resultant lowering of the *total* energy (*cf.* Figure 5). The significant fact is that the present analysis allows one to calculate a numerical value for the magnitude of this effect which can be related to similar situations in other molecules and *correlated* with larger or smaller energy lowerings.

The increase in $\langle r_1^2 \rangle$ for the nitrogen lone pairs and bonding pairs on going from NH_4^+ to N^{3-} and the relative magnitudes of $\langle r_1^2 \rangle$ for bonding and lone pairs in these species is completely in accord with semiclassical ideas. However, when we come to a more complicated example[21] like FCH_2OH, one's intuition does not take one quite so far. Nevertheless, the relative magnitude of $\langle r_1^2 \rangle$ for the different pairs is more or less what one would expect and it is reassuring that the value of $\langle r_1^2 \rangle$ for the different pairs does not change too drastically with rotational angle. The change in the electronic charge distribution with rotational angle is a more subtle effect associated with the nonspherical components of $\langle r_1^2 \rangle$ for the functional groups as a whole. Thus the chemical significance of these results lies in the fact that we have been able to correlate a precisely defined mathematical quantity (which can be extracted from both nonempirical and semiempirical wave functions), the expectation values of dipole length and second moment operators, with a loose semiclassical concept.

It is noteworthy that, using the definition proposed in eq 5, it has been possible to transform a rather complicated wave function into a relatively simple picture. We hope therefore that the present results and the conclusions we have reached will stimulate interest in the generation of similar data from semiempirical wave functions as well as nonempirical ones. Provided that LMO's are used, the results from the semiempirical work should be as meaningful as those from nonempirical calculations. Hopefully, after a sufficient number of sufficiently diverse "model" compounds have been studied, it may be possible to derive a new set of empirical rules to correlate the size of electron pairs or the sizes of functional groups with molecular geometry.

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Thermodynamics of Ionization of Diastereoisomeric Forms of 2,3-Dicarboxylic Acids

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Abstract: Thermodynamic parameters for the ionization of the *dl* and meso isomers of 2,3-dimethylsuccinic acid and tartaric acid have been determined from a temperature dependence study of the ionization constants calculated from potentiometric data obtained using cells without liquid junction. The data are significantly different between isomers of the same acid and these differences are discussed in terms of proximity effects between functional groups.

In a recent publication from this laboratory, advantage was taken of the small differences in ionization constants for the *dl* and meso forms of 2,3-disubstituted succinic acids to develop an analytical procedure to determine the composition of mixtures of the two pure forms using data from pH titrations.[2] Subsequent to this, in order to establish the thermodynamic reasons for the subtle differences in $\Delta G°$ of ionization, pK values were determined as a function of temperature to obtain $\Delta H°$ and $\Delta S°$ for the *dl* and meso forms of 2,3-dimethylsuccinic acid (DMSA) and tartaric acid (TA). The results are presented here and contrary to what might have been anticipated, there are significant differences between the $\Delta H°$ terms for the *dl* and meso forms of the same acid. This result could have significant bearing upon our understanding of the specificity of isomeric forms to reaction at the micro-

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Table I. Thermodynamics of Ionization of Diastereoisomeric Forms of DMSA and TA at 25°

Acid	pK_i	ΔG° [b]	ΔH° [b]	$-\Delta S^\circ$ [c]	B[d]	A[d]	C[d]
dl-DMSA	3.82	5.21	−0.35	18.7	29.1	−1400	−11.4
	5.93	8.10	−2.25	34.7	−27.1	1361	6.7
meso-DMSA	3.67	5.00	−0.30	17.8	68.8	−3076	−25.1
	5.30	7.23	−3.77	36.9	24.4	−622	11.2
dl-TA[a]	3.03	4.14	+0.74	11.4			
	4.37	5.96	+0.20	19.3			
meso-TA	3.17	4.32	+0.81	11.8	67.4	−3290	−24.1
	4.91	6.70	+1.48	17.5	12.8	−1064	−5.7

[a] Data from ref 9. [b] Units are kcal/mol. [c] Units are cal/(mol °K). [d] $B = (\Delta S_0{}^\circ - \Delta C_p{}^\circ)/R$, $A = -\Delta H_0{}^\circ/R$, $C = 2.303\Delta C_p{}^\circ/R$, where $\Delta S_0{}^\circ$ and $\Delta H_0{}^\circ$ are constants of integration and $\Delta C_p{}^\circ$ is considered to be temperature independent.

scopic or cellular level. It may also contribute to a better theoretical model for the ionization of high molecular weight polycarboxylic acids,[3] *e.g.*, ethylene maleic acid copolymer,[2] where as a result of a free radical propagation mechanism *dl* and meso arrangements will be statistically distributed along the backbone of the polymer.[4] In this regard, it may be inadequate to attribute the variation in pK with degree of ionization α solely to a monotically increasing electrostatic work function. We have found an analogous dependence of pK on α to exist when the pH titration curve of a *dl*, meso mixture of DMSA is analyzed as a single acid.

Experimental Section

The separate forms of TA were obtained from Aldrich Chemical Co. and used without further purification although the meso form was stored over silica gel in a vacuum desiccator for a prolonged period prior to its use. DMSA was supplied by Aldrich Chemical Co. as a mixture of the *dl* and meso forms. These were separated by fractional crystallization from deionized water. Melting points[2] agreed with the literature values and molecular weights from titration with KOH agreed to within ±1 weight unit.

Emf measurements were made using a Beckman Research pH meter, Model 1019, which has a relative accuracy capability of 0.1 mV, on a cell without liquid junction.

$$\mathrm{H_2\ (1\ atm),\ Pt|H_\mathit{n}A^{\mathit{z}-},\ H_{\mathit{n}-1}A^{(\mathit{z}+1)-},\ KCl|AgCl,\ Ag}$$

Acid concentrations were always *ca.* 10^{-2} *m*, and the buffer ratio of the solution under study was varied by adding increments of standard molal KOH solution. Each vessel was fitted with two hydrogen electrodes and two reference electrodes allowing four emf measurements to be made for each solution which served as an internal check on the integrity of the individual electrodes. The precautions taken and fuller details of the experiments are explicitly covered in a previous publication.[5] Data were taken at 5, 15, 25, and 35°.

Results

The method employed to calculate the individual thermodynamic ionization constants has been described for adipic acid[6] and basically consists of the simultaneous solution of two equations of the following form (eq 1) constructed using hydrogen ion activities calculated from emf measurements on two independent solutions. This equation is the result of the appropriate combination of the equations for the ionization constants, mass balance, electroneutrality, ionic product of water, and ionic strength. a is the analytical acid molal concentration, $L = b + [\mathrm{H^+}] - [\mathrm{OH}]^-$, where b is the analytical base molal concentration, $\{\mathrm{H^+}\}$ is the hydrogen ion activity, γ_i is the activity coefficient of the ith ion calculated from the Davies equation,[7] and K_0 and γ_0 are both unity. The calculation of K_1 and K_2 is reiterative and is terminated by convergence on a constant value for γ_i. Convergence was considered complete when successive activity coefficients differed by 0.0001 which was usually accomplished in three to four cycles. The minimum number of data points required is two. In practice measurements were made on many more solutions and the two emf values required for simultaneous solution were chosen at random from the ensemble by a random number generator subroutine incorporated into the program.

$$\frac{\gamma_2}{2a - L}\left[\frac{(L)K_0}{\gamma_0}\{\mathrm{H^+}\}^2 + \frac{(L - a)K_1}{\gamma_1}\{\mathrm{H^+}\}\right] = K_1K_2 \quad (1)$$

A precision of ±0.1 mV in the measured emf corresponds to a standard deviation of ±0.003 unit of pH in the calculated pK. Rather than present the values at all temperatures the pK data were fitted to the equation of Everett and Wynne-Jones[8]

$$\log K = B + A/T + C \log T$$

the coefficients of which are given in Table I along with pK, ΔG°, ΔH°, and ΔS° at 25°. The ΔH° and ΔS° data for *dl*-TA are due to Bates.[9] Our values for pK_1 and pK_2 for *dl*-TA at 25° were in excellent agreement and it was decided repetition at all temperatures would be superfluous. Other pK values available in the literature are in excellent agreement.[2] From King's compilation[10] of the errors propagated to the thermodynamic parameters based upon the precision in the measured pK and the experimental temperature range, the relative standard deviations in the present values are estimated to be at most 200 cal/mol in ΔH°, and 0.6 cal/(mol °K) in ΔS°.

Discussion

The data in Table I clearly show that some significant differences exist for equilibria which, from ΔG° data alone, might otherwise have been expected to be equivalent. The factors which operate to produce these results are numerous and any interpretation is at best speculative. In the subsequent discussion we have attempted to use a minimum of assumptions to arrive

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at a consistent interpretation of the results. Different inductive effects of $-CH_3$ and $-OH$ undoubtedly contribute to the contrasting ionization parameters when DMSA is compared with TA. However, these effects are equivalent when the isomers of the same acid are considered. This second comparison is the more interesting and it is discussed at greater length.

The first point to notice is that for TA all ionizations are more extensive than for the corresponding ionizations from DMSA. Without exception the relative strength is imparted to the ionization process by a much more favorable entropy change.[11] This is emphasized by the fact that all enthalpies of ionization are positive for TA and negative for DMSA. Negative $\Delta S°$ values are indicative of electrostriction of the solvent by the ions, an effect which probably exceeds all others in magnitude. For DMSA the larger negative $\Delta S°$ values are partially compensated by a negative $\Delta H°$ so that the resultant $\Delta G°$ values are not too significantly different from the corresponding TA values. Superimposed on this structural reorganization are the lesser relative inductive effects due to substitutents.

Laidler[12] has made the point that if entropy changes are constant and $\Delta H°$ values vary the origin of the effect is quantum mechanical. When comparing the isomers of the same acid inductive effects are equivalent and, of course, resonance effects are absent. The remaining effect of significance is a steric effect which may involve solvent participation. Hydrogen bonding between carboxylic acid groups in the monoanion has been invoked to account for large differences in pK_1 and pK_2 for dicarboxylic acids, the extra stability of the monoanion strengthening the first ionization and concomitantly weakening the second ionization. Usually, however, the molecular structure is more rigid[13] than in the present examples and here $(pK_2 - pK_1) < 4$. We prefer not to commit ourselves, nor to limit our arguments, to only intramolecular hydrogen bonding but rather to think of the steric effect as something more abstruse and call it the "proximity effect." Contributing to this overall effect are cooperative solvation between functional groups on adjacent carbon atoms, electrostatic repulsion of $-COO^-$ groups, and steric hindrance, all of which may operate but to a greater or lesser extent as a function of the degree of ionization. Depending upon one's prejudices the concept of cooperative solvation could be replaced by intramolecular hydrogen bonding. The one distinction is the distance between the electronegative atom centers.

Within experimental error the thermodynamic parameters for first ionizations from the *dl* and meso forms of each acid are identical. The less negative $\Delta S°$ values for TA are indicative of there having been more structure in the diacids than in the undissociated isomers of DMSA. This is perhaps an illustration of cooperative solvation between the polar $-OH$ and $-COOH$ functional groups which when disturbed results in a net positive $\Delta H°$ and a positive contribution to the entropy change for both isomers.

The greatest contrasts of all in thermodynamic parameters are found for the second ionizations. For DMSA $\Delta G°$ (*dl*) > $\Delta G°$ (meso) while the reverse is true for TA, and $\Delta H_2°$ values for isomers of the same acid differ by more than 1 kcal/mol. It is possible to account for these differences using a not too unacceptable structural model for all four monoanions. In this model the $-COOH$ and $-COO^-$ groups are assumed to be locked in the eclipsed conformation through cooperative solvation which is considered to be the predominant intramolecular interaction. Electrostatic repulsion will intercede on the removal of the second proton with the following consequences. In *dl*-TA the preferred dianion conformation is reached when each $-OH$ group eclipses a $-COO^-$ group; only one such arrangement is possible for *meso*-TA. Both ionizations should be accompanied by a relatively small $\Delta S°$, since intramolecular interactions reduce the extent of solvation, but the $\Delta H°$ for the *dl* isomer should be less positive, which is observed. Steric interaction probably complements electrostatic repulsion to determine the preferred conformation in DMSA dianions. The fully staggered arrangement, with $-CH_3$ and $-COO^-$ groups as far removed from each other respectively, is possible in only the meso isomer, as evidenced by the more negative $\Delta H°$ (meso). The very negative $\Delta S_2°$ values are consistent with a lack of intramolecular interactions and more extensive solvation in the dianions of DMSA relative to TA.

It is conceivable that the isomers will complex with metals, etc., with some important differences which may contribute to reaction specificity. This subject will be taken up in further work. As to the ionization properties of polymeric polycarboxylic acids, it seems that first ionizations could be treated independently of the isomer ratio and the electrostatic work function model would be sufficient to describe the process. This is not necessarily true for second ionizations where it is known that the variation of pK_2 with degree of ionization is greater. The pH dependence is frequently described by a linear equation, $pH = pK_i + n_i \log [\alpha/(1 - \alpha)]$. n_i for first ionizations is usually one but it is greater than two for second ionizations.[14]

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