

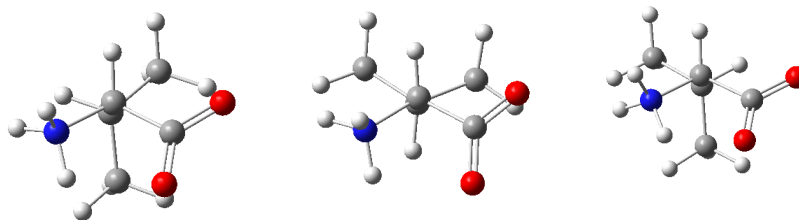
1. Let's return to valine, which we examined in Problem Set 1. Early in the 20th century, Clough, Lutz, and Jirgensons found that if one added strong acid to an aqueous solution of a D-amino acid, thereby protonating it, the optical rotation measured for that amino acid became either *less* positive or, if the original rotation was negative, *more* negative. Conversely, if the optical rotation became *more* positive (or less negative), the amino acid was L. Let's see if valine obeys the CLJ rule.

To do that, optimize the three conformers of zwitterionic D-valine, and of protonated D-valine (you may ignore rotational isomerism of the carboxyl group once protonated—simply choose one oxygen to protonate for each zwitterionic rotamer case); do your work at the M06/6-311+G(d,p) level employing the SMD aqueous solvation model. Next, for each optimized rotamer, compute the optical rotation at the same level of theory. You will need the keywords `polar=optrot` and `cphf=rdfreq` for this calculation. Specify a frequency of 0.07732, which corresponds to measuring the optical rotation at the sodium D line, 589.3 nm.

In a neat and readable table (or tables), report the energies for all of your zwitterionic and protonated species, and then report the Boltzmann averaged molar rotations. Note that G09 reports the *specific* rotation. To convert your specific rotations to molar rotations, multiply by the molecular weight of the compound and divide by 100.

On the next page are tables for the neutral (zwitterion) and protonated species, showing free energies (including solvation), specific and molar rotations, and the Boltzmann average of the latter. Structures are not shown for the protonated species, but in each case the O atom further from the ammonium group was protonated, and otherwise the structures are not much changed.

### Results for zwitterionic D-valine



$G_{298}, E_h$	-402.132 24	-402.131 72	-402.133 32
298 K pop, %	21.3	12.4	66.3
Specific $\alpha$ , deg	-120.0	-27.0	-40.0
Molar $\alpha$ , deg	-140.6	-31.7	-46.9
298 K $\langle \alpha \rangle$ , deg			<b>&lt; -65.0 &gt;</b>

### Results for protonated D-valine

$G_{298}, E_h$	-402.565 66	-402.563 40	-402.566 72
298 K pop, %	24.2	2.2	73.5
Specific $\alpha$ , deg	-133.4	-68.7	-35.1
Molar $\alpha$ , deg	-157.6	-81.2	-41.4
298 K $\langle \alpha \rangle$ , deg			<b>&lt; -70.5 &gt;</b>

Do you predict valine to follow the CLJ rule? Experimentally, D-valine *is* observed to follow the CLJ rule, and the molar rotations of the zwitterion and cation are measured as  $-6.6$  and  $-33.1 \text{ deg cm}^2 \text{ dmol}^{-1}$  (the units are identical to those you'll get from converting G09's output as instructed above). How does the selected level do? If there are discrepancies, what steps might be taken that might be expected to improve agreement with experiment?

This problem was somewhat disappointing. To compare to  $-6.6$  and  $-33.1 \text{ deg cm}^2 \text{ dmol}^{-1}$ , the computed numbers are  $-65.0$  and  $-70.5$ . Thus, I predict the change to match the CLJ rule, but the magnitude is significantly underpredicted. In addition, the quantity  $\alpha$  seems amazingly sensitive to conformation.

I chose this problem because of DOI: 10.1021/ed300680g, but it appears that getting a solid answer may require some fortuitous cancellation of errors in terms of functional choice, basis set, and number of conformers over which averaging is done.

2. Mixing  $\text{Ag}(\text{CN})_2$  and  $\text{Ni}(\text{CO})_4$  in chloroform under a CO atmosphere, you isolate a solid precipitate that microanalysis and mass spectroscopy indicate to be  $\text{NiC}_4\text{N}_2\text{O}_2$ . A  $^{13}\text{C}$  NMR spectrum of the precipitate in chloroform with  $\text{Ni}(\text{CO})_4$  added as an internal standard shows a strong peak 6.6 ppm upfield from  $\text{Ni}(\text{CO})_4$  and a much smaller peak 8.4 ppm upfield from

$\text{Ni}(\text{CO})_4$ . There is also a very strong peak 84 ppm upfield from  $\text{Ni}(\text{CO})_4$ . An IR spectrum of the precipitate in a KBr pellet shows a strong absorption at  $2154\text{ cm}^{-1}$  and very weak absorptions/shoulders at 2143, 2170, and  $2188\text{ cm}^{-1}$ .

After three recrystallizations from diisopropyl ether, your solid is composed of beautifully twinned light orange crystals. NMR and IR spectra of the recrystallized solid show only the strong peaks noted above, and none of the weak ones.

An ultraviolet spectrum of the recrystallized solid in freon (who knew it would be soluble?) shows absorptions at 310 and 333 nm.

Here are the questions:

a. What is the structure of the molecules in the recrystallized solid? In a narrative fashion, describe in some detail how you came to your conclusion. Note that achieving 100% confidence can be very much more expensive than 99% confidence. It is perfectly OK to be satisfied with 99%.

*$\text{Ni}(\text{CO})_4$  is a well known compound that would appear to have some relevance to the subject compounds. Thus, as a starting point, I benchmarked levels of theory based on their ability to compute known properties of nickel tetracarbonyl. A quick search of the web turned up that the molecule is tetrahedral ( $T_d$  symmetry!) with NiC bond lengths of  $1.838\text{ \AA}$  and CO bond lengths of  $1.142\text{ \AA}$  and a CO stretching frequency of  $2058\text{ cm}^{-1}$ . I tested HF/6-31G(d), HCTH/6-31G(d), and B98/6-31G(d). The final method gave bond lengths of  $1.809$  and  $1.146$  for NiC and CO, respectively, and I decided that this was good enough (using a much bigger basis set might have improved things, but I decided that that would cost too much). The CO stretching frequency for  $\text{Ni}(\text{CO})_4$  was computed at the B98 level to be  $2145\text{ cm}^{-1}$ , which is 4% too high—about what is expected since B98 is a hybrid model including HF exchange, and that causes frequencies to be a bit too high. So, I'll scale other frequencies computed at this level by 95.9%. (Note, incidentally, that there is no 6-31G(d) basis set for Ni, but G03 by convention uses a so-called McClean-Chandler basis for the first-row transition metals when 6-31G(d) is listed in the keyword line. Note also that there is no guarantee that we should expect our nickel systems to have singlet ground states, but it is a trivial matter to check that these states are indeed the lowest in energy—most of you probably just defaulted to choosing a singlet state and gave it no further thought.)*

As for the unknown solid, an obvious choice is that the product of the initial reaction is  $\text{Ni}(\text{CO})_2(\text{CN})_2$ .  $\text{Ni}^{\text{II}}$  compounds are usually square planar, so there should be only two stereochemical possibilities, one where the carbonyl groups are trans to one another ( $D_{2h}$  symmetry) and one where they are cis ( $C_{2v}$  symmetry). I optimized the geometries for each at the B98/6-31G(d) level and computed IR frequencies and  $^{13}\text{C}$  isotropic NMR shieldings (I also computed NMR shieldings for  $\text{Ni}(\text{CO})_4$  since that molecule was used as the internal standard for the spectral measurements). Note that NMR chemical shifts are reported as deshieldings usually, so a higher shielding means an upfield shift and a lower shielding means a downfield shift. In any case, here are the data:

Property	Trans ( $D_{2h}$ ) isomer	Cis ( $C_{2v}$ ) isomer
$H_0$ ( $E_h$ )	-1920.245 87	-1920.237 89
High intensity IR peaks scaled by 0.959 ( $\text{cm}^{-1}$ )	2154	2143, 2170, 2188
$^{13}\text{C}$ NMR shieldings relative to $\text{Ni}(\text{CO})_4$ (ppm)	6.6, 84.0	8.4, 84.1

My, my, what remarkably close agreement with experiment... Evidently my solid is a mixture predominantly composed of the trans isomer (which, comfortingly, is the one that's lower in energy, albeit by too much probably to assume that the product mixture is produced from a thermodynamic equilibrium). Recrystallization removes the cis isomer from the crude precipitate.

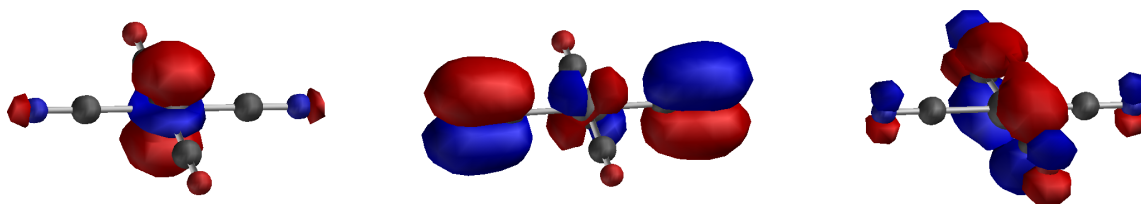
b. To what electronic transitions do the two peaks in the UV spectrum correspond (show pictures of the orbitals)? Based on the nature of these transitions, how might you expect the geometries of the first and second excited states to differ from the ground state (don't do an excited-state geometry optimization, just infer from the orbitals).

A survey of the first 6 excited singlet states using TDDFT (B98/6-31G(d)) finds that only the second and sixth have non-zero oscillator strengths, and fascinatingly enough the predicted absorptions are at 333 and 310 nm. The absorption at 333 nm is predicted to be completely dominated by a HOMO  $\rightarrow$  LUMO transition (orbital 41  $\rightarrow$  42) while the absorption at 310 nm is predicted to be dominated by a 39  $\rightarrow$  42 transition. Pictures of these 3 orbitals are:

39

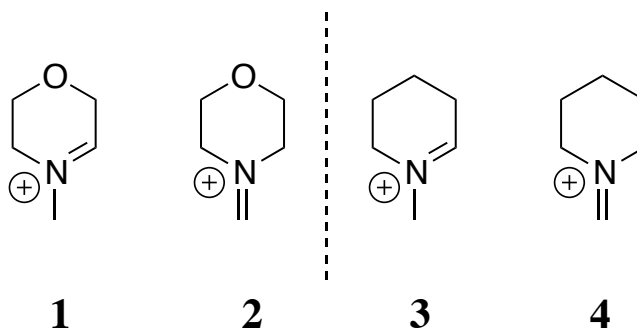
41 (HOMO)

42 (LUMO)



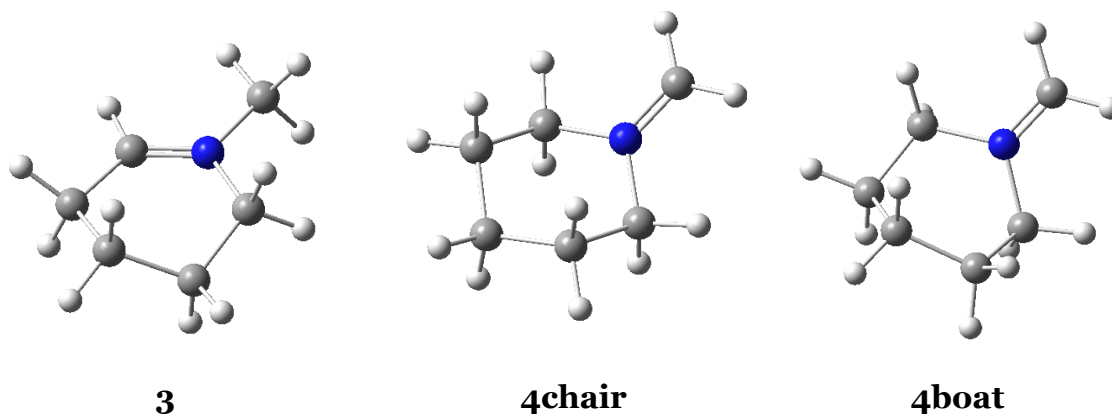
So, orbital 39 is a fairly pure  $d_{22}$  orbital on Ni, orbital 41 is an antisymmetric combination of CN  $\pi$  bonds with a weak antibonding interaction with Ni, and orbital 42 is a symmetric combination of CO  $\pi^*$  antibonds with no significant Ni contribution (only a Ni  $p_z$  orbital would have the right phase behavior to participate in this orbital, and no such orbital is nearby in energy). Thus, we would call the 333 absorption a ligand  $\rightarrow$  ligand transition that moves charge from the CN fragments to the CO fragments. Looking at the orbital phases, depopulating the CN bonding orbitals will lengthen the CN bonds in the excited states and population the CO antibonding orbitals will lengthen the CO bonds. The two carbon atoms of the CO ligands will be drawn closer to the central Ni atom to maximize the bonding  $\pi$  overlap between them and the two carbon atoms of the CN fragments will also be drawn closer to Ni since the depopulated HOMO was antibonding between Ni and C. As for the 39  $\rightarrow$  42 transition, this would be called a metal-to-ligand charge transfer (MLCT) band. The excited state geometry should see the CN fragments largely unaffected (there is no significant contribution of CN orbitals to either the depopulated or populated orbitals in the excited state). Again, however, we expect the CO fragments to draw closer to Ni and to lengthen the CO bond.

3. Consider the two pairs of isomeric iminium ions below that were studied in the last problem set. Our gas phase results were *not* consistent with the exocyclic double bond isomer **2** being more stable than **1**. Let's revisit the problem, as well as the question of activation free energies, using a continuum solvent model, in conjunction with possible explicit water catalysis for the tautomerization reactions.



Reoptimize the minima, and proton-transfer transition-state structures, both with and without water catalysis, at the M06-2X/6-31+G(d,p) levels using the SMD aqueous continuum model. Do frequency calculations to determine thermal contributions to the 298 K free energy at that same level. Finally, do single-point calculations at the SMD/M06-2X/6-311+G(2df,2p) level and add thermal contributions from the lower level to these electronic energies to get a best estimate of the free energy in solution.

For completeness, I will expand the answer key already used for PS2, focusing on the new results. Text in blue in the tables is at the new levels of theory.



Pictures for the piperidine-based local minima are provided above. Nothing too remarkable, other than there being chair and boat conformers for the exocyclic isomer. As expected, the chair is lower in energy (see below).

Again, without pretty formatting, putting piperidine system to left and morpholine to right because I like to think of the latter as being a variation on the former (energies in a.u. followed by relative energies in kcal/mol):

*E*

Level of theory

	<b>3</b>	<b>4chair</b>	<b>4boat</b>	<b>1</b>	<b>2chair</b>	<b>2boat</b>
HF	-288.439 33	-288.426 36	-288.417 57	-324.234 82	-324.225 10	-324.216 77
MP2	-289.691 73	-289.680 70	-289.672 19	-325.561 80	-325.553 61	-325.545 07
Mo6-2X	-290.253 75	-290.241 66	-290.233 72	-326.126 37	-326.117 77	-326.109 21
SMD/small	-290.342 27	-290.331 62	-290.323 34	-326.225 46	-326.218 42	-326.209 73
SMD/large	-290.420 32	-290.409 41	-290.400 96	-326.320 04	-326.312 41	-326.303 69

Level of theory

	<b>3</b>	<b>4chair</b>	<b>4boat</b>	<b>1</b>	<b>2chair</b>	<b>2boat</b>
HF	0.0	8.1	13.7	0.0	6.1	11.3
MP2	0.0	6.9	12.3	0.0	5.1	10.5
Mo6-2X	0.0	7.6	12.6	0.0	5.4	10.8
SMD/small	0.0	6.7	11.9	0.0	4.4	9.9
SMD/large	0.0	6.8	12.1	0.0	4.8	10.3

*G*<sub>298</sub>

Level of theory

	<b>3</b>	<b>4chair</b>	<b>4boat</b>	<b>1</b>	<b>2chair</b>	<b>2boat</b>
HF	-288.279 85	-288.265 47	-288.257 34	-324.100 37	-324.089 11	-324.081 34
Mo6-2X	-290.106 28	-290.092 84	-290.085 47	-326.002 88	-325.992 54	-325.984 70
SMD/small	-290.194 16	-290.182 57	-290.176 06	-326.100 14	-326.092 83	-326.083 94
SMD/large*	-290.272 21	-290.260 37	-290.253 68	-326.194 71	-326.186 81	-326.177 90

Level of theory

	<b>3</b>	<b>4chair</b>	<b>4boat</b>	<b>1</b>	<b>2chair</b>	<b>2boat</b>
HF	0.0	9.0	14.1	0.0	7.1	11.9
Mo6-2X	0.0	8.4	13.1	0.0	6.5	11.4
SMD/small	0.0	7.3	11.4	0.0	4.6	10.2
SMD/large*	0.0	7.4	11.6	0.0	5.0	10.5

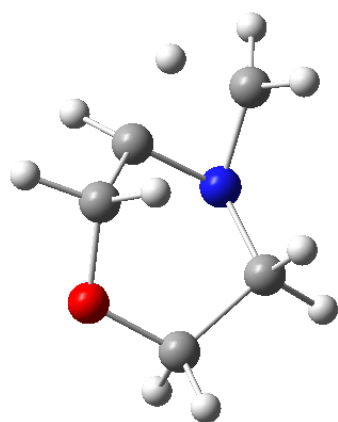
\* *G* defined by adding thermal contributions from smaller basis set to electronic energy computed with larger basis set.

Nothing too exciting about *E* vs *G*. Including aqueous solvation, chair still preferred over boat for exocyclic conformers by 4 to 5 kcal/mol. Endocyclic still preferred over exocyclic, although by slightly reduced margins compared to the gas phase: by about 5 kcal/mol for the morpholine derivative, and by about 7 kcal/mol for the piperidine derivative. The exocyclic boats are stabilized by solvation relative to the endocyclic isomer by about the same margin as the exocyclic chairs are.

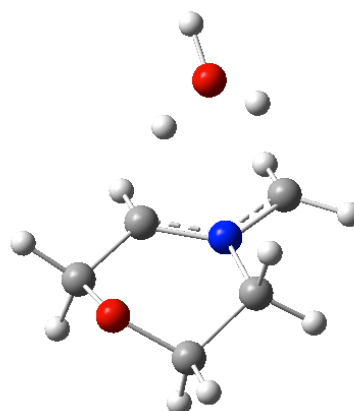
Re-noting that it is observed that refluxing **1** in aqueous solution leads to **2**, is that consistent with these most recent calculations? If a significant change is observed compared to

your earlier gas-phase results (you are welcome to refer to the answer key to Problem Set 2, should you need to), rationalize the effect of solvation. Finally, by how much does water catalysis lower the free energy of activation in the two systems? Note that you will need to pay careful attention to standard-state corrections for solutes, especially when including water as a solute.

**No, the endocyclic double bond is still predicted to be more stable.** In my opinion, the experimental interpretation reported in Rosenau et al. *Tetrahedron* **2004**, *60*, 301 must be incorrect about the equilibrium. Glancing at their Scheme 3, it appears that they must have used a very bad geometry for the endocyclic double-bond isomer, making it artefactually too high in energy (note that the paper is quite confusing – in the text it says the exocyclic isomer is preferred by 2.9 kJ/mol, but the scheme says 17.1 kJ/mol – sloppy). The mechanistic analysis also seems muddy. Worth further study.



**uncatalyzed**



**H<sub>2</sub>O-catalyzed**

The two transition state structures are shown above (for the morpholine derivative). The energetics are (energies in a.u. followed by relative energies in kcal/mol) – solvated results in blue:



*E*, uncat  
Level of theory

	<b>3</b>	<b>TS</b>	<b>4chair</b>	<b>1</b>	<b>TS</b>	<b>2chair</b>
Mo6-2X	-290.238 21	-290.119 56	-290.225 83	-326.110 36	-325.991 74	-326.101 59
HF	-288.522 86	-288.393 01	-288.509 47	-324.336 29	-324.206 21	-324.325 56
MP2	-289.692 96	-289.575 23	-289.682 12	-325.563 54	-325.445 71	-325.555 50
SMD/small	-290.342 27	-290.247 30	-290.331 62	-326.225 46	-326.131 10	-326.218 42
SMD/large	-290.420 32	-290.325 66	-290.409 41	-326.320 04	-326.225 50	-326.312 41

Level of theory

	<b>3</b>	<b>TS</b>	<b>4chair</b>	<b>1</b>	<b>TS</b>	<b>2chair</b>
Mo6-2X	0.0	74.5	7.8	0.0	74.4	5.5
HF	0.0	81.5	8.4	0.0	81.6	6.7
MP2	0.0	73.9	6.8	0.0	73.9	5.0
SMD/small	0.0	59.6	6.7	0.0	59.2	4.4
SMD/large	0.0	59.4	6.8	0.0	59.3	4.8

*G*<sub>298</sub>, uncat  
Level of theory

	<b>3</b>	<b>TS</b>	<b>4chair</b>	<b>1</b>	<b>TS</b>	<b>2chair</b>
Mo6-2X	-290.089 80	-289.974 19	-290.075 98	-325.985 92	-325.870 60	-325.975 45
SMD/small	-290.194 16	-290.101 04	-290.182 57	-326.100 14	-326.006 72	-326.092 83
SMD/large*	-290.272 21	-290.179 40	-290.260 37	-326.194 71	-326.101 12	-326.186 81

Level of theory

	<b>3</b>	<b>TS</b>	<b>4chair</b>	<b>1</b>	<b>TS</b>	<b>2chair</b>
Mo6-2X	0.0	72.5	8.7	0.0	72.4	6.6
SMD/small	0.0	58.4	7.3	0.0	58.6	4.6
SMD/large*	0.0	58.2	7.4	0.0	58.7	5.0

\* *G* defined by adding thermal contributions from smaller basis set to electronic energy computed with larger basis set.

The predicted activation free energies are independent of heterocycle and large, but solvation reduces the activation free energies by about 14 kcal/mol. Difference between *E* and *G*<sub>298</sub> small (the reaction is unimolecular). Also because the reaction is unimolecular, there is no effect from changing the standard state from that of the gas phase (standard state concentration that of an ideal gas at 298 K, which is (1/24.45) M) to that conventionally used for solution (1 M). Making the correction would add  $RT\ln(24.45)$ , or 1.9 kcal/mol, to the free energy of every species, but that effect cancels when the reaction is unimolecular.

Turning to the water catalyzed case (obtained by adding H<sub>2</sub>O values for *E* and *G*<sub>298</sub> to the values in the above table for the minima, while optimizing the TS structure with the water as part of the TS), we have:

$E$ , H <sub>2</sub> O-cat Level of theory	<b>3•H<sub>2</sub>O</b>	<b>TS•H<sub>2</sub>O</b>	<b>4chair•H<sub>2</sub>O</b>	<b>1•H<sub>2</sub>O</b>	<b>TS•H<sub>2</sub>O</b>	<b>2chair•H<sub>2</sub>O</b>
Mo6-2X	-366.611 59	-366.517 12	-366.599 20	-402.483 74	-402.394 68	-402.474 97
HF	-364.576 90	-364.424 94	-364.563 51	-400.390 33	-400.244 73	-400.379 60
MP2	-366.001 99	-365.909 85	-365.991 15	-401.872 58	-401.785 38	-401.864 53
SMD/small	-366.751 71	-366.652 86	-366.741 06	-402.634 91	-402.541 64	-402.627 87
SMD/large	-366.857 37	-366.758 27	-366.846 46	-402.757 08	-402.663 30	-402.749 45
Level of theory	<b>3•H<sub>2</sub>O</b>	<b>TS•H<sub>2</sub>O</b>	<b>4chair•H<sub>2</sub>O</b>	<b>1•H<sub>2</sub>O</b>	<b>TS•H<sub>2</sub>O</b>	<b>2chair•H<sub>2</sub>O</b>
Mo6-2X	0.0	59.3	7.8	0.0	55.9	5.5
HF	0.0	95.4	8.4	0.0	91.4	6.7
MP2	0.0	57.8	6.8	0.0	54.7	5.0
SMD/small	0.0	62.0	6.7	0.0	58.5	4.4
SMD/large	0.0	62.2	6.8	0.0	58.8	4.8

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$G_{298}$ , H <sub>2</sub> O- cat Level of theory	<b>3•H<sub>2</sub>O</b>	<b>TS•H<sub>2</sub>O</b>	<b>4chair•H<sub>2</sub>O</b>	<b>1•H<sub>2</sub>O</b>	<b>TS•H<sub>2</sub>O</b>	<b>2chair•H<sub>2</sub>O</b>
Mo6-2X	-366.459 29	-366.350 31	-366.445 47	-402.355 42	-402.251 58	-402.344 94
SMD/small	-366.599 98	-366.485 49	-366.588 40	-402.505 96	-402.397 37	-402.498 65
SMD/large*	-366.705 63	-366.590 90	-366.693 79	-402.628 14	-402.519 02	-402.620 24
Level of theory	<b>3•H<sub>2</sub>O</b>	<b>TS•H<sub>2</sub>O</b>	<b>4chair•H<sub>2</sub>O</b>	<b>1•H<sub>2</sub>O</b>	<b>TS•H<sub>2</sub>O</b>	<b>2chair•H<sub>2</sub>O</b>
Mo6-2X	0.0	68.4	8.7	0.0	65.2	6.6
SMD/small	0.0	71.8 (67.5)	7.3	0.0	68.1 (63.8)	4.6
SMD/large*	0.0	72.0 (67.7)	7.4	0.0	68.5 (64.2)	5.0

So, the *solvated* energies of activation with a water catalyst are actually **higher** than those without a catalyst, and the *solvated free* energies of activation even more so (even after including a correction for a standard-state concentration of pure water that would be  $RT\ln(55.56*24.45)$ , or 4.3 kcal/mol, reflecting the 55.56 M concentration of solvent water). The molecular structure for the catalyzed TS structure looks far more chemically sensible, but apparently the nitrogen atom is able to accommodate the very strained 1,3-proton transfer TS structures without as much strain as one's intuition might otherwise expect.

So, again, the paper of Rosenau et al. seems significantly flawed. If only we had time to study it further...