformers, represents the one wherein the protonated oxime moiety and the electron-rich aromatic ring attract each other. The C^1-N distance of 2.802 Å which is shorter than the sum of van der Waals radii is caused by hydrogen bonding between the protonated oxygen atom and the C^3 atom. The N–O σ^*-orbital of the oxime moiety in **INT** mixed with the C=N π^*-orbital is low-lying (-1.26 eV, HF/6-31G*//MP2/6-31G*).[7] Thus, aligning the oxime N-O σ^*-orbital for interaction with the aromatic π-orbital in **INT** led smoothly to the TS of the spiro cyclization (**TS2**). The energy of **TS2** was found to be 8.8 kcal mol^{-1} higher than **INT**. The C^1–N distance shortens to 2.534 Å and the N-O distance lengthens to 1.788 Å. As shown in the localized Kohn-Sham orbital of **TS2** in Figure 2,[8,9] the π electrons on C^1, C^2, and C^6 (corresponding to HOMO in **INT**) interact with the σ^*-orbital of the oxime N-O bond. The displacement of the water molecule occurs in a nearly linear manner ($<C^1\text{-N-O} = 155°$). The product **PD2** forms with 36.6 kcal mol^{-1} exothermicity, and will generate **2** upon loss of proton. The calculated energetics thus clearly indicates that the spiro cyclization and the Beckmann rearrangement compete with each other.

With the information above, we examined the effects of acid and solvent for the same oxime substrate **1**. Not unexpectedly,

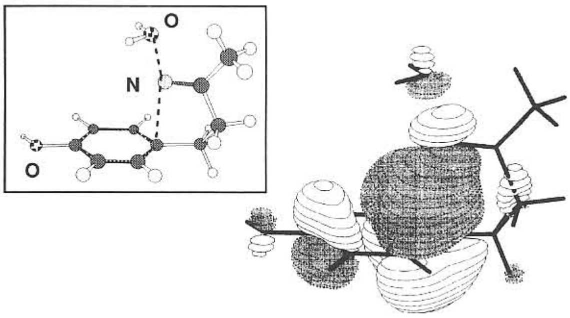


Figure 2. Surface (0.03 e·a.u.$^{-3}$) of localized Kohn-Sham MO of **TS2** showing interaction of benzene π and NO σ^* orbitals (inset: 3D molecular picture).

we found that polyphosphoric acid (PPA)[1c] drives the reaction completely to the Beckmann pathway (Table 1, entry 1). As reported previously,[1b,1c] the rhenium conditions cleanly produced the spiro compound **2** (entry 5). On the other hand, non-nucleophilic CF_3SO_3H in various solvents afforded a mixture of **2** and **4** in a 5:2 to 7:9 ratio (entries 2-4).

Table 1. Reaction **1** with protic acids in various solvents

entry	reagent	solvent	products / %^{d} 2	3	4
1	PPA^a	*m*-xylene	4	0	72
2	$CF_3SO_3H^b$	CH_3CN	47	0	37
3	$CF_3SO_3H^b$	CH_3NO_2	28	10	26
4	$CF_3SO_3H^b$	$ClCH_2CH_2Cl$	50	0	22
5	(*n*-Bu)$_4$ReO$_4$ + $CF_3SO_3H^c$	$ClCH_2CH_2Cl$	91	0	0

^{a}Three equivalents. ^{b}One equivalent. ^{c}0.2 equivalent. ^{d}Isolated yields.

The dramatic contrast between PPA and the rhenium acid is notable and perhaps is outside the range that can be studied by the gas phase theoretical model. PPA is an extremely polar medium with nucleophilic oxygen atoms present. The formation of discrete nitrilium ion is not expected in PPA, and nucleophilic participation of the solvent must take place at an early stage of the reaction. The rhenium reaction in a non-polar solvent, on the other hand, may involve the formation of an oxime perrhenate intermediate and may not be properly modeled by the present theoretical models. The CF_3SO_3H cases, however would represent a reasonable experimental model of the gas phase reaction, which indicated a comparable activation energies for the Beckmann rearrangement and the spiro cyclization. We noted that the oxime substrate undergoes rapid *E*/*Z* isomerization before the reaction, and hence could not determine the influence of the oxime stereochemistry.

In summary, the theoretical analyses have shown that substitution at an sp^2 nitrogen atom is an energetically feasible process and will take place with inversion of stereochemistry at the nitrogen atom. Though this conclusion appears to contradict with the conventional wisdom, recent reports published during the course of the present studies revealed that S_N2-substitution on sp^2 carbon is also feasible.[10] Hence, it must be recognized that S_N2-substitution on sp^2 hybridized atom is now a norm, for cases where the σ^*-orbital of the breaking bond is lower in energy than the π^*-orbital.[10] There have been reported a few cases of related substitution reaction on a nitrogen atom,[11] and they might also involve a similar substition mechanism as judged from the stereospecificity in two of these reactions.[11b,d]

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