

Using PC Model, answer the questions below.

1. Consider the water molecule, H₂O. Using the data for the force field in the PC Model manual and/or parameter files, write the complete MMX energy expression that must be evaluated for this molecule in terms of force field functional forms, constants, and variables. Next, for a geometry having both H–O bond lengths at 1 Å and the H–O–H angle at 110 deg, compute the energy from your expression. Compare this value to what is predicted by the software. In the event of disagreement, assess what may be wrong and summarize your results.

A careful reading of the PC Model manual from pp. 138-141 suggests that the energy expression needed to evaluate U for water is

$$\begin{aligned}
 U = & k_{2,\text{H}_a\text{O}}(r_{\text{H}_a\text{O}} - r_{\text{eq},\text{H}_a\text{O}})^2 \left[1 - k_3(r_{\text{H}_a\text{O}} - r_{\text{eq},\text{H}_a\text{O}}) + k_4(r_{\text{H}_a\text{O}} - r_{\text{eq},\text{H}_a\text{O}})^2 \right] \\
 & + k_{2,\text{H}_b\text{O}}(r_{\text{H}_b\text{O}} - r_{\text{eq},\text{H}_b\text{O}})^2 \left[1 - k_3(r_{\text{H}_b\text{O}} - r_{\text{eq},\text{H}_b\text{O}}) + k_4(r_{\text{H}_b\text{O}} - r_{\text{eq},\text{H}_b\text{O}})^2 \right] \\
 & - k_{2,\text{H}_a\text{OH}_b}(\theta_{\text{H}_a\text{OH}_b} - \theta_{\text{eq},\text{H}_a\text{OH}_b})^2 \left[1 + k_6(\theta_{\text{H}_a\text{OH}_b} - \theta_{\text{eq},\text{H}_a\text{OH}_b})^4 \right]
 \end{aligned} \tag{1}$$

where I have written things in a reasonably standard notation. The manual, alas, is plagued with some font errors, and one math error that becomes clear when comparing the by-hand calculation to the computer calculation. But, in any case, connection to the manual is provided by the following definitions:

$$\begin{aligned}
 k_{2,\text{HO}} &= \text{bu} * \text{ks}_{\text{HO}} \\
 (r_{\text{HO}} - r_{\text{eq},\text{HO}}) &= \delta r \\
 k_3 &= \text{cs} \\
 k_4 &= \text{qs} \\
 k_{2,\text{HOH}} &= \text{au} * \text{kb}_{\text{HOH}} \\
 (\theta_{\text{H}_a\text{OH}_b} - \theta_{\text{eq},\text{H}_a\text{OH}_b}) &= \delta \Theta \\
 k_6 &= \text{sf}
 \end{aligned} \tag{2}$$

where the manual specifies that for the MMX force field, the values of the constants bu , cs , qs , au , and sf are 71.94, -2.0 , 2.333333, 0.02191418, and 0.00000007. Further, using these constants, bond lengths should be measured in ångströms, angles in degrees, in which case the resulting energies will be in kcal/mol.

Note that my definitions above seem to have left out a factor of $1/2$ appearing in the manual expressions for stretching and angle bending. However, it is apparent that this factor of $1/2$ has already been absorbed into the tabulated force constants, since it is only by assuming this that a by-hand (well, by-spreadsheet...) calculation agrees with the program.

In any case, we still need to find the constants $k_{2,HO}$, $k_{2,HOH}$, $r_{eq,HO}$, and $\theta_{eq,HOH}$. These constants vary with atom type, so we need to assign atom types to the H and O atoms in water. The simplest thing to do is to draw water in PC Model, save an output file, and open it with a text editor to see what atom types the program assigns. Alternatively, one can read the manual and make a reasonable guess. But, the bottom line is that the H atoms are both atom type 21 and the O atom is atom type 6. Looking in the parameter file, we see that the force constants are 4.6 and 0.5 for $k_{2,HO}$ and $k_{2,HOH}$, respectively, and the equilibrium values are 0.942 and 104.5 for $r_{eq,HO}$, and $\theta_{eq,HOH}$, respectively (all units as noted above).

With all of these constants, and values for r_{HO} and θ_{HOH} of 1.0 and 110.0, respectively, the expression for U above yields an energy of 2.317 kcal/mol. Computing the same energy using the program (either by reading in a proper geometry from an appropriate text file or by fixing the distances and angles in the Mark menu) provides 2.310 kcal/mol. The source of the 0.007 kcal/mol difference (about $1/3$ of 1%) may be associated with round-off error (perhaps). The separate components of the strain, stretching and bending, are 1.986 and 0.331 kcal/mol, respectively. As expected, there are no other contributors to the MMX energy for this triatomic molecule, that has no torsions or atoms related to one another in a non-bonded way.

Now, let us take a particular set of cartesian coordinates for a water molecule having the geometry listed above. Thus, we will place the various atoms at the coordinates listed in the table.

Atom	Cartesian coordinates, Å		
	x	y	z
H _a	-0.458861	0.819152	0.000000
O	0.114715	0.000000	0.000000
H _b	-0.458861	-0.819152	0.000000

Considering *only* the bond stretching contributions, what is the force on atom H_a in the x direction? (Note that while it is convenient to define energies in terms of internal coordinates like bond lengths, angles, torsions, etc., these are *not* very useful coordinates for geometry optimization because of strong coupling between the internal degrees of freedom and non-bonded distances. Instead, it is more convenient to compute geometry changes in cartesian coordinates, taking account of each degree of internal freedom's contribution to a cartesian move.) While you do not have to derive a number, explain in general what would need to be done to include the contribution from the angle bending term to the force on atom H_a in the x direction.

In order to do this problem, we pretty much need to become very, very good friends with the Chain Rule of calculus. We are told that we can consider only the bond stretching piece of U (let's call that portion U'), and it is clear that the stretching energy between O and H_b has no dependence on the position of H_a, so the part of U' that is sensitive to H_a may be written as

$$U' = k_{2,\text{H}_a\text{O}}(r_{\text{H}_a\text{O}} - r_{\text{eq},\text{H}_a\text{O}})^2 \left[1 - k_3(r_{\text{H}_a\text{O}} - r_{\text{eq},\text{H}_a\text{O}}) + k_4(r_{\text{H}_a\text{O}} - r_{\text{eq},\text{H}_a\text{O}})^2 \right] \quad (3)$$

We may derive from the chain rule, eq. (1), and the definition of force as the negative derivative of the potential with respect to a geometric coordinate

$$-\frac{\partial U}{\partial x_{\text{H}_a}} = -\frac{\partial U}{\partial r_{\text{H}_a\text{O}}} \frac{\partial r_{\text{H}_a\text{O}}}{\partial x_{\text{H}_a}} - \frac{\partial U}{\partial \theta_{\text{H}_a\text{OH}_b}} \frac{\partial \theta_{\text{H}_a\text{OH}_b}}{\partial x_{\text{H}_a}} \quad (4)$$

and, noting that we've been permitted to ignore the angle-dependent second term on the right-hand-side, we have

$$-\frac{\partial U'}{\partial x_{\text{H}_a}} = -\frac{\partial U'}{\partial r_{\text{H}_a\text{O}}} \frac{\partial r_{\text{H}_a\text{O}}}{\partial x_{\text{H}_a}} \quad (5)$$

To proceed further, we can separately evaluate the two derivatives on the right-hand side of eq. (5), taking our definition for $r_{\text{H}_a\text{O}}$ as

$$r_{\text{H}_a\text{O}} = \sqrt{(x_{\text{H}_a} - x_{\text{O}})^2 + (y_{\text{H}_a} - y_{\text{O}})^2 + (z_{\text{H}_a} - z_{\text{O}})^2} \quad (6)$$

in which case the required derivatives are

$$\begin{aligned} -\frac{\partial U}{\partial r_{\text{H}_a\text{O}}} = & -2k_{2,\text{H}_a\text{O}}(r_{\text{H}_a\text{O}} - r_{\text{eq},\text{H}_a\text{O}}) \left[1 - k_3(r_{\text{H}_a\text{O}} - r_{\text{eq},\text{H}_a\text{O}}) + k_4(r_{\text{H}_a\text{O}} - r_{\text{eq},\text{H}_a\text{O}})^2 \right] \\ & - k_{2,\text{H}_a\text{O}}(r_{\text{H}_a\text{O}} - r_{\text{eq},\text{H}_a\text{O}})^2 \left[1 - k_3 + 2k_4(r_{\text{H}_a\text{O}} - r_{\text{eq},\text{H}_a\text{O}}) \right] \end{aligned} \quad (7)$$

and

$$\frac{\partial r_{\text{H}_a\text{O}}}{\partial x_{\text{H}_a}} = \frac{(x_{\text{H}_a} - x_{\text{O}})}{\sqrt{(x_{\text{H}_a} - x_{\text{O}})^2 + (y_{\text{H}_a} - y_{\text{O}})^2 + (z_{\text{H}_a} - z_{\text{O}})^2}} \quad (8)$$

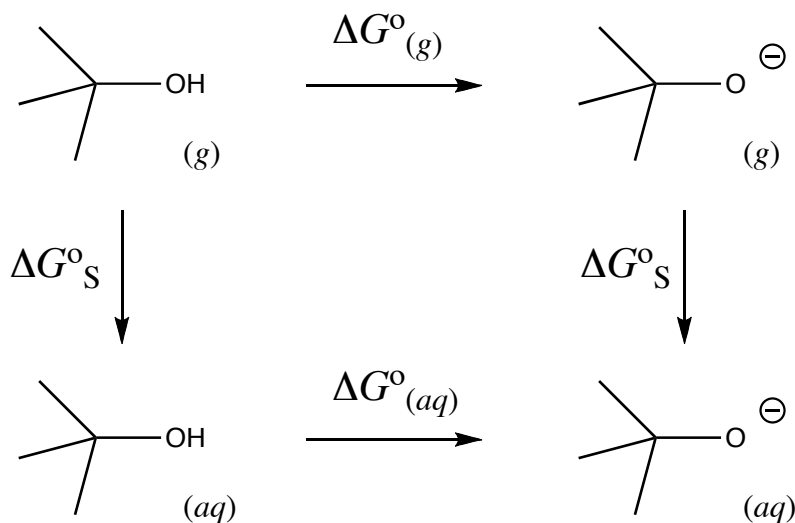
All that's left is to plug the cartesian coordinates from the above table into eq. (8) (result is -0.573576 (unitless)) and the already discussed constants into eq. (7) (result is -46.78241 kcal/mol $\cdot\text{\AA}$) and multiply the two to arrive at a final force on H_a in the x direction of -2.7133798 kcal/mol $\cdot\text{\AA}$.

As for the remainder of the problem, if we wanted to include the effect of angle bending, we would need to evaluate the *second* product of derivative terms on the right-hand-side of eq. (4). The second term *in* the product would involve expressing the bond angle in terms of cartesian coordinates and then taking the derivative with respect to one of those coordinates. From the law of cosines, we may derive

$$\theta_{\text{H}_a\text{OH}_b} = \arccos \frac{r_{\text{H}_a\text{O}}^2 + r_{\text{H}_b\text{O}}^2 - r_{\text{H}_a\text{H}_b}^2}{2r_{\text{H}_a\text{O}}r_{\text{H}_b\text{O}}} \quad (9)$$

One can see that expanding the r terms in cartesians and then embracing the Chain Rule further to derive the partial derivative of θ would be a decidedly unpleasant exercise, so I elected to spare you the pleasure.

2. What is the experimentally measured 298 K free energy required to deprotonate *tert*-butanol in the gas-phase? What is the aqueous pK_a of *t*-butanol? Given that pK_a , what is the 298 K free energy of deprotonation of *t*-butanol in aqueous solution? The two quantities may be related by the below free energy cycle, which has as its vertical legs the free energies of aqueous solvation of neutral *t*-butanol and negatively charged *t*-butoxide. What is the difference in solvation free energies for these two species?



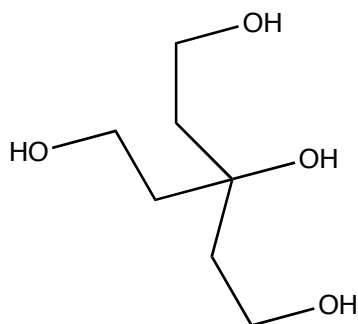
The NIST Webbook lists the gas-phase deprotonation free energy for *t*-butanol as about 368 kcal/mol. The aqueous pK_a is usually tabulated as about 18. From the formula relating pK_a to free energy change

$$\begin{aligned} \Delta G_{(aq)} &= -RT \ln K_a \\ &= -2.303RT \log K_a \\ &= 1.38 \cdot pK_a \end{aligned}$$

which implies a free energy change of about 25 kcal/mol. As the free energy difference for deprotonation in the gas phase and aqueous solution is 343 kcal/mol, this must also be the difference in solvation free energies for the left and right sides of the thermodynamic cycle. Note, however, that the thermodynamic cycle as given is not chemically balanced (the proton on the right side is missing). If we find the solvation free energy of the proton (it's in the course textbook as -264 kcal/mol — we won't worry too much about standard state issues here, as we've not really discussed them yet in the course), that means the remaining 79 kcal/mol reflects the difference in aqueous solvation free energy of the *t*-butoxide anion and the neutral *t*-butanol. So, if you like, *t*-butanol

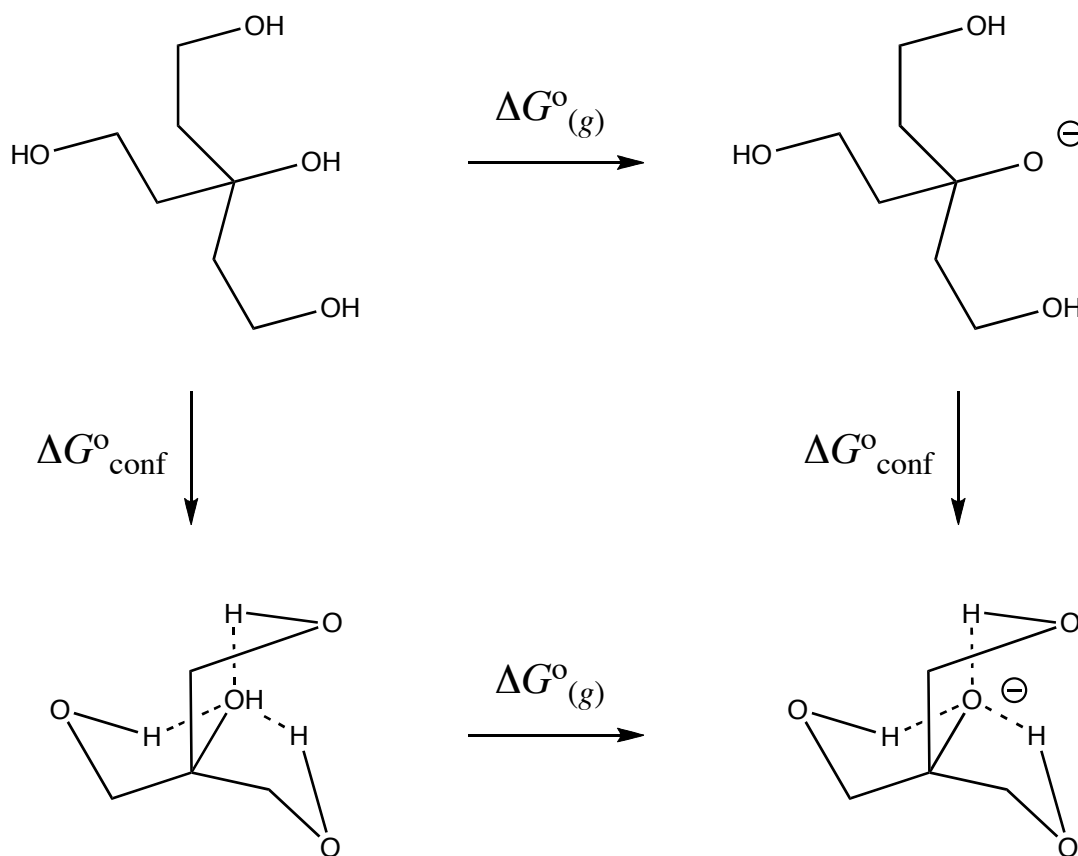
is a much better acid in water than in the gas phase because solvation substantially stabilizes the anion relative to the neutral. The idea of solvation stabilizing the conjugate base to increase acidity can be exploited by building solvation *into* the acid molecule itself, as outlined below:

In ongoing work in the Chemistry department of the University of Minnesota, the Kass group is exploring the fascinating influence of internal hydrogen bonding on the acidity of groups commonly regarded as poor acids or bases. Consider the simple example below:



What would you expect the gas-phase deprotonation energy of this compound to be? (Hint: Consider a thermodynamic cycle similar in spirit to the one shown above, albeit with different vertical legs, and note the experimental data that you already have in hand.) If we now consider a dipolar aprotic solvent (e.g., dimethylsulfoxide (DMSO) or acetonitrile (MeCN)), how much more acidic would you expect the Kass compound to be than *t*-butanol?

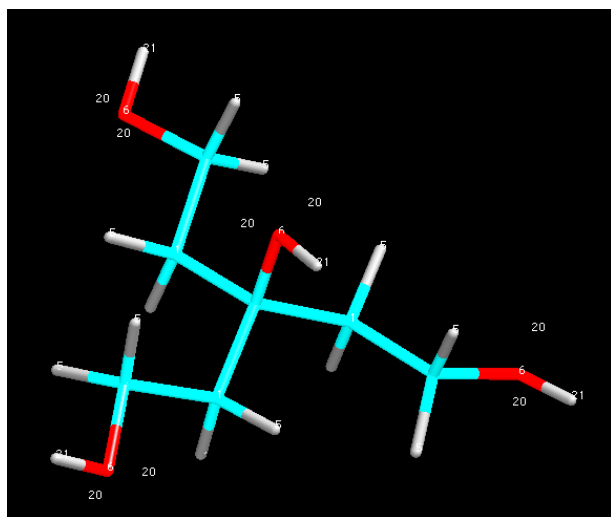
Let us now consider the below thermochemical cycle. The top leg is the gas-phase deprotonation of a fully extended tetraol at the central alcohol, a process that is effectively the same as deprotonation of *t*-butanol with some spectator groups. Thus, we might assume a deprotonation free energy of 368 kcal/mol for the top leg.



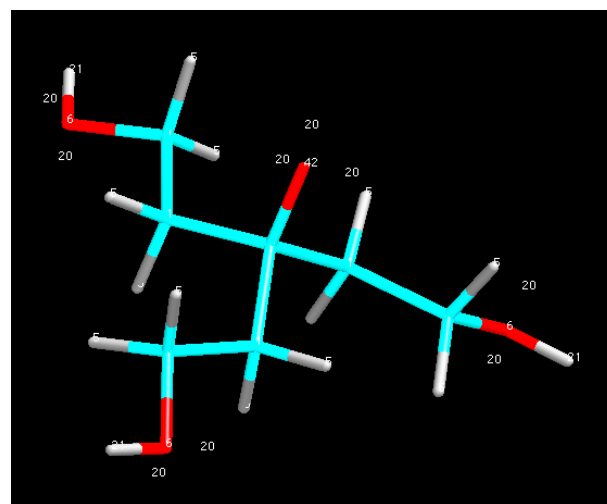
But, internal hydrogen bonding seems likely to lead to lower energies for both the neutral and the anion (and probably by a lot more for the anion). So, we'd really like to know the value for the *bottom* leg of the thermochemical cycle. Happily, the two legs are related by the conformational (free) energy changes associated with the vertical legs of the cycle, and a force field is a good way to estimate that (I'll ignore energy vs free energy here, but a more careful analysis could put it in).

So, a strategy would be to use GMMX to find the lowest energy conformer of the tetraol and its conjugate base, compare those to the energies of the fully extended systems (minimized in that conformation), and the differential internal hydrogen-bond stabilizations added to the *t*-butanol estimate for the top leg with give the bottom-leg gas-phase deprotonation energy. As the "solvation" is intrinsic to the tetraol itself, this stabilization should be nearly as effective in a non-hydrogen bonding solvent as in the gas phase (in a hydrogen bonding solvent, there is no particular advantage in the internal hydrogen bonds; indeed, they may be regarded as entropically unfavorable as they reduce the conformational mobility of the alkyl arms).

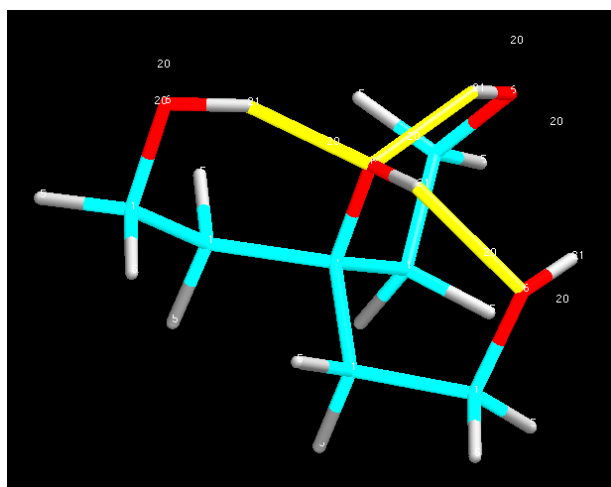
Illustrated below are the structures that I found (with MMX energies *with H-bonding turned on* indicated). Note that a more sophisticated analysis would use a Boltzmann-weighted average energy of possibly many low-energy internally hydrogen-bonded conformers, but for simplicity I use only the lowest one here (the error in this estimation approach likely exceeds the averaging effect...)



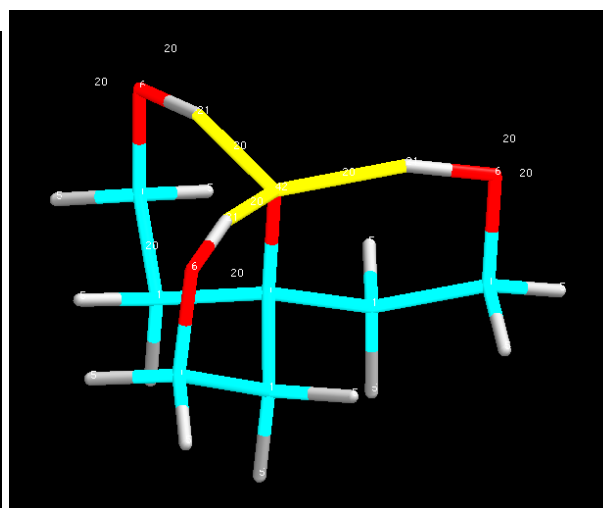
4.7



11.4



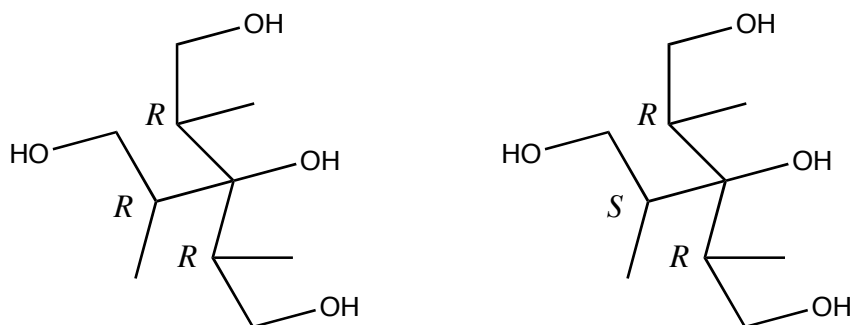
-4.8



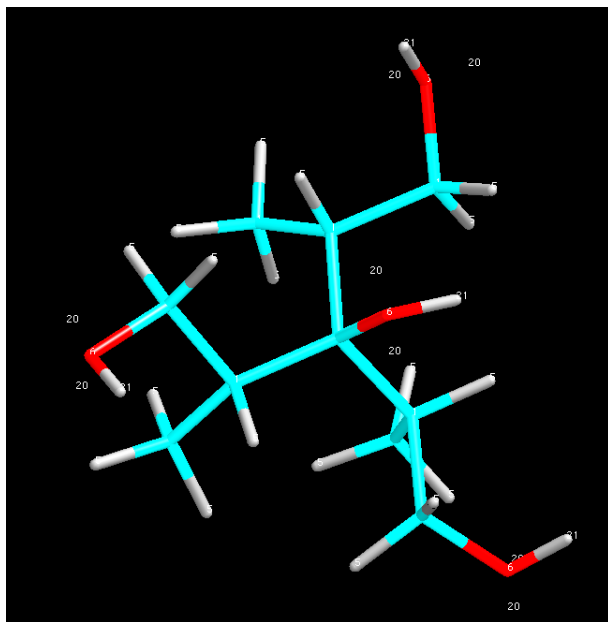
-31.5

So, internal hydrogen bonding stabilizes the neutral minimum (relative to its fully extended conformation) by 9.5 kcal/mol, but the anion by 42.9 kcal/mol. Thus, the gas-phase acidity of the tetraol should be enhanced by about 33.4 kcal/mol compared to *t*-butanol (i.e., a final value of about 335 kcal/mol). That's roughly 24 p*K* units of enhanced acidity!

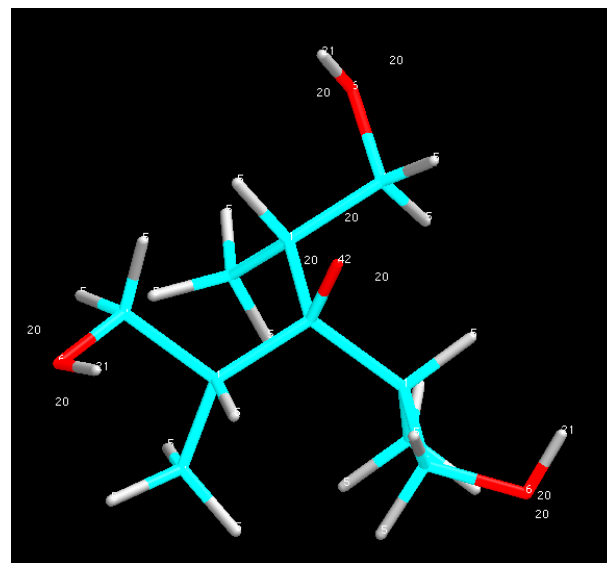
What can you say about the relative acidities of the parent tetraol shown above, and the two isomeric trimethylated species shown below? Rationalize any trend (or lack thereof).



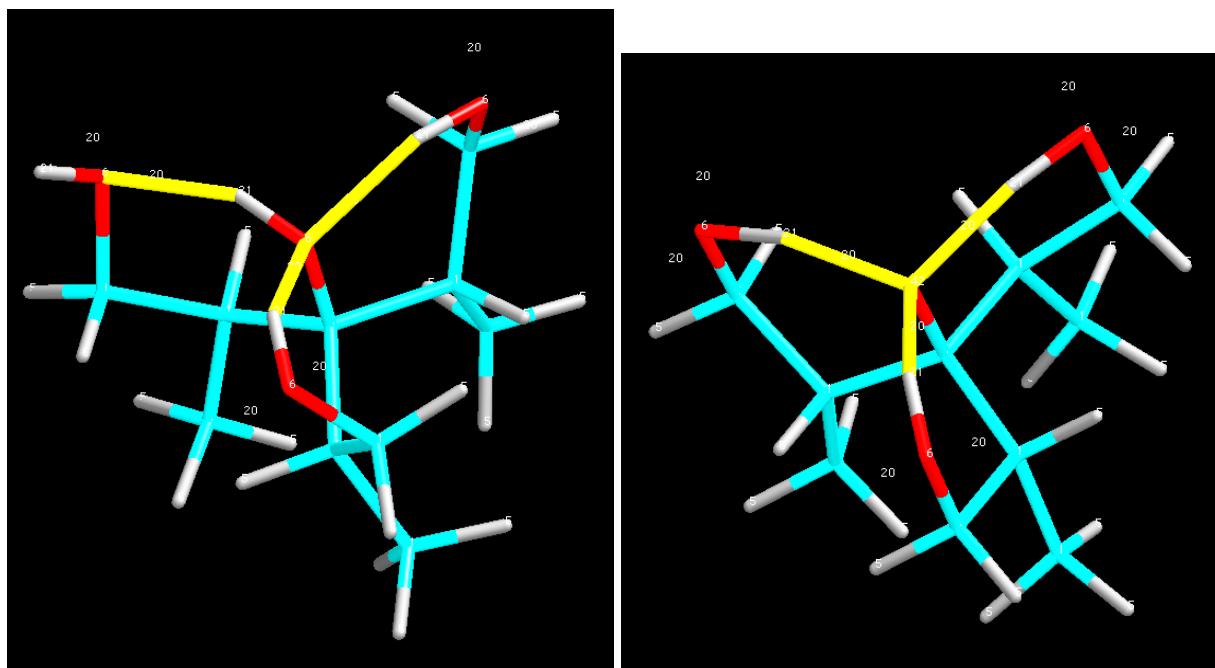
This part of the question essentially asks whether the indicated methylation patterns will affect the relative stabilities of extended vs. internally hydrogen-bonded forms. It's hard to make an intuitive call on this question, but the brute-force searching of the force field makes it fairly straightforward to assess the issue. If I consider first the (*R,R,R*) stereoisomer (with pleasing C_3 symmetry for the anion!), I find, by analogy to the analysis above:



21.3



24.6

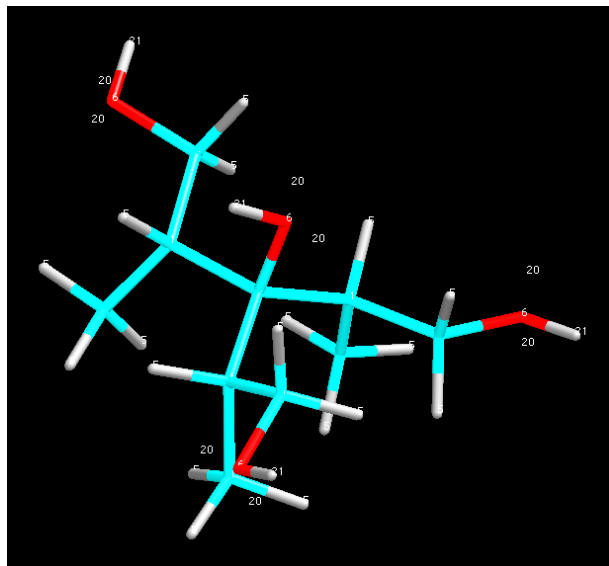


8.8

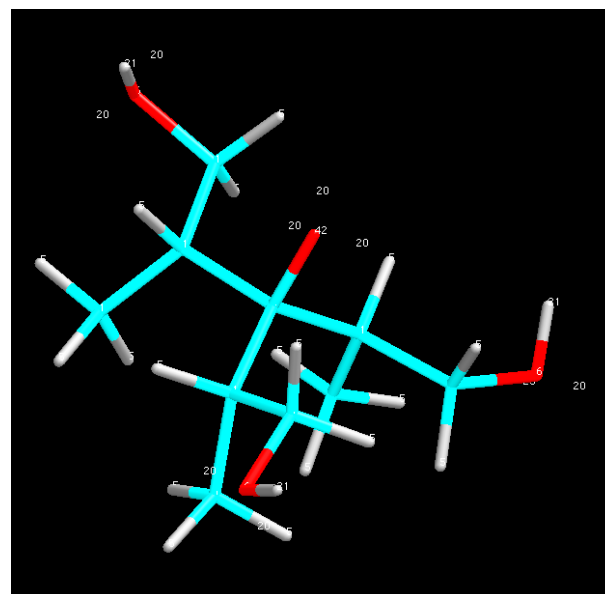
-14.2

Now internal hydrogen bonding stabilizes the neutral minimum (relative to its fully extended conformation) by 12.5 kcal/mol, and the anion by 36.8 kcal/mol. Thus, the gas-phase acidity of the tetraol is now enhanced by only 24.3 kcal/mol, compared to 33.4 kcal/mol for the unsubstituted case.

If we consider the (*R,R,S*) isomer, which is asymmetric with respect to the nature of the methyl substitution adjacent to the acidic alcohol group, the analogous results are



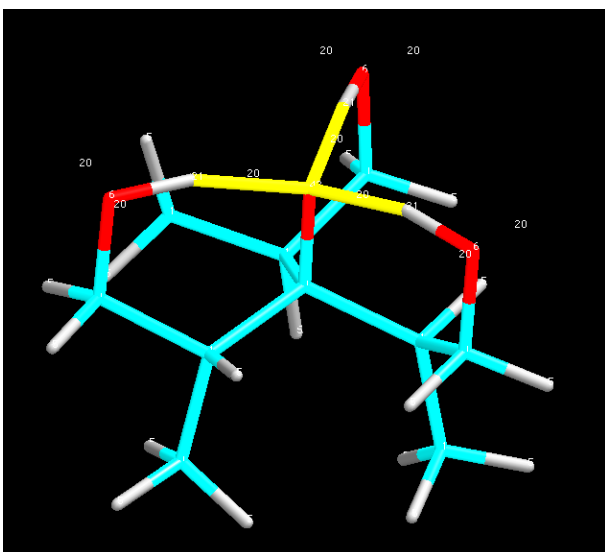
19.8



27.3



6.3



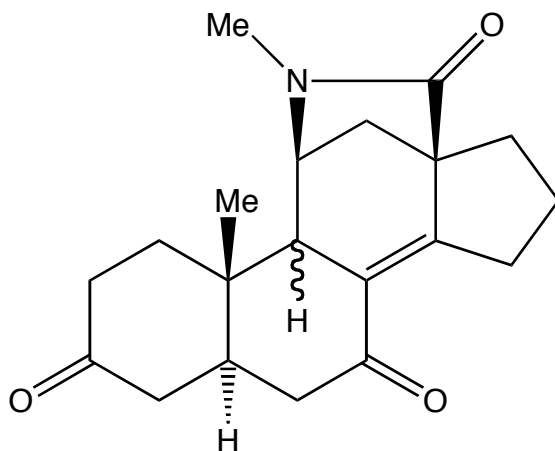
-16.5

Here internal hydrogen bonding stabilizes the neutral minimum (relative to its fully extended conformation) by 12.5 kcal/mol (same as the *(R,R,R)* case), and the anion by 43.8 kcal/mol. Thus, the gas-phase acidity of the tetraol is now enhanced by 31.3 kcal/mol, compared to 33.4 kcal/mol for the unsubstituted case and 24.3 for the *(R,R,R)* case. So, this methylated isomer is predicted to be about as good an acid as the unmethylated case, but the symmetric methylated isomer is predicted to be a much poorer acid. The difference is entirely attributable to the anion (since internal hydrogen bonding stabilizes both neutrals by the same amount). The fully symmetric methylation forces unfavorable torsional strain in

the internally hydrogen-bonded conformer of the anion (just like an unfavorable 1,3-diaxial interaction in a cyclohexane) that can be substantially relieved when one of the three methyl groups is permitted to be moved to a pseudo-equatorial position.

Note that this is a research-like question. There are not “perfect” answers, *per se*—a number of different logical analyses and approaches to addressing this question might be valid. While the answer key will present the instructor’s approach, well reasoned alternative applications of PC Model to answer this question will be considered equally correct from a grading perspective. Thus, please be detailed in your answers as to the kinds of calculations you do and *why* you did them. Persuade the reader of your logic.

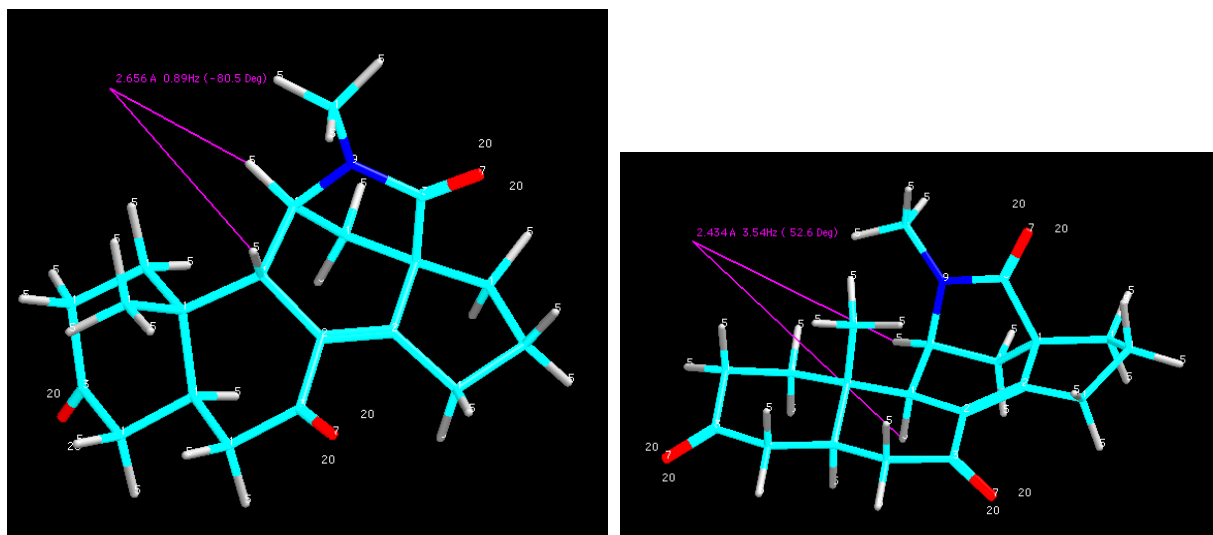
3. You have made the steroid derivative shown below, but are not certain of the stereochemistry of the indicated ring-junction proton. Happily, this proton is readily seen in the NMR spectrum, since it is allylic and coupled to only a single other proton. The doublet coupling constant is 3.6 Hz. Which isomer did you make? Explain how you arrived at your answer.



If you had carried out the reaction under thermodynamic conditions (i.e., conditions that would give an equilibrium distribution of the two epimers) what ratio of the two products would you expect at 298 K based on default MMX, MM3, and MMFF calculations (show your computations, please)? What assumption(s) did you use in arriving at these answers? Finally, for the MMX force field, switch from using a charge-charge electrostatic term to a bond-dipole/bond-dipole term. How would your answer change vis a vis the equilibrium distribution? What if with all three force fields you maintain the default electrostatic method (charge-charge or dipole-dipole), but change the internal dielectric constant to 4.0? (Note that as you switch between force fields,

you may want to use the H-A/D menu button to ensure that lone pairs on oxygen atoms are properly represented as a function of force field.)

The two optimized epimers are shown below, with *cis* (Me,H) ring relationship at left and *trans* (Me,H) at right. The coupling constants for the geometries optimized with the standard MMX force field are 0.9 Hz and 3.5 Hz. The former is almost quantitatively identical to the experimental value, and offers strong support for the *trans* stereochemistry in the isolated product.



If we consider the expected population of the two structures (which are sufficiently rigid that a GMMX minimization of 100 steps gave only a single stereoisomer for me), we can compute the 298 K fraction of each epimer as

$$f_{\text{epimer}} = \frac{e^{-E_{\text{epimer}} / RT}}{e^{-E_{\text{cis}} / RT} + e^{-E_{\text{trans}} / RT}}$$

The force field energies and fractions computed from those energies are listed here in tabular form. The above equation assumes (i) a single isomer for each potential population of isomers and (ii) that the force field energy is representative of a population *free* energy.

Force Field	<i>cis</i> (Me,H)		<i>trans</i> (Me,H)	
	Steric <i>E</i>	<i>f</i>	Steric <i>E</i>	<i>f</i>
MMX (std)	49.3	0.01	46.6	0.99
MM3 (std)	74.5	0.00	67.6	1.00
MMFF94 (std)	79.6	0.00	72.4	1.00
MMX (dip-dip)	32.2	0.09	30.8	0.91
MMX ($\epsilon = 4$)	49.7	0.02	47.2	0.98
MM3 ($\epsilon = 4$)	74.3	0.00	67.6	1.00
MMFF94 ($\epsilon = 4$)	78.5	0.00	72.8	1.00

It is apparent that only the MMX force field predicts a non-negligible amount of the *cis* isomer in 298 K thermal equilibrium. It is not (yet) clear which force field may be most correct. The effect of dipole-dipole electrostatics vs. charge-charge electrostatics is non-trivial for MMX, but does not change the qualitative interpretation. The dielectric constant variation is reasonably small for all force fields.