tunately, because the triazines are relatively rigid, their conformational flexibility is limited, and thus this effect on the computed free energies might be small. Thirdly, no electronic degrees of freedom were included. Although most MD studies do not allow for different electronic states, it may be important to this system because of structural changes induced by electronic transitions.

Conclusion

Through extensive force field parameter development and the use of the MD/FEP method we were able to calculate the relative binding free energies between three triazine inhibitors of the reaction center of *Rps. viridis* prior to the experimentally determined values. The calculations quantitatively reproduce the experimental relative binding free energies of the herbicides, prometon < atraton < ametryn. There are several limitations that should be addressed in future MD simulations of the RC that include the missing lipid bilayer and the contributions of the conformational flexibility of the ligands to the free energy. These simulations allowed us to evaluate the contributions of the inhibitor substituents to the overall relative binding free energies.

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Supplementary Material Available: Listings of the input files to the AMBER PREP module (17 pages). Ordering information is given on any current masthead page.

Contribution of Charged Side Chains, Mg^{2+}, and Solvent Exclusion to Enzymatic β-Decarboxylation of α-Keto Acids

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Abstract: The origin of the enzymatic rate enhancement of one class of biochemical carbon–carbon bond cleavage reactions, metal-dependent decarboxylation at the β-carbon of an α-keto carboxylic acid, has been investigated by classical electrostatic calculations. The three-dimensional structure of the isocitrate dehydrogenase complex with Mg^{2+} and isocitrate was used to model the charge distribution in the ground and transition states in the decarboxylation reaction. The calculated transition-state stabilization by Mg^{2+} increases from −2 kcal/mol in aqueous solution to −26 kcal/mol in the low-polarizability environment of the enzyme active site. Ionized groups in the active site contribute −43 kcal/mol to binding energy but destabilize the transition state by 11 kcal/mol relative to the enzyme-bound ground state. The overall calculated transition-state stabilization of −13 kcal/mol is in reasonable agreement with the experimental rate enhancement of $>10^8$ for this enzyme class. The low polarizability of the active-site cleft is thus the major factor in enhancement of metal ion catalysis, while ionized groups of the enzyme are required to provide binding energy by stabilizing the ground state.

Introduction

The formation and cleavage of carbon–carbon bonds are of central importance in the biochemistry of all living organisms. Only a limited number of mechanisms are available under physiological conditions to carry out this type of reaction.[1] One prominent class of carbon–carbon bond-breaking reactions catalyzed by enzymes is metal-dependent decarboxylation at the β-carbon of an α-keto carboxylic acid (Figure 1). In a classic set of experiments, Westheimer and co-workers showed that this reaction is catalyzed by Mg^{2+}, Mn^{2+}, and similar ions in solution[2] but proceeds more rapidly by a factor of $>10^8$ in the presence of the enzyme.[3] Westheimer and co-workers proposed that the enzyme served two purposes: to provide substrate specificity and to act as a complexing agent to enhance the catalytic power of the metal ion. It has been suggested that the exclusion of solvent from the active site was the major factor in the enhancement of metal catalysis,[4] but this has until now not been quantitatively tested.

Electrostatic forces are the strongest noncovalent interaction available for enzyme catalysis and have been shown in several cases to play the key role in transition-state stabilization.[5-7] A finite difference solution to the Poisson–Boltzmann equation (FDPB) allows calculation of the electrostatic potential in an enzyme active site based on a realistic model which takes into account the complex shape of the protein, differences in polarizability between solvent and protein regions, and nonzero ionic strength.[8] Using the three-dimensional structure of magnesium(II) isocitrate bound to isocitrate dehydrogenase (IDH)[4,9] as a starting point for a model of the structure of the transition state, this technique has been applied to determine whether effects on the electrostatic field in the active site can account for the dramatic difference in reaction rate between enzyme and solution.

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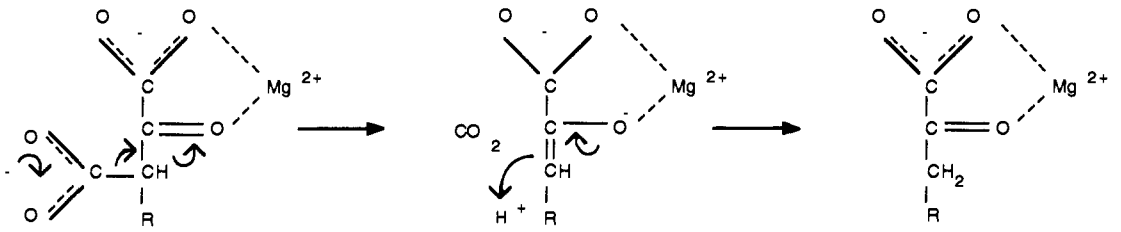

Figure 1. General scheme for metal-assisted decarboxylation at the β-carbon of an α-keto carboxylic acid.

The Model

The reaction pathway for IDH and other decarboxylating dehydrogenases is thought to proceed via oxidation from an alcohol to a ketone intermediate, followed by decarboxylation of this ketone intermediate[10] (Figure 1). The immediate products of decarboxylation are CO_2[11] and an enolate. The enolate is then rapidly protonated while bound to the enzyme to yield the ketone form.[12] By the Hammond postulate, which states that where there is an unstable intermediate on a reaction pathway, the transition state will most closely resemble this intermediate, it is assumed that the transition state will resemble the enolate in this reaction.

It is assumed here that oxalosuccinate, the ketone intermediate in the overall IDH reaction, is the ground state for the decarboxylation reaction. It is also assumed that the transition state closely resembles the enolate form of α-ketoglutarate. The structures of oxalosuccinate and α-ketoglutarate are not available complexed with IDH. The structure of the IDH–isocitrate complex was used as a model for both the oxalosuccinate reactant and the hypothetical α-ketoglutarate enolate-like transition state. Although isocitrate is not isosteric with either of these compounds, the approximate location of each charged atom, the identity of adjacent groups on the enzyme, and the nature of metal ion coordination are likely to be very similar for all three.

Computational Procedures

The electrostatic potentials ϕ due to the Mg^{2+} ion and charges on the enzyme were calculated by the FDPB method[8] using the program and procedures described previously.[7] This program has been modified to calculate ϕ on a 129^3 grid, running on a Stardent ST-3000. The grid spacing is 1 Å, and the protein approaches no closer than 15 Å to the edge of the box. All calculations used the solution to the linearized Poisson–Boltzmann equation:

$$\nabla\cdot(\epsilon\nabla\phi) - \bar{\kappa}^2\phi = -4\pi\rho$$

In the linearized approximation, separately calculated potentials for components of the total charge distribution can be summed to obtain the total potential at any point in space. Because the dielectric ϵ_p assumed for the protein interior is the least certain parameter in these calculations, calculations were repeated with the protein dielectric constant taken as $\epsilon_p = 4.0$ and $\epsilon_p = 10.0$. Although $\epsilon_p = 10.0$ is larger than generally considered reasonable, this calculation allows the ϵ_p dependence of the results to be determined. The bulk-solvent region was assigned a dielectric constant $\epsilon_s = 80.0$, approximately equal to the low-frequency dielectric constant of water at 298 K. The ionic strength was set equal to 0.15 M, and the temperature to $T = 298$ K. All groups were assumed to be in the ionization state expected at pH 7.0, with the exception of Asp 283′. Asp 283′ is probably the catalytic base in the dehydrogenation step which precedes decarboxylation in the IDH reaction,[9] and calculations were carried out for both ionization states of this group. A set of calculations was carried out including only full charges on ionized groups. On the basis of the crystal structure of the enzyme–substrate complex, it was expected that only these groups would play a major role in binding and catalysis. To estimate the contribution of main-chain-peptide dipoles, a calculation using partial charges derived from the AMBER united-atom parameter set[13] was also carried out. The peptide N and H charges were combined, and the charges used were as follows: N, –0.27; C^α, 0.24; C, 0.53; O, –0.50. Crystallographically bound waters were treated as part of the bulk-solvent region. The IDH dimer was used in all calculations. The second active site was assumed to be unoccupied, as there is no evidence for any cooperativity in the kinetics of IDH.

Solvation energies were estimated by two methods. The Born equation

$$U = 332q^2(1/\epsilon_p - 1/\epsilon_s)(1/(2a))\ \text{kcal/mol}$$

where $q = -1$ is the total charge on the ionized oxygen and $a = 1.4$ Å is the radius of the oxygen atom was used first. The Born energy of a charge shared by the two oxygens of a carboxylate group is substantially different from the Born energy of a full charge on a single atom. The following expression can be derived by considering the work required to put a charge of $q/2$ on each of two spheres of radius a followed by the work required to move the two spheres from infinite separation to a separation d:

$$U = 332(q/2)^2(1/\epsilon_p - 1/\epsilon_s)(1/a + 1/d)\ \text{kcal/mol}$$

Here $q = -1$ is the total charge on the carboxylate and $d = 2.23$ Å is the O5–O6 distance. The above formula is purely classical and excludes the resonance stabilization energy of the ionized carboxylate. This formula will only provide an adequate description of the change in solvation energy of the carboxylate if the resonance energy is unchanged between high- and low-dielectric phases. Atoms O5 and O6 of the β-carboxylate of isocitrate are completely inaccessible to solvent,[14] and the hydroxyl oxygen O7 has a negligible solvent accessibility of 1 $Å^2$. For purposes of these solvation energy calculations, these atoms were treated as completely buried in a low-dielectric continuum when bound to the enzyme.

A second set of solvation energy calculations were carried out using the FDPB method.[15] The calculations were carried out on a 1.0-Å grid with $\epsilon_p = 4.0$. The 1.0-Å grid is expected to lead to numerical errors of about 4%, based on comparison to cases for which analytical solution is possible.[15] To calculate the solvation energy of the β-carboxylate, charges of –0.5 were placed on each of the two β-carboxylate oxygens and the potential due to both charges was evaluated. The calculated potentials were used to evaluate the self-energy of an isolated charge on the α-keto oxygen and the twin charges on the β-carboxylate by

$$U(\text{enolate}) = \tfrac{1}{2}\phi(\text{O7})\ q(\text{O7})$$

$$U(\text{carboxylate}) = \tfrac{1}{2}(\phi(\text{O5})\ q(\text{O5}) + \phi(\text{O6})\ q(\text{O6}))$$

The potential calculated in a reference state consisting of a continuum with $\epsilon = 4.0$ and $I = 0.0$ was subtracted to obtain the potential due to the solvent reaction field in the enzyme-bound state. The change in solvation energy between aqueous solution and enzyme-bound states was obtained from $\Delta G(\text{aq} \rightarrow \text{enzyme}) = \Delta G(\text{aq} \rightarrow \text{gas}) + \Delta G(\text{gas} \rightarrow \text{enzyme}) = \Delta G(\text{Born}) + \Delta G(\text{FDPB})$. Here "gas" refers to a gas-phase-like low-dielectric continuum with $\epsilon = 4.0$ everywhere.

The electrostatic potential due to Mg^{2+} in solution was calculated directly from the Debye–Huckel formula. With $\epsilon = 80$, $I = 0.15$, and $T = 298$ K, $1/\kappa = 7.93$ Å.

$$\phi = 332q_{Mg}e^{-\kappa r}/\epsilon_s r\ \text{kcal/(mol·e)}$$

The metal ion was assumed to bind to isocitrate in solution with the same geometry observed in the enzyme-bound structure. Distances from Mg^{2+} to O5, O6, and O7 are 4.38, 4.40, and 1.92 Å.

Results

Both Mg^{2+} and the ionized groups of the enzyme contribute to a large, positive electrostatic potential and to a strong electrostatic field in the active site. The effects of the metal and protein charges on the potential difference between the ground state and transition state, however, are opposite (Table I). Although the result is substantially dependent on the choice of ϵ_p, the qualitative features of the solutions are the same in all cases. Below, the results for the widely used value $\epsilon_p = 4.0$ will be quoted. Results are quoted for the potential calculation with no partial

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Table I. Electrostatic Potential ϕ (kcal/mol·e)[a]

	Mg^{2+} (aq)	Mg^{2+} ($\epsilon_p = 4$)	Mg^{2+} ($\epsilon_p = 10$)	enz ($\epsilon_p = 4$)	283′⁻ ($\epsilon_p = 4$)	283′⁻ ($\epsilon_p = 10$)	pd ($\epsilon_p = 4$)
O1	1.2	9.9	6.3	9.3	7.2	3.1	1.6
O2	2.8	35.2	17.2	12.3	8.6	3.0	1.8
O3	0.6	3.4	2.7	1.9	0.4	−0.1	1.5
O4	0.6	4.0	2.8	4.0	2.6	1.1	2.6
O5	1.0	12.7	6.8	15.5	12.6	5.1	2.7
O6	1.0	11.8	6.4	9.3	5.4	2.1	3.3
O7	3.4	38.6	18.8	1.2	−6.3	−3.5	2.0
Mg				−8.4	−17.8	−8.7	1.7
$\Delta G^{\ddagger}$	−2.4	−26.4	−12.2	11.2	15.4	7.1	1.0
ΔG(bind)				−43.0	−54.0	−24.6	−3.4

[a] The electrostatic contribution to the free-energy difference between the ground and transition states $\Delta G^{\ddagger}$ is calculated from $\Delta G^{\ddagger} = G(\text{ts}) - G(\text{gs}) = \sum(\phi(O_i)\, q(O_i,\text{ts})) - \sum(\phi(O_i)\, q(O_i,\text{gs})) = -\phi(O7) + {}^1/_2(\phi(O5) + \phi(O6))$. The contribution to ground-state binding ΔG(bind) (including Mg^{2+} binding) due to electrostatic interaction with enzyme charges is calculated by $\Delta G(\text{bind}) = \sum(\phi(O_i)\, q(O_i,\text{gs})) + \phi(Mg)\, q(Mg) = -{}^1/_2\sum\phi(O_i)$ (i = 1, 6) + 2ϕ(Mg). "enz" refers to the calculation for ionized groups of the enzyme with Asp 283′ neutral. "283′⁻" refers to calculations for all ionized groups of the enzyme, including an ionized Asp 283′, and "pd" refers to the calculation with only the partial charges for peptide groups.

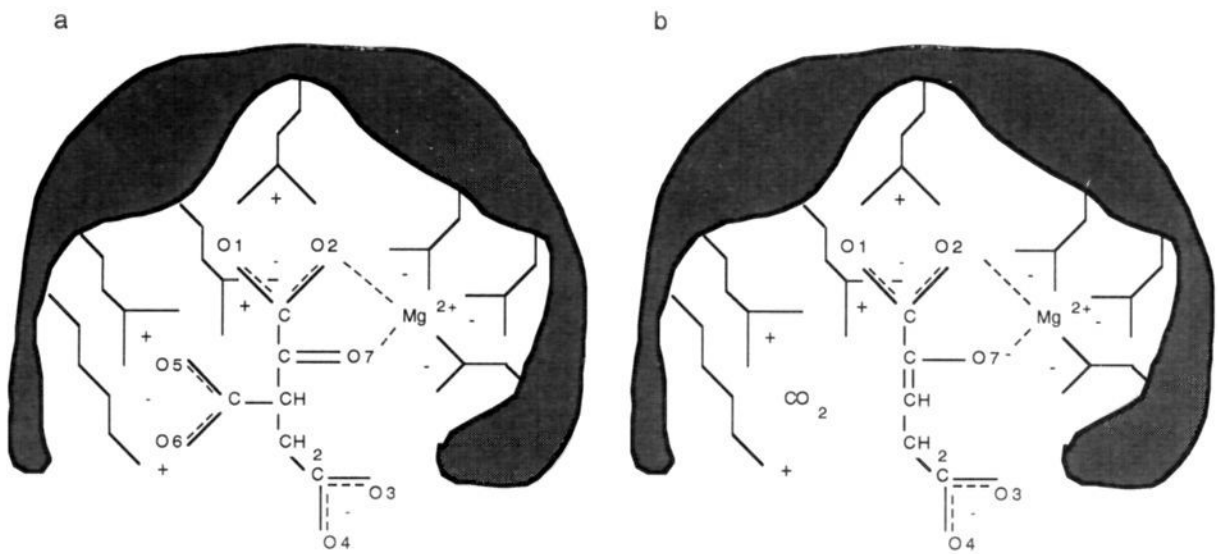

Figure 2. (a) The ground state and (b) the enolate intermediate which is used as the transition-state model in the IDH decarboxylation reaction. Charged residues in the active site of IDH within 4 Å of the substrate are shown.

charges. Main-chain partial charges contribute only 1.0 kcal/mol to the calculated $\Delta\Delta G^{\ddagger}$ (Table I). The values quoted below are those calculated with an uncharged Asp 283′. Upon enzyme binding, the potential difference due to Mg^{2+} favors the transition state by $\Delta G^{\ddagger}(\text{Mg}) = -26.4$ kcal/mol. The enzyme charges favor the gound state, leading to $\Delta G^{\ddagger}(\text{enz}) = 11.2$ kcal/mol. The net electrostatic field in the active site of IDH thus favors the transition state by $\Delta G^{\ddagger} = -26.4 + 11.8 = -15.2$ kcal/mol over the ground state. To determine the rate enhancement relative to the rate in solution, the calculated $\Delta G^{\ddagger}(\text{Mg,aq}) = -2.4$ kcal/mol transition-state stabilization by Mg^{2+} in solution must be subtracted. The increase in electrostatic transition-state stabilization is thus $\Delta\Delta G^{\ddagger} = -15.2 + 2.4 = -12.8$ kcal/mol.

On the basis of the modified Born equation with $\epsilon = 4$, the solvation energies of the ground and transition states change by 22.9 and 28.2 kcal/mol. This leads to a difference of $\Delta\Delta G^{\ddagger}(\text{Born}) = 5.3$ kcal/mol. Destabilization of the transition state by this effect of desolvation occurs because the charge on the β-carboxylate is shared between two oxygens in the ground state but concentrated on the α-keto oxygen in the transition state. If this term is included, the calculated transition-state stabilization decreases to $\Delta\Delta G^{\ddagger} = -7.5$ kcal/mol. Solvation energies were also calculated with the FDPB method. The calculated interaction energies of the enzyme-bound α-keto oxygen and β-carboxylate with bulk solvent are −15.8 and −6.8 kcal/mol, favoring the transition state by −9.0 kcal/mol. Based on an expected 4% error in the individual solvent-interaction energies, the error in the calculated difference is roughly 0.7 kcal/mol. The difference in transition-state stabilization by bulk solvent between aqueous solution and the enzyme-bound state is obtained by adding this term to the change in the Born energy, since the FDPB energies were calculated relative to a low-dielectric continuum reference state. The FDPB calculation suggests that differential solvation actually stabilizes the transition state by $\Delta\Delta G^{\ddagger}(\text{sol}) = 5.3 - 9.0 = -3.7$ kcal/mol.

Discussion

The physical basis for enzymatic rate enhancement now seems clear. Simply moving the Mg^{2+}–isocitrate complex into a low-polarizability environment increases the potential difference due to Mg^{2+} between the α-keto oxygen and β-carboxylate by −24.0 kcal/mol. In order to move the complex into the active site, however, some stabilization of ground-state binding is required (Figures 2 and 3). The ionized groups in the active site, which contribute −43 kcal/mol to substrate binding, actually destabilize the transition state by 11.8 kcal/mol relative to the enzyme-bound ground state. This is the opposite of what might have been expected, since it is sometimes assumed that charged groups in the active site of an enzyme are always likely to be involved in promoting catalysis.

The largest sources of error in the calculated energies are the limitations of the uniform dielectric model and the uncertainty in the best choice of dielectric constant. The calculated $\Delta G^{\ddagger}(\text{Mg})$ varies from −26.4 to −12.2 kcal/mol for $\epsilon_p = 4.0$ and $\epsilon_p = 10.0$. In addition, the most explicit comparison of experimental rates for solution and enzymatic reactions has been made for malic enzyme, rather than IDH. The kinetic isotope effect data for IDH were obtained for pig heart $NADP^+$-dependent IDH,[16] but the

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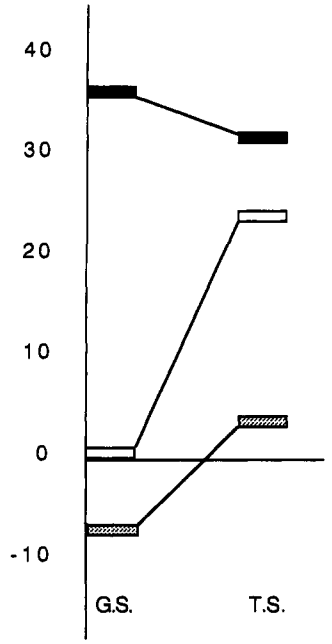

Figure 3. Schematic representations of ground-state and transition-state energies in solution (open boxes), in an enzyme-bound state (cross-hatched boxes), and in a hypothetical gas-phase-like state bound to a charge-free enzyme with a low-dielectric interior (solid boxes). The ground state in solution is arbitrarily taken as the zero-energy reference point. The energy of the ground state bound to the enzyme is a guess based on the experimental dissociation constant for isocitrate from IDH,[21] K_d = 5 μM. The energy of the transition state in solution is obtained from the experimental rate constant in the presence of Mn^{2+}, k = 0.0058 min^{-1}, by applying $\Delta G^{\ddagger} = -RT \ln (hk/k_B T)$ at T = 298 K. All other quantities are based on electrostatic calculations with ϵ_p = 4 and Asp 283′ uncharged. All components are at 1 M concentration.

only structure now available is that of the *Escherichia coli* enzyme.[17] Sequence alignment shows that all residues involved in binding the metal ion and the α- and β-carboxylates of isocitrate are conserved between the yeast[18] and *E. coli* enzymes.[4,19] A peptide which is labeled by *N*-ethylmaleimide upon inactivation of pig heart IDH[20] can be aligned with the yeast IDH sequence in the vicinity (residues 278–287 of yeast IDH, 292–302 of *E. coli* IDH) of the metal-binding site, suggesting a close relationship of the pig heart enzyme with the other two. Although there will be differences in detail, the qualitative features of these results are likely to hold for any functionally related enzyme which contains a deep active-site cleft, basic carboxylate-binding residues, and acidic metal-binding residues. The calculated rate enhancement of 1.4×10^9 at 298 K based on $\Delta\Delta G$ = −12.8 kcal/mol appears reasonable in light of the isotope effect data.[3,16] This suggests that the qualitative insights achieved into the nature of the roles of enzyme and metal ion may be valid.

Stereochemical and geometric factors have so far been neglected in the present analysis. No sign of covalent-bond distortion was detected in the substrate in the crystal structure of the IDH–isocitrate complex. Such distortion might not have been fully evident at the moderate resolution of the structural study. On the basis of the AMBER force field,[13] even a 10° distortion of the bond angle at C^{β} would contribute only about 2 kcal/mol to destabilization of the ground state relative to the transition state. It is also possible that the enzyme positions Mg^{2+} in an orientation more favorable for catalysis than might normally occur in solution. The calculation of the electrostatic stabilization of the transition state in solution was carried out on the basis of the orientation observed in the crystal structure, however. The calculated $\Delta G^{\ddagger}$(Mg,aq) = 2.4 kcal/mol is in fact larger than the experimental value[2] of 0.4 kcal/mol in the presence of Mn^{2+}, based on an increase in the rate of decarboxylation of dimethyloxaloacetic acid from 0.0024 to 0.0058 min^{-1} at 298 K. This might be due to any of several factors, one of which could be a small orientation effect. What is clear is that these factors alone are not sufficient to account for the observed rate enhancement.

Interaction with solvent is a potentially important factor in the relative energies of ground and transition states but is difficult to calculate reliably. The use of the Born equation alone may overestimate the destabilization of the transition state, since even atoms which are completely buried by solvent-accessibility criteria still interact with bulk solvent. The FDPB solvation energy calculation suggests that the stronger interaction with bulk solvent of the charged α-keto oxygen more than compensates for the increased concentration of charge on this atom during the transition state. On the other hand, the FDPB calculation may overestimate the contribution of bulk solvent to transition-state stabilization, since the use of the low-frequency value ϵ_s = 80 is not necessarily valid for calculation of the reaction field produced by very short-lived changes in the charge distribution of the substrate. These solvation energy calculations also suffer from uncertainty in the best choice of effective atomic radii and from the assumption of a symmetric charge distribution in the carboxylate. Some asymmetry is likely to be introduced into the charge distribution on the β-carboxylate on binding to the enzyme. Such asymmetry would be expected to simultaneously destabilize the ground state and to decrease the difference in solvation energy between ground and transition states. The calculated differences in transition-state stabilization $\Delta\Delta G^{\ddagger}$(sol) = 5.3 kcal/mol and $\Delta\Delta G^{\ddagger}$(sol) = −3.7 kcal/mol obtained by the Born equation alone and by the FDPB method serve to estimate upper and lower bounds to the solvation effect. Although the sign of this term is uncertain, these values suggest that the magnitude of the difference in solvation energy is substantially less than that of differences in interaction energy involving charged side chains and Mg^{2+}. Differential interaction with bulk solvent is thus probably not a central factor in the reaction pathway.

Although the decarboxylation step provides the most direct opportunity to compare experimental and calculated reaction rates, these results also have implications for the dehydrogenation step. Dehydrogenation of the alcohol moiety is thought to involve polarization of the carbon–oxygen bond, which would clearly experience a large electrostatic enhancement by Mg^{2+} on the basis of the calculated electrostatic potential at O7. If Asp 283′ is, as proposed, the catalytic base in this step, this would provide a particularly elegant way of coupling the two steps. Protonation of Asp 283′ in the first step decreases $\Delta G^{\ddagger}$ for the second step by 15.4 − 11.2 = 4.2 kcal/mol (Table I).

In every enzyme, a balance must be maintained between binding and catalysis. In the present case, the number and location of charged groups in and around the active site have probably been adjusted during evolution to fine-tune this balance. Binding and kinetic studies on site-directed mutants[19,21] may eventually determine whether this is the case. Such experiments will also provide a further quantitative test for this type of calculation.

There has been some debate as to whether enzymes in general rely on desolvation[22] or whether enzymes work by "solvation substitution".[23] Because partitioning of charged species into a low-dielectric phase is so unfavorable, a gas-phase-like model is inadequate to explain the origin of enzymatic catalysis. Following the conceptual treatment of Warshel and co-workers,[23] we determined that the IDH decarboxylation reaction in a charge-free low-polarizability environment involves a "transition state" which is actually lower in energy than the ground state but the energy

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of the ground state itself is unfavorably high (Figure 3). The charged side chains in the active site lower the energy of the ground state to a much more favorable value, while not completely abolishing the transition-state stabilization gained in the low-polarization environment of the active site. This phenomenon is not unique to IDH and related decarboxylating dehydrogenases. For example, an antibody which catalyzes the decarboxylation of 3-carboxybenzisoxazoles can be induced by a hapten designed to elicit positively charged carboxylate-binding residues and an apolar environment to stabilize the transition state.[24] When the requirements for binding energy and transition-state stabilization are considered together, it becomes clear that both the low-polarizability environment and strong electrostatic field in the active site are critical for enzyme function.

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Molecular Dissimilarity: A Momentum-Space Criterion

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Abstract: Quantitative measures of the similarity of momentum-space electron densities are investigated using ab initio and semiempirical wave functions. The model series CH_3OCH_3, CH_3SCH_3, and $CH_3CH_2CH_3$ is examined. A family of molecular dissimilarity indices $D_{AB}(n)$ appears to be particularly useful. The electron densities of individual C-F bonds and C-H bonds in CH_4, CH_3F, CH_2F_2, CHF_3, and CF_4 are compared. Values of $D_{AB}(-1)$ relative to CH_4 are consistent with the relative reactivities of CH_3F, CH_2F_2, and CHF_3 with the hydroxyl radical.

Introduction

The general concept of molecular similarity is becoming increasingly important[1] in many areas of chemistry; it can be especially useful when the molecular processes are very complex, as in pharmacology. A number of authors have proposed quantitative definitions of molecular similarity, with particular emphasis on comparing electrostatic potentials or position-space electron densities,[2-4] including topological analysis of the three-dimensional shapes of charge densities.[5,6] In a previous paper,[7] we suggested a novel alternative based on momentum-space electron distributions, which concentrates on the outer valence-electron density and which is not subject to many of the drawbacks of the more conventional approaches. In this paper, we introduce more discriminating quantities, which we term "momentum-space dissimilarity indices", and we investigate the use of these definitions with ab initio and semiempirical wave functions.

Momentum-Space Molecular Similarity

The most straightforward means of obtaining momentum-space wave functions is to take the Fourier transform of the more familiar position-space wave function. The relationship in **p**-space between the wave function $\Psi(\mathbf{p})$ and the total electron density $\rho(\mathbf{p})$ is exactly the same as in **r**-space. In the case of an SCF wave function, for example, the contribution to $\rho(\mathbf{p})$ of an electron in molecular orbital $\psi(\mathbf{p})$ is simply $|\psi(\mathbf{p})|^2$. The momentum-space electron density falls off very rapidly with increasing $p = |\mathbf{p}|$, and thus it is dominated by low values of **p**, which correspond in position space to the slowly-varying outer valence-electron density.

In our previous work,[7] we defined a family of momentum-space similarity indices $S_{AB}(n)$ according to

$$S_{AB}(n) = \frac{100 I_{AB}(n)}{\frac{1}{2}(I_{AA}(n) + I_{BB}(n))} \qquad (1)$$

in which

$$I_{PQ}(n) = 2\int p^n \rho_P(\mathbf{p})\, \rho_Q(\mathbf{p})\, d\mathbf{p} \qquad (PQ = AA, BB, \text{or } AB) \qquad (2)$$

and A and B label the two molecules. The different powers of p in the integrands emphasize different regions of the momentum-space valence-electron density; typical values of n are -1, 0, 1, and 2. The values of $S_{AB}(n)$, which lie in the range 0-100, are insensitive to the core-electron densities. Small displacements (in **r**-space) of heavy atoms have negligible effects on the indices. In addition, the values of $S_{AB}(n)$ are dependent on the relative orientation of the two molecules in **r**-space, but not on the distances between them.

The evaluation of $S_{AB}(n)$ using ab initio momentum-space electron densities is relatively straightforward, and it is not computationally expensive. In our previous work,[7] we considered the model systems H_2O, H_2S, CH_3OCH_3, CH_3SCH_3, and $CH_3CH_2CH_3$. It is mainly the cost of carrying out ab initio SCF calculations which limits the use of our procedure for the routine study of large series of large molecules. Consequently, it seems very worthwhile to investigate the reliability of values of $S_{AB}(n)$ computed using much more readily obtainable semiempirical wave functions. Accordingly, we have reexamined the model systems

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