1. What factors or processes account for the high efficiency of enzyme catalysis.

[Note: focus can be slippery in shifting between k_{cat} and k_{cat}/K_M.]
[Note: because a comment is listed, does not mean it is correct.]

1. REDUCTION OF CHARGE SEPARATION IN TS
   ELECTROSTATIC CATALYSIS
   - — ga/gb catalysis - (ionizable groups)
   - — nucleophilic/electrophilic catalysis - (charged groups)
   - — charges or partial charges in TS envrionment
     enzyme active site is polar environment
2. REDUCTION OF $T\Delta S^{\ddagger}$
   - — multiple substrates, multiple catalytic groups
   - — organization of ground state and TS
3. APPROXIMATION AND ORIENTATION
   ground state and TS
   - — precise arrangement of reactants/catalytic groups in TS
   - — orbital steering, etc..... Mildvan's "FARCE"
   - — NAC's - near attack conformers
4. STRAIN AND STRESS
   - — rack mechanism (earliest suggestion: Haldane; later, Lumry)
   - — distortion (of E or S) in ground state, relieved in TS (E binds TS)
   - — NOTE - enzymes are floppy and cannot exert large forces on substrate (Levitt and Warshel)
5. ENZYME BINDS TS (COMPLEMENTARY TO TS) - Pauling suggestion
   - — encompasses all above, if understood loosely
   - — implies strong binding of TS to E, if taken strictly
6. EVOLUTION
   - — optimization of k_{cat}/K_M
   - — optimization of $K_M \gg [substrate]$
7. ACTIVE SITE "SOLVATES" REACTANT AND CATALYTIC GROUPS
   REDUCTION OF SOLVENT REORGANIZATION ENERGY - (also 1 above)
   - — solvent water replaced by hydrophobic environment
   - — solvent water replaced by organized polar environment

8. LOW BARRIER HYDROGEN BONDS - (1 and 4 above)
9. CONTROL OF REACTION PATH
    - chemistry and changes within active site during reaction favor one of several possible reaction paths (e.g., competition between solvent water and acceptor substrate in phosphoryl transfer, etc.)
    - induced fit
    - allostery
10. SEQUENCE OF ES INTERMEDIATES
    of increasing lifetime and generally of comparable stability
    - adjustments of E and S to more favorable confomation for RDS barrier passage;
      proton movements, small and large conformational changes, etc.
    - break difficult process into parts, in order to optimize
    - provides wide range of time scales and thus a wide range of processes that can contribute to the catalysis;
11. DYNAMICS
    - Kramers' model - effects during barrier passage:
      small decrease in rate from TST prediction
    - correlated motions during barrier passage, between protein matrix and TS;
      necessary for low energy adjustments during barrier passage;
      the relatively stable and organized enzyme is sufficiently floppy;
      an enzyme must DO NO HARM in solvating the TS
    - all events of lifetime faster than that of an intermediate are at equilibrium and thus are correlated statically at the time of barrier passage for that intermediate
    - correlated dynamics in electron and proton transfer;
      quantum mechanical treatment;
      tunneling

2. What are the special properties of proteins that contribute to the high efficiency of enzyme catalysis? [Or, why is all that protein there?]

1. SEQUENCE OF ES INTERMEDIATES
of increasing lifetime and generally of comparable stability

   Proteins are macromolecules with a homogeneous backbone chemistry and varied side-chain chemistry.

   They form stable and long-lived 3-D structures that are floppy in the sense that they can undergo adjustment of conformation in response to small forces. Barriers between substates are low. Diffusive exploration of the energy landscape allows sampling of states separated by barriers higher than the thermal energy.

   Thus an ES complex can evolve through the participation of processes of successively longer lifetimes: proton movement/pK shifts; small conformation adjustments; larger conformational changes; etc. Small-molecule catalysts do not have this option of employing such a wide range of chemical and physical tools.

   The evolution of the ES complex is analogous to protein folding.

2. IMPORTANCE OF LONG-LIFETIME INTERMEDIATES

   Long-lifetime intermediates are necessary for there to be an effect of most protein processes upon a reaction rate.

   There can be neither static nor dynamic correlation of a reaction rate with a slower process.

   However, there can be static correlation between a protein process, such as a conformational change, and the reaction rate (height of RDS barrier) for any processes of lifetime shorter than that of the reacting intermediate: all faster processes are at equilibrium wrt the reacting intermediate.

   Dynamic correlations are found during barrier traversal. This is fast (ps), and dynamic correlations must be with processes of comparable time scale.

3. EVOLUTION

   What is possible wrt reduction in $\Delta G^{\ddagger}$ likely will be found: convergent evolution of enzymes; same catalytic rate for an enzyme in widely different species (e.g., higherplants and animals).

   An enyme optimally uses the catalytic tools at its disposal.

   To find a small-molecule catalyst with the efficiency of an enzyme, is effectively to pit the organic chemist against Mother Nature.

4. ORGANIZATION OF THE ACTIVE SITE (1, 2, 3, and 7 above)

   Distinguish between organization of free enzyme of and ES complex participating in RDS.

   An enzyme mechanism can be a complex catalytic process, in the sense it can make use of multiple tools.

5. CONTROL OF REACTION PATH