Rate of Decarboxylation of Benzisoxazole-3-carboxylate Ions as a Probe of Solvation in Biological and Other Media

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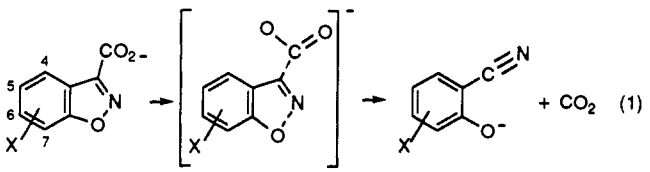
Abstract: The influence of solvent donor–acceptor properties and polarity on the rates of decarboxylation of benzisoxazole-3-carboxylate ions is analyzed with the unified solvation model. When the dissolved species is a separated ion pair, solvent polarity decreases the rate. When an equilibrium exists between an ion pair and the dissociated ion pair, solvent polarity and donor strength increase the rate by increasing the extent of dissociation. Hydrogen bonding to the carboxylate functionality causes a significant decrease in rate. When using this probe to measure the solvation properties of solvents, micelles, polymers, or biological assemblies, these different effects must be sorted out to interpret the influence of the medium on the observed rate. The unified solvation model provides a means of sorting out these various contributions.

Introduction

The rate of decarboxylation of benzisoxazole-3-carboxylate anions (Bzco), eq 1, varies by 8 orders of magnitude in water and aprotic solvents.[1] As a result of the medium sensitivity, this



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reaction has been suggested as a probe of medium effects in micelles, bilayers, macrocyclic hosts, polymers, and catalytic antibodies.[2-10] In the latter example,[9,10] the reaction rate is accelerated 19 000 times compared to that of water. Our main concern will be with the reactant carboxylate with the tetramethylguanidinium countercation ($TMGH^+$).[1]

A variety of effects have been reported to influence the rate of the decarboxylation reaction. On the basis of results from solvent extraction studies, Kemp[1] proposed that dispersion interactions slow the rate by stabilizing the charge-delocalized transition state.[1b] The decarboxylation reaction rate is decreased in hydrogen bonding solvents. Ion pairing between the carboxylate and the cation also has been shown to be a factor when additions of alkali metal salts significantly decreased the decarboxylation rates in acetonitrile solvent.[1] On the other hand, addition of Li^+, Na^+, or K^+ had little effect on the rate in DMSO. These results suggest that ion pairing occurs in CH_3CN but is negligible[1] in DMSO. The rate trends observed in aprotic solvents have been attributed to ion pairing and not dispersion interactions with the transition state by Smid and co-workers.[2] In ether solvents, the[1] observed rates result[2] via very low concentrations of the free carboxylate anions present.

Kemp attempted to correlate the observed rate data in a large variety of solvents to $E_T(30)$ and Z solvatochromatic parameters[11] but was unsuccessful.[1] A more orderly correlation of the data occurred between the rate and an electronic transition of the reaction product (a parameter they refer to as H).[1] The correlation is less than satisfying as the solvents are assigned to three nearly parallel lines. No reason nor insights are given about the relationship of the solvent sensitivity of the reaction to the electronic transition of the products.

A recent attempt to unravel the complexity of the multiple solvent effects on this rate was reported[10] in an attempt to better understand the medium that exists in catalytic antibodies. The multiparameter methods[12] of Kamlet, Abboud, Abraham, and Taft (KAAT) were employed.

In order to apply Bzco as a probe to provide information about medium effects in complex media, the influence of solvent polarity, ion pairing, and hydrogen bonding on rates needs to be understood. In this article we report an analysis using the unified solvation model (USM),[13] which provides a more complete picture and resolves some of the conflicting literature reports about the solvent influence on this probe. USM considers the physicochemical measurement in the absence of solvation and uses independently determined parameters to account for each of the individual energy contributions that influence the reaction under the conditions measured.

When probes undergo solvent shifts from nonspecific solvation with no donor–acceptor contribution, the data are fit to eq 2. In

$$\Delta\chi = S'P + W \qquad (2)$$

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Table 1. Rate Constants for 6-Nitrobenzisoxazole-3-carboxylate Ions in Several Solvents

no.	solvent (C/E)	E_B (or E_A')	C_B (or C_A')	S'	k (s^{-1})	ln(k)
1	CCl_4	0	0	1.49	1.5×10^{-3}	-6.50
2	C_6H_6 (0.64)	0.70	0.45	1.73	4.8×10^{-3}	-5.34
3	$(C_2H_5)_2O$ (0.91)	1.80	1.63	1.73	0.090	-2.41
4	$(CH_3O)_2CH_2$ (DMM)			1.88[a]	0.036	-3.32
5	$O(CH_2CH_2)_2O$ (diox) (0.69)	1.86	1.29	1.93	0.040	-3.22
6	$(CH_2)_4O$ (THF) (1.3)	1.64	2.18	2.08	4.0	1.38
7	$(CH_3OCH_2CH_2)_2O$ (diglyme)			2.22[b]	5.0	1.61
8	$[(CH_3)_2N]_3PO$ (HMPA) (0.53)	2.87	1.52	2.52	700	6.55
9	$(CH_3)_2CO$ (0.72)	1.74	1.26	2.58	24	3.18
10	$CH_2CH_2CH_2CONCH_3$ (NMP) (0.78)	2.14[c]	1.66[c]	2.62	250	5.52
11	C_6H_5CN (0.45)	1.65[c]	0.75[c]	2.63	2.5	0.92
12	$CH_3CON(CH_3)_2$ (DMA) (0.56)	2.35	1.31	2.70	160	5.08
13	$HCON(CH_3)_2$ (DMF) (0.60)	2.19	1.31	2.80	37	3.61
14	$(CH_2)_4SO_2$ (sulfolane)			2.88	64	4.16
15	$(CH_3)_2SO$ (DMSO) (0.61)	2.40	1.47	3.00	10	2.3
16	CH_3CN (0.43)	1.64	0.71	3.00	2.9	1.06
17	CH_3NO_2			3.07	0.58	-0.54
18	$CHCl_3$ (0.28)	(1.56)	(0.44)	1.74	8.0×10^{-4}	-7.13
19	CH_2Cl_2 (0.13)	(0.86)	(0.11)	2.08	0.047	-3.06
20	C_2H_5OH (0.9)	(1.33)	(1.23)	2.80	1.0×10^{-3}	-6.91
21	CH_3OH (1.0)	(1.55)	(1.59)	2.87	2.5×10^{-4}	-8.29
22	$HCONH_2$ (1.2)	(1.13)	(1.35)	3.13	7.4×10^{-4}	-7.21
23	H_2O (0.9)	(1.91)	(1.78)	3.53	7.4×10^{-4}	-11.81
24	$HCONH(CH_3)$ (NMF) (2.1)	(0.22)	(0.47)	3.63	8.1×10^{-3}	-4.82

[a] Not included in the fit and calculated from $(E_T(30) - 19.63)/8.61$. [b] Not included in the fit and average value calculated from $E_T(30)$ and $(\delta^{31}P + 8.91)/5.09$. [c] Tentative value.

eq 2, $\Delta\chi$ is the solvent shift, S' is the solvent polarity parameter, P is the probe sensitivity and W is the value of the property at $S' = 0$. When the reaction is studied in a polar, donor solvent, solvent polarity and donor–acceptor interactions can influence $\Delta\chi$. The former is accommodated by eq 2. Donor–acceptor interactions involving the donor solvent are accommodated with the electrostatic–covalent model E_B and C_B parameters.[14] The sum of these two effects is given in eq 3. E_A^* and C_A^* are the acceptor parameters for the acceptor probe.

$$\Delta\chi = E_A^* E_B + C_A^* C_B + S'P + W \qquad (3)$$

Most of the donor–acceptor parameters are enthalpy based. Unusual entropy effects can cause deviations in a data fit so the existence of such contributions can be recognized when free energies or free energy related quantities are correlated with enthalpy based parameters.[14]

Measured values of $\Delta\chi$ lead to a series of equations consisting of one for each measured value. Reported values[14] for the solvent's electrostatic bond forming tendencies, E_B, and covalent bond forming tendencies, C_B, as well as the solvent polarity, S',[13c] are substituted into each equation. The series of equations in the different solvents are solved for four unknowns: the reactive probes electrostatic, E_A^*, and covalent, C_A^*, bond-forming tendencies, as well as the probes susceptibility to solvation, P, and intercept, W. The definition of the minimum is best obtained by including measurements from solvents that do not undergo donor–acceptor interactions.

When a reaction is studied in acceptor solvents,[13c] the interactions are accommodated with

$$\Delta\chi = E_A' E_B^* + C_A' C_B^* + S'P + W \qquad (4)$$

The terms have the same meaning as in eq 3. The reported E_A', C_A', and S' values of acceptor solvents[13c] are substituted into the equations for each measured $\Delta\chi$, and a series of equations for the different acceptor solvents are solved for the probe basicity parameters E_B^*, and C_B^*, the susceptibility of the probe to solvation, P, and the intercept, W.

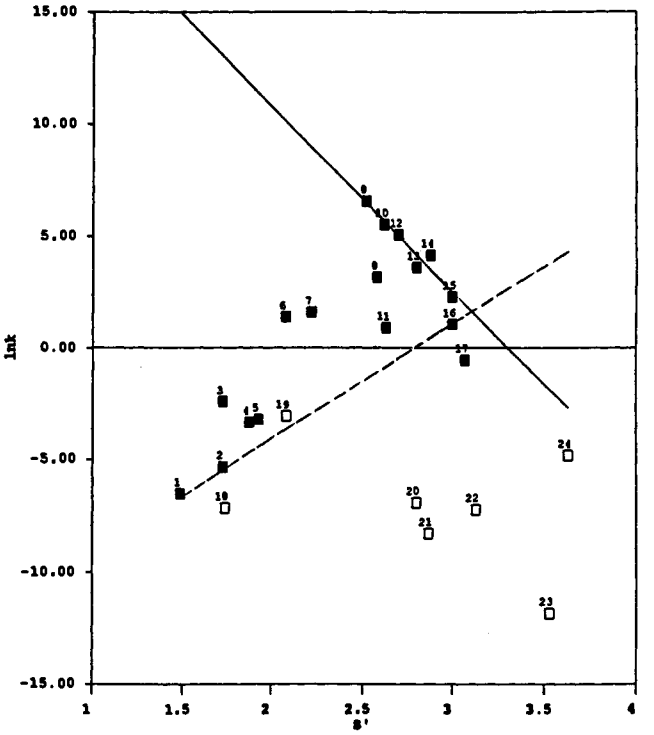

Figure 1. Plot of the natural log of the decarboxylation rates vs S'. Closed squares are for aprotic solvents; open squares are for protic solvents. Label numbers match those in Table 1. The solid line is a plot of eq 6 and the dashed line a plot of the $S'(5.15) - 14.35$ component of eq 7.

Results and Discussion

Contributing Solvation Effects. The values of k and $\ln(k)$ for the decarboxylation of $TMGH^+RCO_2^-$ in various solvents and the reported solvent S' values of the solvents are given in Table 1. A plot of $\ln(k)$ vs S' is shown in Figure 1. The significance of the lines drawn in this figure will be discussed shortly. Despite a poor plot, as reported for E_T and Z value correlations, several

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Table 2. Solvents from the Dissociated Ion Pair Category Fit to Eq 6

no.[a]	solvent	$\ln(k)_{exptl}$	$\ln(k)_{calcd}$[b]
8	$[(CH_3)_2N]_3PO$ (HMPA)	6.55	6.46
10	$CH_2CH_2CH_2CONCH_3$ (*N*-Methylpyrrolidone) (NMP)	5.52	5.64
12	$CH_3CON(CH_3)_2$ (DMA)	5.08	4.98
13	$HCON(CH_3)_2$ (DMF)	3.61	4.15
14	$(CH_2)_4SO_2$ (sulfolane)	4.18	3.50
15	$(CH_3)_2SO$ (DMSO)	2.30	2.51

[a] Numbers correspond with those in Table 1. [b] Calculated using $P = -8.24$ and $W = 27.24$. $\bar{x} = 0.29$ and % fit = 6.8.

of the reported aspects of solvent influences are evident from the plot. Hydrogen bonding solvents cause a pronounced decrease in the rate. The rate is also slowed by ion pairing in poorly solvating solvents. There are several aprotic and protic solvents which have similar S' values but vastly different rates. For example, the rate in THF is 100 times as fast as the rate in CH_2Cl_2 (numbers 6 and 19) and the rate in DMF is nearly 40 000 times as fast as that in ethanol (numbers 13 and 20).

Aprotic Solvents. In order to interpret the solvent effects on eq 1, the influence of the aprotic solvents on the ion-pairing equilibrium, eq 5, will be considered first. Two distinct solvent

$$RCO_2^-TMGH^+ + xS \rightleftharpoons RCO_2(S)_y^- + TMGH(S)_z^+ \quad (5)$$

properties cause any ion pair to dissociate: increased solvent donor strength and increased polarity. Donor solvents compete with the carboxylate in hydrogen bonding to the ammonium ion. Polar solvents nonspecifically solvate the cation and anion. Dissociation of the ion pair increases the rate because ion pairing, which in this case also involves a hydrogen bonding interaction of the carboxylate functionality with the N-H proton, tends to localize the electron density on the carboxyl groups stabilizing the ground state. This stabilization inhibits the transfer of charge to form a neutral CO_2 molecule (eq 1). Polar solvents also nonspecifically solvate the carboxyl group in the anion and in the ion-pair, stabilize the ground state and are expected to slow the rate.

In donor solvents where the ion pair is not extensively (>90%) dissociated, solvent donor strength dissociates the ion pair by coordination to the cation, and this is treated with the $E_AE_B + C_AC_B$ term of eq 3. The influence of solvent polarity in nonspecifically solvating the carbonyl group is less effective than its influence on the extent of ion pairing. Thus in weakly solvating solvents where the dissociation of the ion pair is not complete, the decrease in ion pairing with an increase in solvent polarity leads to a net P value for eq 3 from these two effects that is positive (a large positive contribution from the increased amount of dissociated ion pairs produced from the solvent polarity and a smaller negative value from nonspecific solvation of the dissociated anion). When the combined effects of solvent polarity and basicity are large enough to cause nearly complete separation of the ion pair, further increase in solvent polarity will cause a decrease in the rate and the value of P will be negative. In this region, any increase in the solvent donor strength has no influence on the rate. Thus, measurements in this solvent will be treated with eq 2 and both the value and the sign of P will differ from that in eq 3. In those solvents where the ion pair is fully dissociated, an increase in solvent polarity leads to a solvent effect that is in keeping with the Hughes–Ingold rules for medium effects on a reaction proceeding from a reactant with a charge localized on the carboxyl group to a charge-delocalized transition state (eq 1).

Solvents 8, 10, 12, 13, and 15 have strong basicity and high polarity. In these solvents, the solute exists as a dissociated ion pair and the observed rates are dominated by nonspecific solvation. Accordingly these systems are fit to eq 2. Preliminary results indicated that solvent 14 is also in this category. Accordingly

Table 3. Solvents from the Ion Pair Category Fit to Eq 7

no.[a]	solvent	$\ln(k)_{exptl}$	$\ln(k)_{calcd}$[b]
1	CCl_4	−6.50	−6.68
2	C_6H_6	−5.34	−5.06
3	$(C_2H_5)_2O$ (ether)	−2.41	−2.68
4	$(CH_3O)_2CH_2$ (dimethoxymethane)	−3.32	(−2.17)[c]
5	$O(CH_2CH_2)_2O$ (dioxane)	−3.22	−3.04
6	$(CH_2)_4O$ (THF)	1.39	1.48
7	$(CH_3OCH_2CH_2)_2O$ (diglyme)	1.61	(−1.77)[c]
9	$(CH_3)_2CO$	3.16	(0.42)[d]
11	C_6H_5CN	0.92	(−1.07)[d]
16	CH_3CN	1.06	0.70
17	CH_3NO_2	−0.54	0.48[e]

[a] Numbers correspond with those in Table 1. [b] Calculated using $E_A^* = -1.86$, $C_A^* = 3.75$, $P = 5.15$, and $W = -14.35$. $\bar{x} = 0.34$ and % fit = 4.3. [c] Solvents were not used in the data fit because E_B and C_B values are not available. The number is calculated using the S' for the solvent and E_B and C_B values for $(CH_3)_2O$ for dimethoxymethane and E_B and C_B values for $(C_2H_5)_2O$ diglyme. [d] Solvents were not used in the data fit. Calculated from resulting parameters and solvent, E_B, C_B, and S' values. [e] E_B and C_B values for nitromethane were estimated from nitrobenzene's values (from ref 14). A lower weight was assigned to nitromethane in the data fit. The deviations observed are due to the uncertainity in the E_B and C_B values.

systems 8, 10, and 12–15 were fit to eq 2, providing eq 6 for

$$\ln(k) = S'(-8.24) + 27.24 \quad (6)$$

solvents that are basic enough and polar enough to dissociate the ion pair completely. The $\ln(k)$ values calculated for all of the solvents that are assigned to this category are given in Table 2 and connected by the solid line in Figure 1. Note that all the aprotic solvents besides those in Table 2 fall below the line for eq 6 shown in Figure 1. When $\ln(k)$ values for some weakly basic, polar solvents are calculated with eq 6, the following results given as solvent/$\ln(k)_{exptl}$/$\ln(k)_{calcd}$ are found: $(CH_3)_2CO$/3.18/5.79; C_6H_5CN/0.92/5.56; CH_3CN/1.06/2.51; CH_3NO_2/−0.54/1.43. In these weakly basic solvents, lower rates than calculated occur because some of the probe exists as an ion pair. Thus, in spite of a large S', the weak basicities of solvents 11, 16, and 17 lead to conditions that do not fully dissociate the ion pair. Acetone is weakly basic and moderately polar.

The next set of data considered are measured in low polarity, donor solvents that do not completely dissociate the ion pair. Solvents 1–7 (Table 1) clearly belong in this ion pair category (the "left" side of Figure 1 ($S' < 3.2$), along with solvents 16 and 17, which were not fit by eq 6. The $\ln(k)$ values for the donor solvent, ion pair category are fit to eq 3 using the reported E_B, C_B, and S' values for the solvents. The data fit for solvents 1–7, 16, and 17 to eq 3 result in eq 7. The data fit is given in Table

$$\ln(k) = -1.86E_B + 3.75C_B + S'(5.15) - 14.35 \quad (7)$$

3. The nonspecific solvation component of this eq (*i.e.* $5.15S' - 14.35$), given by the dashed line in Figure 1, illustrates the importance of the donor–acceptor component by the deviation of an ion-paired point from this line. The E_A^* and C_A^* parameters for this system are poorly determined because of the limited range of the C_B/E_B ratio of the solvents studied.[14] The parameters should not be used to predict $\ln(k)$ for donor solvents whose $C_B/$

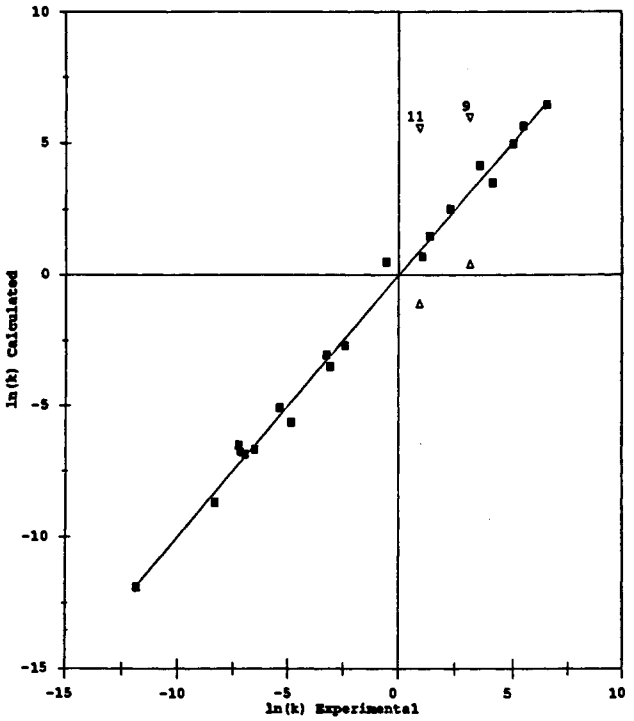

Figure 2. Plot of calculated ln(k) vs the experimental ln(k). The line is the ideal case. The △ and ▽ symbols represent the calculated values for solvents 9 and 11 using eqs 6 and 7, respectively.

E_B ratio is outside the range 1.3–0.4. Accurate predictions are expected for solvents in this range. Future studies should involve solvents that extend this range.

The values for ln(k) are calculated for HMPA and sulfolane (solvents 8 and 14) using eq 7 and give HMPA/6.55/–1.02 and sulfolane/4.18/0.47. Note the very low predicted value. These solvents belong to the fully dissociated ion pair category and cannot be treated by the P and W values for the ion-paired systems where P is a combination of the anion nonspecific solvation and decreased ion-pairing influences.

Solvents 4 and 7 can be used to illustrate the qualitative insights that can be obtained with the USM. The value of ln(k) for dimethoxymethane is calculated with S' for this solvent and E_B and C_B for $(CH_3)_2O$. If the $-CH_2OCH_3$ group were to lower the basicity of $(CH_3)_2O$ enough to reduce C_B from 1.5 to 1.2, the ln(k) value would be predicted accurately. On the other hand, diglyme is much more effective at ion pair dissociation than the diglyme S' and the enthalpy-based parameters of diethyl ether would predict. Five-membered ring formation is possible with diglyme along with the ensuing chelate stability from enthalpy and entropy effects.

The combined fit of aprotic solvent data with the appropriate equation is illustrated in Figure 2. Acetone and benzonitrile are the only aprotic solvents that do not correlate with either eq 6 or eq 7 (Tables 2 and 3). With eq 6 they are overpredicted ($\ln(k)_{calcd} > \ln(k)_{exptl}$), and with eq 7 they are underpredicted ($\ln(k)_{calcd} < \ln(k)_{exptl}$). Benzonitrile is less polar but of similar donor strength (E_B and C_B) to acetonitrile. If benzonitrile is assigned to the ion-paired category, the E_B and C_B parameters are uncertain enough to account for the deviation observed. Acetone's deviation from both equations suggests that some solvents exist which do not belong to either category but constitute a transition region from one category to the other. The P value for the ion pair category is the net of a linear change from ion pair dissociation brought about by solvent basicity and polarity and a linear change in the opposite direction from nonspecific solvation of the anion. Once the basicity and polarity are sufficient to fully dissociate the ion pair, further increases in E_B, C_B, and S' lead to predicted values with eq 7 that are too small. All solvents in the dissociated ion pair category give predicted values that are too small. Acetone behaves as a dissociated ion-pair in the fit to eq 7. However, when acetone is correlated with eq 6, it deviates in the same direction as all the ion-paired systems. Thus, acetone has a combination of basicity and polarity that leads to too large a fraction of dissociated ion pairs to be treated with the linear change in dissociation and anion solvation required for eq 7 but not dissociated completely enough to be treated by eq 6.

So far the USM has accounted for two of the contributions to the observed[1] solvent sensitivity of this reaction, ion pair effects and nonspecific solvation of the anion. When the former effect is dominant, the solvent will be fit by eq 7, and when anion solvation is more important, eq 6 will fit the solvent. In both equations the W term is the value of ln(k) in a solvent which has no specific or nonspecific interactions with the solute (*i.e.*, E, C, and S' are all zero). In the case of eq 7, W is the rate at which the nonsolvated ion pair would react. In this case $k = \exp(W) = 5.9 \times 10^{-7}$. The ability of the solvent to break up the ion pair increases the rate from this point. In the case of eq 6, the W value is the ln(k) for the completely dissociated nonsolvated carboxylate anion. For this case $k = \exp(W) = 7.5 \times 10^{11}$. As the polarity of the solvent increases, the charged carboxylate group is stabilized compared to the charge-delocalized transition state and the rate is decreased from this point.

The impact of these two competing mechanisms can be seen graphically by considering the two lines in Figure 1. The better the donor in the ion pair solvents the greater the deviation from line generated by S'P + W from eq 7 toward the line generated from eq 6. This is exemplified by benzene and ether (2 and 3). Both solvents have identical S' values, but ether is a much better donor. The transition zone (*i.e.*, the place were the nonspecific solvation interactions dominate over ion-pairing interactions) occurs at $2.5 < S' < 3.1$. This varies with solvent donor strength. All the aprotic solvents that are in the dissociated ion pair category fall in this range. Because of weak donor strength, acetonitrile and nitromethane are in the ion pair category and acetone is transitional. The intersection of the two lines occurs at $S' = 3.11$. An interesting prediction is made by USM. Strong donor, poorly solvating solvents that completely dissociate the ion pair will lead to the fastest reactions. In this context, it would be of interest to carry out the reaction in pyridine and triethylamine to determine if they belong to the fully dissociated category.

The mixed solvents systems studied by Kemp are readily understood with the USM interpretation of the data. When increasing amounts of DMSO are added to diglyme, acetonitrile, and benzene, the rates improved significantly after only small additions (<2 M [DMSO]). DMSO provides the donor strength to break up the ion pair in the weak donor, polar solvent. It is anticipated that a strong donor that is nonpolar would behave in a manner similar to that of DMSO in weakly basic polar solvents. When DMSO is added to diglyme and benzene, the rates in several of the solvent mixtures are faster than found in either pure solvent. In these solvent mixtures the ion pair is dissociated by the DMSO without the retardation from the solvent polarity of pure DMSO.

Protic Solvents. The next contribution for solvent influence on the rate is hydrogen bonding of the carboxylate anion by protic solvents.[1] The specific and nonspecific interactions of the solvent with the reactant are illustrated in eq 8. The predominant

$$TMGH^+RCO_2^- + xHX \rightleftharpoons RCO_2(HX)_x^- + TMGH(HX)_x^+ \quad (8)$$

contribution from specific solvation involves hydrogen bonding to the carboxylate group. As was previously mentioned, protic solvents with similar S' values to those of aprotic solvents have rates which are orders of magnitudes slower. Further, the 4-OH derivative of benzisoxazole-3-carboxylate, which is intramolecu-

Table 4. Fit of the Specific Solvation Component in Protic Solvents

no.[a]	solvent	$\ln(k)_{spc}$ (exptl)[b]	$\ln(k)_{spc}$ (calcd)[c]
18	$CHCl_3$	−1.73	−1.36
19	CH_2Cl_2	0.59	0.15
20	C_2H_5OH	−6.97	−6.92
21	CH_3OH	−8.71	−9.12
22	$HC(O)NH_2$	−8.64	−7.94
23	H_2O	−9.95	−10.03
24	$HC(O)NHCH_3$	−2.13	−2.94

[a] Numbers correspond with those in Table 1. [b] $\ln(k)_{spc}$ is $\ln(k) - (SP' + W)$. [c] Calculated using $E_B^* = 1.03$ and $C_B^* = -6.74$. $\bar{x} = 0.49$ and % fit = 4.6.

larly hydrogen bonded, decarboxylates slowly in all solvents.[1] Large solvent effects were observed[1] for the 6-OH and 6-OCH_3 derivatives. These results show that specific hydrogen bonding of the solvent with the carboxylate slows the rate as expected for reactant stabilization.

The influence of a specific hydrogen bonding interaction on $\ln(k)$ will be accommodated by eq 4 using the reported E_A' and C_A' values for protic solvents. The question arises about which set of P and W values (fully dissociated ion pair eq 6 or ion-paired eq 7) should be used to fit the nonspecific portion of the solvation in hydrogen bonding solvents. Clearly, CH_2Cl_2 and $CHCl_3$ are solvents in which ion pairing exists and H_2O and $HC(O)NHCH_3$ have basicity and polarity to fully dissociate the ion pair. The assignment of the alcohols and formamide to the ion pair or fully dissociated category is uncertain.

This data is fit by calculating the $S'P + W$ portion with the appropriate ion-paired or dissociated ion pair parameters and subtracting this contribution from $\ln(k)$. The remaining portion, $\ln(k) - (S'P + W)$, was fit to the $E_A'E_B + C_A'C_B$ portion of eq 4. Initial data fits which included the alcohols and formamide in each group indicated that the alcohols were better fit using the P and W values for associated ion pairs (eq 7), while formamide is fit better by values for the fully dissociated ion pair (eq 6). The results of the final data fit are given in Table 4 and yield $E_B^* = 1.03$ and $C_B^* = -6.74$ or eq 9. These E_B^* and C_B^* values indicate

$$\Delta\chi = 1.03E_A' - 6.74C_B' + S'P + W \qquad (9)$$

that covalency in the hydrogen bonding interaction dramatically reduces the rate. The delocalization of the carboxylate electron density via covalency in the hydrogen bonding interaction lowers the energy of the ground state and increases the energy for electron transfer out of the CO_2 functional group. This proposal is supported by the activation parameters reported by Kemp.[1] The $\Delta H^{\ddagger}$ value in water is 7–9 kcal/mol greater than in acetonitrile, DMSO, or HMPA (25, 24, and 23 kcal/mol, respectively).[1] The rate in water predicted by the nonspecific solvation, $S'P$ term, alone is 0.16. The actual rate is 7.4×10^{-6} (Table 1), corresponding to a reduction of over 4 orders of magnitude (~21 000 times) due to the hydrogen bonding by water. Again, the E_B^* and C_B^* parameters are poorly determined and predictions are limited to solvents whose C_A'/E_A' ratio is in the range 0.1–2. This range encompasses most protonic solvents.

In summary, the USM is able to accurately predict or account for the rates in all of the solvents. A plot of the calculated vs experimental $\ln(k)$ values obtained with the relevant equations ((6), (7), or (9)) is shown in Figure 2 (solvents 4 and 7 are not included because E_B and C_B parameters are not available). Excluding benzonitrile because of the uncertainty in E_B and C_B as well as acetone, vide supra, a regression of the solid squares gives a slope of 1.00 (±0.02) and an intercept of 0.01 (±0.46) with an $R^2 = 0.993$.

The most significant aspect of the USM is its use to provide a quantitative test of qualitative explanations of solvent influences on reactivity. In the above discussion, the solvents were classified according to the specific and nonspecific interactions influencing the equilibria in eqs 5 and 8. These models were then tested by a quantitative fit to eq 6, 7, or 9. The quantitative tests have provided insights and understanding not detected by other analyses. In this context a comparison can now be made with a modeling study[10] based on the KAAT approach. As will be seen, except for the obvious feature of increased rate in donor solvents and decreased rate in acceptor solvents, different insights regarding the role of the solvent result.

Comparisons of USM and KAAT Interpretations. It should be emphasized that many of the final conclusions regarding solvent effects by Grate, McGill, and Hilvert (GMH)[10] employed literature results and were not based solely on the KAAT analysis. The purpose of this section is to examine the conclusions that one would draw from the KAAT statistical results alone. The $\log_{10}(k)$ for a group of 20 of the 24 solvents in Table 1 for which solvent parameters are available was fit[10] to eq 10 of the KAAT

$$\Delta\chi = \text{constant} + (S\pi^* + d\delta) + a\alpha, +b\beta_1 + h(\delta_H^2) \qquad (10)$$

model. A fair fit of the experimental values results (the correlation coefficient is 0.976). No immediate insight is provided about the solvation mechanism for this group of solvents called group A. The KAAT approach recommends using a "judicious selection" of solvent subsets to see if it is possible to improve the data fit of the subset with a smaller number of parameters. Sets of solvents were removed[10] in four increments. The first solvents that were removed were those with the least ability to solvate and separate the ion pairs (1, 2, 3, and 5). The remaining solvent set was called group B. This set of 16 solvents gave parameters similar to those of group A and a better fit (the correlation coefficient is 0.985 for the remaining solvents).[10] Solvents 6, 18, and 19 are removed from subset B to get solvent set C. Note at this point that all of the solvents from the left hand side of Figure 1 are eliminated and the remaining solvents (except for solvent 14, vida supra) are being analyzed. With subset C, the intercept and polarity contribution change sign (negative to positive) and these two parameters as well as the cavity term became statistically equivalent to zero. The correlation coefficient for this subset improves to 0.988.[10] For the final two solvent subsets, benzonitrile and acetone are removed to produce set D and E, respectively. At this point the only statistically non-zero contributions are the solvent acceptor and donor properties, respectively. The correlation coefficient for both sets is 0.988.[10]

The five solvent sets were refit using only donor, acceptor, and intercept parameters. The correlation coefficients ranged from 0.906 (for A) to 0.987 (for D and E). GMH conclude that the two-parameter equation provided a good statistical fit of the reaction in all but the weakly polar solvents (those solvents thrown out to make set C). The two-parameter equation predicts that solvents 1, 2, 3, 5, 6, 18, and 19 are all faster than observed with some of the aprotic solvents having a predicted rate that is 2–3 orders of magnitude faster than observed.

The interpretation of the solvent influence on rate is based on either the five-parameter fit to solvent set A (A5) or the two-parameter fit to solvent set C (C2)[10] as well as the trends in the parameters. Group A (A5) indicates that, among the aprotic solvents in the entire data set, there is a clear trend of increasing rate with increasing solvent polarity.[10] As the solvent set is reduced, however, the solvent polarity term becomes statistically zero, leading to the conclusion that solvent basicity has the dominant influence on the rate. The KAAT interpretation of the C2 fit of the data would be no solvent polarity dependence. It follows that one would assume solvent basicity to be the most important property that increases the rate by dissociating the ion pair. This interpretation requires that ion pairs exist in the basic polar solvents that were classified as dissociated in the USM analysis. Once the solvent is basic and polar enough to dissociate the ion pair, eq 6 results in the USM treatment with no basicity component. The USM conclusion is supported by the report that

the addition of cations to DMSO has no influence on the rate. Focusing on basicity as the important parameter[10] leads to inconsistencies for aprotic solvents with similar basicities. NMP, DMA, and DMSO all have similar β parameters (0.76, 0.77, and 0.77, respectively, and $\alpha = 0$), yet the rate in NMP is 50% faster than the rate in DMA, which is 16 times faster than that in DMSO (Table 1)! Also, the rate in DMF ($\beta = 0.69$) is four times that of DMSO.

Kemp's mixed solvent system data (vida supra) showed that a benzene–DMSO mixture had a faster rate than either pure solvent.[1] This result which was explained with USM also contradicts the absence of a solvent polarity effect.

The GMH analysis identifies hydrogen bonding by the solvent as the largest single factor influencing the decarboxylation rates. This conclusion results from every data fit using either the five- or two-parameter equation. This obvious conclusion is a common result for both GMH and the unified solvation model. It is important here to stress a major difference in the two models when it comes to hydrogen bonding by the solvent. In the KAAT model, nitromethane, acetonitrile, and acetone are considered hydrogen bonding acids ($\alpha = 0.22$, 0.19, and 0.08, respectively). In fact, nitromethane's α value is similar to that of an established hydrogen bonding solvent dichloromethane ($\alpha = 0.30$). There is no unambiguous thermodynamic or spectroscopic data, including that referenced by GMH, to substantiate that nitromethane, acetonitrile or acetone can behave as a hydrogen bonding acid to any donor with basicity comparable to that of a carboxylate. In the unified solvation model, nitromethane, acetonitrile, and acetone are considered to be only capable of specific interactions as donors. Donors of moderate strength in these solvents are only involved in nonspecific solvation. This important distinction can be seen with the solvents dioxane ($\alpha = 0, \beta = 0.37$), benzonitrile ($\alpha = 0$, $\beta = 0.37$), and acetonitrile ($\alpha = 0.19$, $\beta = 0.37$). The unified solvation model correctly predicts the correct order for the rates (Table 3). The GMH (C2) analysis predicts that dioxane ($\log(k)_{exptl} = -1.39$, $\log(k)_{calcd} = 1.11$) is equal to benzonitrile ($\log(k)_{exptl} = 0.40$, $\log(k)_{calcd} = 1.11$), which is greater than acetonitrile ($\log(k)_{exptl} = 0.46$ $\log(k)_{calcd} = 0.02$).

USM Interpretation of the Solvation Properties of Antibodies. An important application of the effect of different solvents on the rate of the decarboxylation reaction is to further understand the reactivity of the monoclonal antibody 21D8.[9] Desolvation of the substrate and transition state by the active site of an enzyme is generally believed to accelerate the rate in enzymes.[15] Therefore, understanding the solvent influence on the rate of decarboxylation will yield insight into the mechanism of rate acceleration by the active site.

In order to interpret the reactivity in the monoclonal antibody, it is important to appreciate some of the evidence available. First of all, the structure of antibody 21D8 is not known. Experiments with fluorophores that bind to the catalytic site demonstrate that the aqueous solvent shell is stripped from the substrate when it is bound and that the bound substrate is not accessible to small probe ions or molecules.[9] Since the antibody was only successfully isolated after immunizations with negatively charged haptens, it has been proposed that the binding site contains protonated lysine or protonated arginine residues.[9] The rate of the decarboxylation reaction is 19 000 times faster in the antibody than the rate in water ($k \approx 0.14$).[9] The carbon kinetic isotope effect was measured for the uncatalyzed reaction in aqueous media, for the reaction in mixtures of dioxane and water (from 0 vol % of water to 100% water), and for the protein catalyzed reaction.[16] The isotope effects under all three conditions were similar, indicating that carbon–carbon bond cleavage is fully rate limiting (*i.e.*, the structure of the transition state for this decarboxylation does not change significantly for these different conditions).[16]

Using the conclusions based on the two-parameter model (C2) and the above evidence, it was suggested[10] that the positively charged amino acid residue hydrogen bonds to the carboxylate. A positive charge in the binding site is necessary to provide the binding energy to overcome the loss of solvation energy when the carboxylate is transferred out of water.[10] The hydrogen bonding by the residue would also reduce the rate of the reaction. The reduction, however, would not be as drastic as that in the 4-OH compound where the hydrogen bond is intramolecular.[1,10]

The unified solvation model is consistent with the GMH conclusion but also provides alternative explanations. The binding of the substrate need not necessarily involve a charged active site (*e.g.*, ion pairing to the charged amino acid). Upon binding of the substrate to the active site, the accompanying release of water would provide an entropic driving force for the binding of the substrate. The amino acid would provide the necessary cation for charge balance. Hydrogen bonding of the cation to the carboxylate is modified further by the many amino acid residues that may be near or at the binding site which can also hydrogen bond to the cation and reduce its ability to hydrogen bond to the bound carboxylate. In this scenario, the needed positive charge for charge balance would be provided by the equivalent of a solvent-separated ion pair. The net effect is a binding site containing a dissociated ion pair. If the binding site were indeed similar in polarity to water but without the specific hydrogen bonding interaction, the rate would be greatly accelerated. Indeed the rate for water in the absence of hydrogen bonding is 0.16 (vida supra). The similarity in this value for nonspecifically interacting water and the antibody may be serendipity, but it is worth noting.

The observed rate in the antibody also could be achieved by various combinations of the binding site "solvating ability" and hydrogen bonding capability.[10] For example, an S' of 2.5 and a hydrogen bonding interaction comparable to methanol ($E_A' = 1.55$, $C_A' = 1.59$) would produce the observed rate.

Interactions that receive quantitative support for their existence in solution by the USM analysis can be applied with confidence to interpret the reactivity in the antibody. When structural information about the nature of the active site becomes available, the different explanations offered by the USM can be distinguished.

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(16) Lewis, C.; Paneth, P.; O'Leary, M. H.; Hilvert, D. *J. Am. Chem. Soc.* **1993**, *115*, 1410 and references therein.