

## Effects of Medium on Decarboxylation Kinetics: 3-Carboxybenzisoxazoles and Their Potential Use as Environmental Probes in Biochemistry

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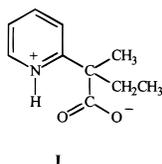
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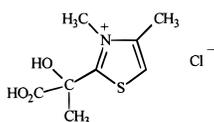
The decarboxylation rate of the tetramethylguanidinium salt of 3-carboxy-6-nitrobenzisoxazole in 24 pure solvents and 36 dimethyl sulfoxide binary mixtures with diglyme, acetonitrile, benzene, dichloromethane, chloroform, and methanol was analyzed in the light of the SPP, SA, and SB pure solvent scales. The results allow one to rationalize the high sensitivity of this kinetics to the reaction medium and to assess the potential use of this compound as a probe in biochemical environments. The natural environment for comparison of this kinetics was found to be the gas phase rather than the aqueous medium. In the latter, the process is much faster owing to such high polarity, which, however, is strongly diminished by the high acidity of the medium. Based on our calculations, the rate constant for the decarboxylation kinetics in the gas phase must be in the region of  $2 \times 10^{-10} \text{ s}^{-1}$  (i.e., 3 orders of magnitude smaller than in water).

### Introduction

In 1934, Verhoek<sup>1</sup> published the first of a series of papers in which he demonstrated that the decarboxylation kinetics of trichloroacetic,<sup>1–3</sup> trifluoroacetic,<sup>4</sup> and trinitrobenzoic acids<sup>5,6</sup> and of sodium *p*-toluenesulfonyl acetate<sup>7</sup> are first-order in the concentration of the carboxylate ion and, especially, that the decarboxylation rate is sensitive to the reaction environment. Thus, at 75 °C, sodium *p*-toluenesulfonyl acetate is decarboxylated roughly 10 times faster in ethyleneglycol ( $k = 0.481 \times 10^{-5} \text{ s}^{-1}$ ) than in water ( $k = 0.0542 \times 10^{-5} \text{ s}^{-1}$ ); also, under these conditions, trinitrobenzoate is decarboxylated about 1000 times faster in a 20:80 water/1,4-dioxane mixture ( $k = 2450 \times 10^{-5} \text{ s}^{-1}$ ) than in pure water ( $k = 2.30 \times 10^{-5} \text{ s}^{-1}$ ). Doering and Pasternak<sup>8</sup> found the decarboxylation of 2-methyl-2-(2-pyridyl)butyric acid to be faster in neutral aqueous solutions than in strongly acidic or alkaline solutions and thus identified the reactive species with a zwitterion (I). A similar conclusion was reached by Crosby et al.<sup>9</sup> in relation to the decarboxylation of 2-(1-carboxy-1-hydroxyethyl)-3,4-dimethylthiazolium chloride (II), a prototype of enzymic decarboxylation of the pyruvate–thiamine complex.



I



II

In its most simple form, the decarboxylation process involves the cleavage of a carbon–carbon bond in a

carboxylate ion to give carbon dioxide and an organic residue containing an unshared pair of electrons. As a rule, the organic product stabilizes this electron pair by delocalization, which is especially significant in enzymic reactions, where an electron sink is usually provided by a coenzyme (e.g., pyridoxal 5'-phosphate, thymine pyrophosphate), by a metal ion bound to an enzyme (typically an oxidative decarboxylase), or by a prosthetic group (e.g., a lysine amino group or covalently bound pyruvate). That decarboxylation reactions, whether catalyzed or otherwise, are especially significant in the biological and organic synthesis fields is currently a widespread perception. Consequently, any contribution to improving our understanding of these processes will be equally significant.

In some cases, the rate of the decarboxylation process depends very strongly on the particular reaction environment. Thus, the decarboxylation rate of the pyruvate–thiamine complex at 26 °C is 9000 times greater in ethanol ( $k = 0.180 \text{ min}^{-1}$ ) than in water ( $k = 2 \times 10^{-5} \text{ min}^{-1}$ ).<sup>9</sup> Kemp and Paul<sup>10</sup> demonstrated that the decarboxylation rate of the tetramethylguanidinium salt of 3-carboxy-6-nitrobenzisoxazole at 30 °C increases by a factor of 94 000 000 in going from water ( $k = 7.4 \times 10^{-6} \text{ s}^{-1}$ ) to hexamethylphosphoramide ( $k = 7.0 \times 10^2 \text{ s}^{-1}$ ); the rate of this process relative to water can be adjusted by using appropriate solvents. The extremely interesting results reported by Kemp and Paul led some to consider the decarboxylation of 3-carboxy-6-nitrobenzisoxazole a highly suitable process for probing not only solvents but also such varied media as micelles, bilayers, macrocyclic

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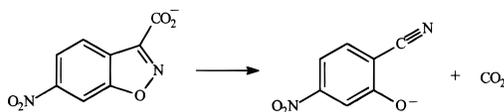
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**Scheme 1. Decarboxylation of the Tetramethylguanidinium Salt of 3-Carboxy-6-nitrobenzisoxazole**



hosts, and polymers with respect to water.<sup>11–22</sup> In addition, some polymers accelerate the reaction in organic solvents.<sup>23,24</sup> Likewise, the reaction rate can be increased by a factor about 19 000 relative to water inside a binding pocket in a catalytic antibody.<sup>25</sup> The ease with which antibodies can be genetically engineered makes these systems highly suitable for studying the effects of solvents as their catalytic properties are dictated by the protic character of the solvent.

The monoclonal antibody 21D8 has been used as a very simple system to study the effect of solvation on enzyme catalysis.<sup>25</sup> By comparison with the rate constant relative to water, the occurrence of a hydrogen bond in the binding site between the carboxylate group and lysine or arginine was concluded. The presence of this bond decreases the rate of decarboxylation.

The efficiency for proton transfer catalysis in enzymes and models is deeply analyzed by Kirby.<sup>26</sup> Hollfelder et al.<sup>27</sup> reported that serum albumin proteins catalyze the conversion of Kemp's reaction, but they use a lysine side chain as the catalytic general base rather than the carboxylate group, thereby allowing the contribution of the medium effect for this catalysis.

Kemp and co-workers<sup>10,28,29</sup> examined the decomposition of the tetramethylguanidinium salt of 3-carboxy-6-nitrobenzisoxazole to form carbon dioxide and the corresponding 2-cyano-5-nitrophenolate (Scheme 1) in a series of 24 pure solvents including polar and nonpolar solvents with protic, nonprotic, and amphiprotic connotations, as well as in binary mixtures of dimethyl sulfoxide (DMSO) with diglyme, acetonitrile, benzene, dichlo-

romethane, chloroform, and methanol. They also studied the decarboxylation of four other tetramethylguanidinium salts of 3-carboxy-6-X-benzisoxazole (with X = NH<sub>2</sub>, MeO, H, and Cl) to obtain additional information on the influence of various electronic effects of the benzisoxazole derivative on the decarboxylation process. All of this information is thoroughly analyzed in this work with a view to its rationalization and to assessment of the potential of this process for studying catalytic and noncatalytic biochemical environments.

The amazing results of Kemp and co-workers<sup>10,28,29</sup> for the decarboxylation of the tetramethylguanidinium salt of 3-carboxy-6-nitrobenzisoxazole allowed three factors to be identified as the sources of the increased reaction rates relative to water: (a) the decreased acidity of the medium, which is bound to accelerate the reaction through a less extensively interaction with the anion (the reactive species); (b) the ion-pair interactions arising from the presence of the anion and the tetramethylguanidinium cation, which will also be modulated by the nature of the solvent; and (c) the stabilization of the transition state of the process through dispersion interactions. Kemp and Paul<sup>10</sup> tried to rationalize their rates by using the single-parameter solvent scales available at the time, the  $E_T(30)$  scale of Reichardt<sup>30</sup> and the  $Z$  scale of Kosower,<sup>31</sup> but found no correlation. In response,<sup>10</sup> they introduced a new scale based on the solvatochromism of the decarboxylation product of 2-cyano-5-nitrophenolate, which they called the "H scale". However, the 24 solvents studied clustered in three nearly parallel arrangements with no physical significance, at least not in relation to the nature of the solvent in each group.

To the authors' knowledge, there have been only three subsequent attempts at rationalizing the behavior of the tetramethylguanidinium salt of 3-carboxy-6-nitrobenzisoxazole in the solvent series studied by Kemp and Paul.<sup>10</sup> In 1993, Grate et al.<sup>32</sup> used parameters  $\pi^*$ ,  $\delta$ ,  $\alpha$ ,  $\beta$ , and  $\delta_H^2$  in the solvent scheme of Taft and Kamlet<sup>33,34</sup> with 20 of the 24 solvents formerly studied by Kemp and Paul.<sup>10</sup> In 1994, Drago et al.<sup>35</sup> analyzed the 24 solvents examined by these authors, using parameters  $E_B$ ,  $E_A$ ,  $C_B$ ,  $C_A$ , and  $S$  in their own solvent scheme. Finally, also in 1994, Famini and Wilson<sup>36</sup> analyzed the solvents on the basis of their solvent descriptors  $M_{mc}$ ,  $\pi_1$ ,  $\delta_H^2$ ,  $\epsilon_B$ ,  $\epsilon_A$ ,  $q_-$ , and  $q_+$ . As shown below, these analyses led them to classify the solvents in different families outside which the fitting of their results was rather poor.

As shown in discussing the reaction model below, the decarboxylation process is complicated by the occurrence of side effects such as the presence or absence of an ion-pair; this depends on the particular nature of the solvent, which, among others, dictates the concentration of the active species (the anion). Because the reactants and products in the presence of solvent are linked by several simultaneous equilibria, the solvent will exert various modulating effects; fortunately, the effects will be gov-

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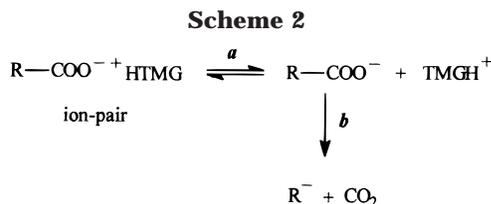
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erned by the same interactions with the solvent, so a precise enough one can be accomplished by using pure-solvent scales such as the SPP,<sup>37,38</sup> SB,<sup>39</sup> and SA.<sup>40,41</sup>

This work was undertaken with the aim of rationalizing the decarboxylation of the trimethylguanidinium salt of 3-carboxy-6-nitrobenzisoxazole not only in the 24 pure solvents studied by Kemp and Paul<sup>10</sup> but also in binary mixtures of DMSO with diglyme, acetonitrile, benzene, dichloromethane, chloroform, and methanol.

### Experimental Section

All solvents used were of the highest available purity and purchased from Merck in Uvasol grade. Solvent mixtures were prepared from freshly opened bottles, using Brand II 25.00 mL burets to transfer the liquids.

Polarity (SPP), basicity (SB), and acidity parameters (SA) were obtained from the wavenumbers of the UV-vis absorption maxima for the following probe/homomorph couples: 2-(dimethylamino)-7-nitrofluorene/2-fluoro-7-nitrofluorene,<sup>37,38</sup> 5-nitroindoline/1-methyl-5-nitroindoline,<sup>39</sup> and *o*-*tert*-butylstilbazolium betaine dye/*o*,*o'*-di-*tert*-butylstilbazolium betaine dye.<sup>40</sup> The last couple was replaced with the probe 3,6-diethyl-1,2,4,5-tetrazine<sup>41</sup> in the DMSO/methanol mixture at DMSO concentrations below 8 M.

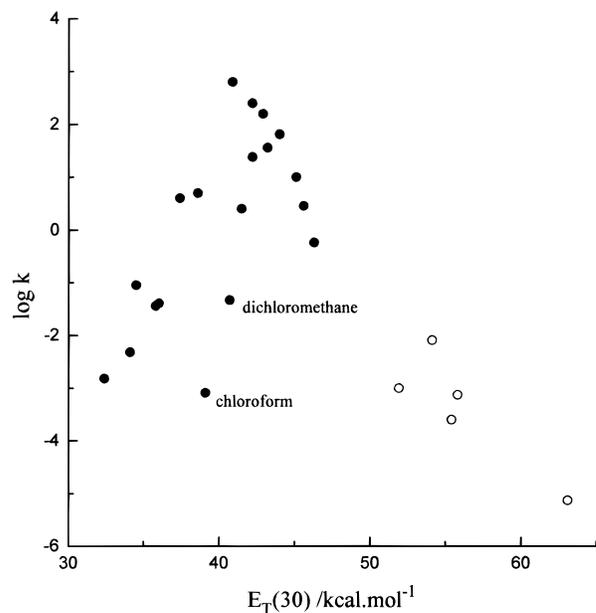
UV-vis measurements were made on a Shimadzu 2100 spectrophotometer, the monochromator of which was calibrated by using the 486.0 and 656.1 nm lines from a deuterium lamp. The instrument was routinely checked for wavelength accuracy by using holmium oxide and didymium filters. All spectral measurements were performed at 25 °C, using a matched pair of quartz cells of 1 cm path length.

### Results and Discussion

**Solvent Sensitivity of the Decarboxylation Scheme.** The decarboxylation of the tetramethylguanidinium salt of 3-carboxy-6-nitrobenzisoxazole studied by Kemp and co-workers<sup>10,28</sup> can be schematized as follows (Scheme 2):

In step **a**, the carboxylate ion (the reactive species) is released from the ion pair to an extent dependent on the equilibrium constant of the process; in step **b**, the decomposition of the carboxylate ion produces carbon dioxide and the organic anion. Because of that, it is important to determinate the influence of the environment on steps **a** and **b** or, in other words, on the overall decarboxylation process.

The decarboxylation step, **b**, will obviously be determined by the solvent acidity, which will have two effects, the solvation of the carboxylate ion (the active species) and its charge dispersion. This dual effect eventually results in a decrease of the decarboxylation rate when the solvent acidity is increased. Also, because this reac-



**Figure 1.** Plot of the  $\log k$  values for the decarboxylation of the tetramethylguanidinium salt of 3-carboxy-6-nitrobenzisoxazole in 24 pure solvents against the corresponding  $E_T(30)$  values ( $\circ$ , protic solvents).

tion step involves charged species, the reaction rate can be expected to vary with increasing solvent polarity. In summary, step **b** will be clearly disfavored by an increased solvent acidity and very likely favored by an increased polarity.

Step **a** is quite important with a view to rationalizing the rate of the decarboxylation process; in fact, it produces the active species (the carboxylate ion, which is initially stabilized by formation of an ion pair with the protonated tetramethylguanidine salt). This step will obviously be favored by the solvent cleaving the ion pair, both through its polarity and through its acidity, which will help stabilize the carboxylate ion. A similar effect will be exerted by the solvent basicity, which will stabilize the protonated form of tetramethylguanidine.

In summary, the solvent increases the rate of the decarboxylation process through its polarity and basicity but also decreases it in sequestering the active species (the carboxylate ion) through its acidity. As noted earlier, some effects of the solvent acidity favor the process, whereas others deactivate it. On the basis of Palit's rule,<sup>42</sup> however, the deactivating effect must prevail, since those solvents that block the active site of a reactant suppress its reactivity. On the basis of the previous reasoning, the decarboxylation rate of the tetramethylguanidinium salt of 3-carboxy-6-nitrobenzisoxazole must be increased by increased solvent polarity and basicity and decreased by an increased acidity.

**Decarboxylation Rate versus Solvent Scales. Interpretation Based on Single-Parameter Scales.** Kemp and Paul<sup>10</sup> used two single-parameter scales to rationalize the decarboxylation rate of 3-carboxy-6-nitrobenzisoxazole, viz., the  $E_T(30)$  scale of Reichardt<sup>30</sup> and the  $Z$  scale of Kosower.<sup>31</sup> Figure 1 shows the variation of the logarithmic constants in the 24 pure solvents studied by these authors<sup>10</sup> against the corresponding  $E_T(30)$  values recently compiled by Reichardt.<sup>30</sup> As formerly

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noted by Kemp et al., there is absolutely no correlation between these two data sets. However, it should be noted that, if chloroform and dichloromethane are excluded, the solvents cluster in two groups. One group exhibits an increase in decarboxylation rate with increase in solvent polarity, whereas the other encompasses protic solvents and reflects a marked decrease in reaction rate with increasing solvent acidity. This is consistent with the fact that  $E_T(30)$  is virtually a 50–50 combination of solvent polarity and acidity.<sup>41</sup> Similar results were obtained by plotting the data for the 19 solvents with reported Kosower's  $Z$  values.

In view of the poor results obtained by Kemp and Paul<sup>10</sup> with these two solvent scales, they used the similarity principle to represent the effect of the solvent on the decarboxylation kinetics in terms of the influence of the former on the organic anion resulting from the decarboxylation, as measured by the energy, in kcal/mol, of its first electronic transition, which they called  $H$ . The end result was that the 24 solvents clustered in three nearly parallel straight lines with no physical significance, at least not in relation to the nature of the solvents in each group. This treatment is thus seemingly useless with a view to rationalizing the decarboxylation data.

In conclusion, the single-parameter scales appear not to be flexible enough to provide an accurate description of the complicated decarboxylation process studied by Kemp and Paul.<sup>10</sup>

**Interpretation Based on Multiparameter Scales.** Grate et al.<sup>32</sup> used the multiparameter model of Taft and Kamlet<sup>33,34</sup> to account for this kinetics, using the following general equation:

$$\Delta\chi = \text{constant} + (S\pi^* + d\delta) + a\alpha_1 + b\beta_1 + h\delta_H^2 \quad (1)$$

where parameters  $\pi^*$  and  $\delta$ ,  $\alpha_1$ ,  $\beta_1$ , and  $\delta_H^2$  represent the dipolarity and polarizability, the acidity, basicity, and cohesive energy of the solvents. They applied this model to 20 of the 24 solvents studied by Kemp and Paul,<sup>10</sup> excluding *N*-methylformamide, sulfolane, dimethoxymethane, and diglyme, and found the data to fit the equation

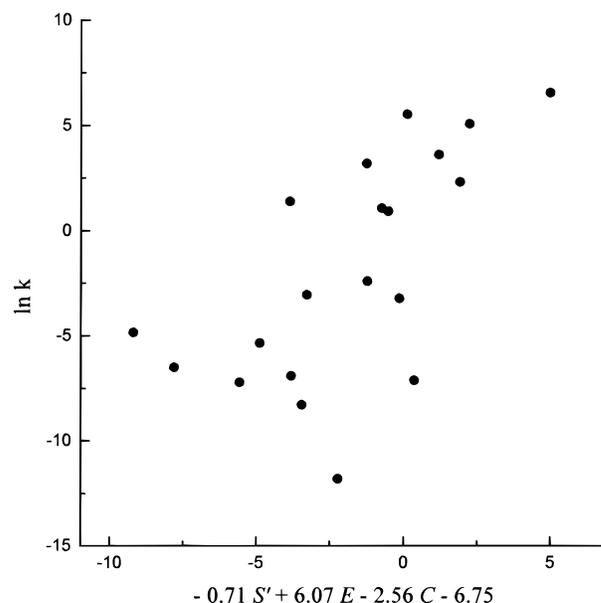
$$\log k = 5.45(\pm 0.89)\pi^* - 1.46(\pm 0.45)\delta - 3.03(\pm 0.65)\alpha + 1.80(\pm 0.66)\beta - 1.06(\pm 0.25)\delta_H^2 - 2.97(\pm 0.52) \quad (2)$$

with  $n = 20$ ,  $r = 0.976$ , and  $SD = 0.58$ .

However, for consistency with subsequent comparisons, which were to include all 24 solvents, we added the four solvents initially excluded from the fitting, using the parameter values reported by Marcus.<sup>43</sup> By exception, those for dimethoxymethane, which were unavailable, were replaced with the values for diethoxyethane. The  $\delta_H^2$  values for these four solvents were obtained from Famini and Wilson.<sup>36</sup> The data fitted the resulting equation

$$\log k = 5.23(\pm 0.95)\pi^* - 1.58(\pm 0.62)\delta - 3.77(\pm 0.65)\alpha + 1.36(\pm 0.74)\beta - 0.84(\pm 0.27)\delta_H^2 - 2.80(\pm 0.56) \quad (3)$$

with  $n = 24$ ,  $r = 0.959$ , and  $SD = 0.70$ .



**Figure 2.** Plot of  $\ln k$  in 20 solvents as a function of  $S'$ ,  $E$ , and  $C$  parameters.

The positive signs of the polarity and basicity coefficients and the negative signs of the polarizability and acidity coefficients are quite consistent with the above-described solvation model.

Ferris and Drago<sup>35</sup> examined the problem in the light of the following scheme:

$$\Delta\chi = (E_A * E_B) + C_A * C_B + SP + W \quad (4)$$

where the solvent shift,  $\Delta\chi$ , can be described in terms of electrostatic ( $E_A \times E_B$ ), covalent ( $C_A \times C_B$ ), or polarity contributions ( $S$ ). These authors developed an elegant treatment by which they divided the 24 solvents into three groups. In one, which included the highly polar and basic solvents (hexamethylphosphoramide, *N*-methylpyrrolidine, *N,N*-dimethylacetamide, *N,N*-dimethylformamide, DMSO, and sulfolane), the ion pair is assumed to be virtually completely dissociated and  $\ln k$  to be described by polarity interactions through the equation  $\ln k = -8.24S + 27.24$ . In the second group, which comprises the scarcely polar, scarcely basic solvents (tetrachloromethane, benzene, ether, dimethoxymethane, 1,4-dioxane, tetrahydrofuran, diglyme, acetone, benzonitrile, acetonitrile, and nitromethane), the ion pair is assumed to be only partially dissociated and the rate to be described by the equation  $\ln k = -1.86E_B + 3.75C_B + 5.15S - 14.35$ . Finally, in the third group, formed by the protic solvents (chloroform, dichloromethane, ethanol, methanol, water, formamide, and *N*-methylformamide), the decarboxylation rate conforms to the equation  $\ln k = 1.03E_A' - 6.74C_B' + SP + W$ . However, application of this treatment to the 20 solvents for which definitive parameter values are available provides the following fit

$$\ln k = -0.71(\pm 1.74)S' + 6.07(\pm 1.96)E - 2.56(\pm 2.44)C - 6.75(\pm 4.58) \quad (5)$$

with  $n = 20$ ,  $r = 0.649$ , and  $SD = 4.42$ , which does not reproduce the experimental results (see Figure 2). It should be noted that the uncertainty in the polarity coefficient is more than twice the coefficient itself, so its values make no sense.

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**Table 1. Results Obtained by Fitting Data for 3-Carboxy-6-X-benzisoxazole Derivatives to SPP, SA, and SB Scales in 14 Solvents According to  $\log k = aSPP + bSA + cSB + \log k_0$** 

	X =				
	NO <sub>2</sub>	Cl	H	OMe	NH <sub>2</sub>
<i>a</i>	11.19 ± 4.12	11.72 ± 4.23	11.22 ± 4.21	11.72 ± 4.04	11.60 ± 4.13
<i>b</i>	-6.57 ± 0.78	-6.50 ± 0.80	-6.12 ± 0.80	-6.14 ± 0.77	-5.80 ± 0.78
<i>c</i>	0.90 ± 1.16	0.71 ± 1.19	0.50 ± 1.19	0.50 ± 1.14	0.21 ± 1.17
log <i>k</i> <sub>0</sub>	-9.40 ± 4.05	-10.20 ± 4.15	-10.67 ± 4.14	-10.84 ± 3.97	-11.22 ± 4.05
<i>n</i>	14	14	14	14	14
<i>r</i>	0.966	0.963	0.959	0.963	0.957
SD	0.77	0.79	0.79	0.76	0.77

Famini and Wilson<sup>36</sup> use a linear solvation energy relation similar to that of Taft and Kamlet<sup>33</sup> but based on a series of descriptors including  $V_{mc}$ ,  $\pi_1$ ,  $\epsilon_B$ ,  $q_-$ ,  $\epsilon_A$ ,  $q_+$ , and  $\delta_H^2$ , which denote the molecular volume, polarizability, covalent basicity, electrostatic basicity, covalent acidity, electrostatic acidity, and cohesive energy, many of which were evaluated on a semiempirical level using the MNDO method.<sup>44</sup> The equation obtained by fitting the values for the 24 solvents was

$$\log k = 0.26(\pm 1.23)V_{mc} - 25.07(\pm 54.81)\pi_1 + 48.09(\pm 31.37)\epsilon_B + 4.87(\pm 2.07)q_- + 27.21(\pm 27.87)\epsilon_A - 18.14(\pm 6.48)q_+ - 0.95(\pm 1.06)\delta_H^2 - 9.08(\pm 4.44) \quad (6)$$

with  $n = 24$ ,  $r = 0.876$ , and  $SD = 1.27$ . It should be noted that uncertainty in the polarity in this equation is more than twice the coefficient itself, and so is the case with the molar volume ( $V_{mc}$ ), whereas uncertainty is of the same order for the solvent cohesive energy ( $\delta_H^2$ ), i.e., the fitting results in a high uncertainty in  $\log k$ .

The analysis of the decarboxylation rates in the 24 solvents based on the SPP, SA, and SB pure solvent scales based on the scheme

$$\log k = a \cdot SPP + b \cdot SA + c \cdot SB + \log k_0 \quad (7)$$

proposed by Catalán et al.<sup>38,40,41</sup> results in the following fitting:

$$\log k = 10.37(\pm 1.47)SPP - 5.93(\pm 0.58)SA + 2.59(\pm 0.74)SB - 9.74(\pm 1.17) \quad (8)$$

with  $n = 24$ ,  $r = 0.951$ , and  $SD = 0.73$ , which reproduces the sensitivity of the decarboxylation rate to the pure solvents studied by Kemp and Paul more than acceptably. In addition, it clearly shows that the decarboxylation rate increases dramatically with increase in the solvent polarity and also, to a lesser extent, with its basicity; by contrast, the rate decreases considerably with increasing solvent acidity. This behavior is quite consistent with the solvent effect scheme proposed at the beginning of this section.

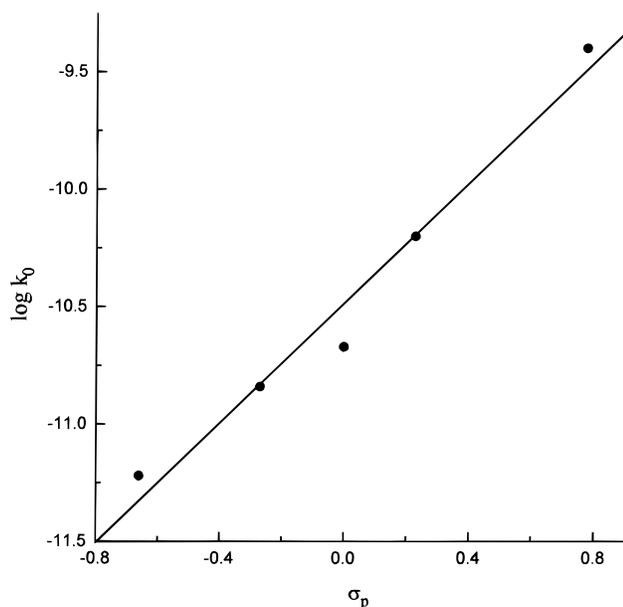
In addition, this fitting provides highly interesting information. In fact, its independent term,  $\log k_0$ , which would correspond to the logarithmic decarboxylation rate in the gas phase ( $SPP = 0$ ,  $SA = 0$ , and  $SB = 0$ ), is  $-9.74$ , so the rate would be  $k = 1.82 \times 10^{-10} \text{ s}^{-1}$ . At this point, it is interesting to examine the reason the decarboxylation rate in water reported by Kemp and Paul<sup>10</sup> was about  $10^3$  times greater ( $k = 7.4 \times 10^{-6} \text{ s}^{-1}$ ).

At this point one will wonder why the decarboxylation rate in water is so small. On the basis of the previous fitting, it must be a result of the high polarity of water ( $SPP = 0.962$ ) increasing the rate by 10 logarithmic units and its high acidity ( $SA = 1.062$ ) decreasing it by more than 6 logarithmic units. It therefore seems inappropriate to continue to use water as the reference solvent for the decarboxylation rate of 3-carboxy-6-nitrobenzisoxazole when it seems clear that its small value in water is a result of the two different properties. Consequently, it seems advisable to refer rates to the natural medium for comparing solvent effects, i.e., the absence of solvent (gas phase).

Kemp and Paul<sup>10</sup> analyzed the decarboxylation rate of four other 3-carboxy-6-X-benzisoxazoles (with  $X = \text{NH}_2$ , MeO, H, and Cl) in 14 different solvents; if these data are supplemented with those for the nitro derivative, a set of five derivatives with electronic substituent effects ranging from a typical electron-releasing function (the amino group) to a typical electron acceptor (the nitro group) becomes available. Table 1 gives the results obtained by fitting the data for these five derivatives in the 14 solvents to the SPP, SA, and SB scales. The decarboxylation of the five derivatives is similarly sensitive to the solvent: the rate of the process increases with increasing polarity and basicity and decreases with increasing acidity, the prevailing effect being that of polarity, followed by that of acidity. Because some of these derivatives contribute active sites to the solvating effect, the small changes in some of these terms are rather difficult to rationalize. Also, because, as noted earlier, the independent term ( $\log k_0$ ) represents the rate of the process in the gas phase and is thus an intrinsic value, changes in the term must be related to the electronic properties of the substituents. As can be seen from Table 1, the independent term varies markedly with the nature of the solvent. Also, as shown in Figure 3, these terms vary linearly with parameter  $\sigma_p$  for the substituent. This behavior confirms that our scales accurately reproduce the behavior in the gas phase.

Kemp and Paul<sup>10</sup> also reported the decarboxylation rates for the tetramethylguanidinium salt of 3-carboxy-6-nitrobenzisoxazole in a series of binary mixtures of DMSO with diglyme, acetonitrile, benzene, dichloromethane, chloroform, and methanol. Figure 2 in their paper<sup>10</sup> shows the variation of  $\log k$  with the DMSO concentration in each mixture. Such a figure warrants some interesting comments. Thus, as the DMSO ( $SPP = 1$ ,  $SB = 0.647$ ,  $SA = 0.072$ ) is enriched with acetonitrile ( $SPP = 0.895$ ,  $SB = 0.286$ ,  $SA = 0.044$ ), the reaction rate undergoes a slight, monotonic decrease resulting from the lower basicity and polarity of the latter. On the other hand, enriching the DMSO with chloroform ( $SPP = 0.786$ ,  $SB = 0.071$ ,  $SA = 0.047$ ) results in a marked

(44) Dewar, M. J. K.; Thiel, W. J. *Am. Chem. Soc.* **1977**, *99*, 4899.



**Figure 3.** Plot of the independent term ( $\log k_0$ ) of different fits versus the  $\sigma_p$  parameters.

decrease in the reaction rate owing to the much less polar and basic character of the latter solvent, the decrease being especially prominent when the mixture contains chloroform almost exclusively. Worth special emphasis in this respect is the mixture with methanol (SPP = 0.857, SB = 0.545, SA = 0.605). Because this solvent is much less basic and polar and much more acidic than DMSO, raising its content in the mixture causes a sustained decrease in the decarboxylation rate. The fact that the rate apparently varies linearly with the DMSO concentration is, to our minds, coincidental.

This peculiar variation of the decarboxylation rate with the mixture composition and the strong dependence of this behavior on the nature of the solvent mixed with the DMSO (note that gradually changing from DMSO to acetonitrile decreases the rate by a factor of only 3, whereas changing to methanol reduces it 40 000 times) prompted us to determine SPP, SB, and SA for the mixtures studied by Kemp and Paul<sup>10</sup> (see Table 2). It is very interesting and significant that, adding these data for the mixtures to those for the 24 above-mentioned pure solvents provides the following global fitting:

$$\log k = 10.03(\pm 1.05)\text{SPP} - 5.73(\pm 0.40)\text{SA} + 2.41(\pm 0.49)\text{SB} - 9.58(\pm 0.83) \quad (9)$$

with  $n = 60$ ,  $r = 0.933$ , and  $\text{SD} = 0.60$ , very similar to that previously established for the pure solvents. Equation 9 warrants some interesting comments (see Figure 4):

(a) This is the first global explanation for the experimental data of Kemp and Paul<sup>10</sup> including all their pure solvents and mixtures.

(b) Our probes provide accurate descriptions for the behavior of the binary mixtures of DMSO with diglyme, acetonitrile, benzene, dichloromethane, chloroform, and methanol.

(c) The fact that our scales allow solvent mixtures to be examined as if they were pure solvents is very interesting and appealing.

**Table 2.** SPP, SB, and SA Values for Dimethoxymethane and Binary Mixtures of DMSO with Diglyme, Acetonitrile, Benzene, Dichloromethane, Chloroform, and Methanol

solvent	[DMSO] (M)	SPP	SB	SA
dimethoxymethane		0.648	0.359	0
DMSO/diglyme	1.1	0.873	0.616	0.008
	7.3	0.936	0.642	0.043
	9.0	0.952	0.634	0.056
	10.5	0.970	0.639	0.057
DMSO/acetonitrile	1.1	0.915	0.404	0.052
	2.8	0.923	0.530	0.060
	7.3	0.938	0.606	0.070
	10.7	0.957	0.628	0.072
DMSO/benzene	0.11	0.694	0.202	0
	0.28	0.710	0.553	0
	1.1	0.790	0.637	0.005
	2.2	0.861	0.629	0.020
	3.9	0.901	0.637	0.034
	5.6	0.911	0.638	0.044
	9.0	0.953	0.645	0.056
	9.0	0.953	0.645	0.056
DMSO/dichloromethane	0.56	0.882	0.261	0.033
	1.1	0.881	0.399	0.027
	2.8	0.901	0.577	0.041
	3.9	0.906	0.635	0.051
	5.6	0.919	0.667	0.063
	8.4	0.942	0.670	0.076
DMSO/chloroform	0.56	0.837	0.230	0.028
	1.6	0.869	0.459	0.041
	3.4	0.892	0.620	0.067
	5.6	0.904	0.665	0.093
	8.4	0.919	0.665	0.107
	11.5	0.942	0.643	0.090
DMSO/methanol	2.5	0.900	0.543	0.489 <sup>a</sup>
	4.5	0.909	0.546	0.467 <sup>a</sup>
	6.6	0.934	0.581	0.425 <sup>a</sup>
	7.7	0.935	0.599	0.416 <sup>a</sup>
	8.7	0.959	0.611	0.299 <sup>a</sup>
	9.4	0.953	0.608	0.285 <sup>b</sup>
	10.2	0.952	0.617	0.279 <sup>b</sup>
	11.3	0.969	0.625	0.267 <sup>b</sup>
	11.9	0.976	0.618	0.260 <sup>b</sup>

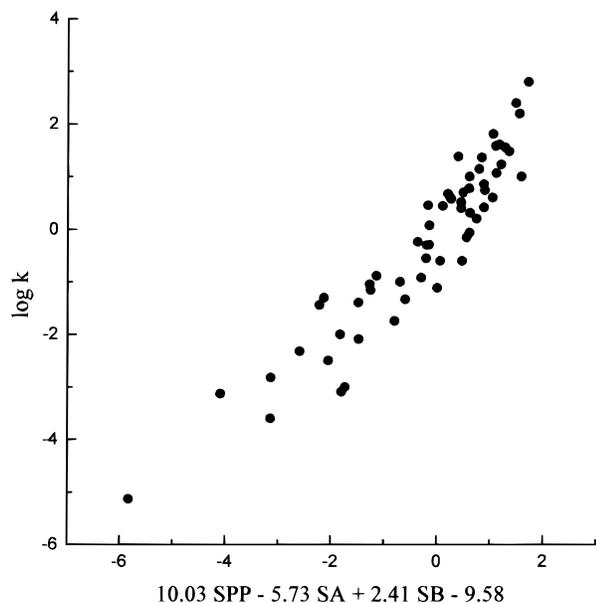
<sup>a</sup> Obtained from the wavenumbers of the UV-vis absorption maxima for the probe DETZ.<sup>41</sup> <sup>b</sup> Obtained from the wavenumbers of the UV-vis absorption maxima for the TBSB/DTBSB couple.<sup>40</sup>

(d) The reference medium to be used to compare decarboxylation rates for this system is the gas phase, the only one where the highly influential effects of polarity, basicity, and acidity are completely absent.

Following the behavior described by the eq 9, it can be predicted that, whereas the trifluoroethanol addition to water does not change the constant rate for decarboxylation (i.e., for a mixture of 0.5 molar fraction  $\log k$  results in  $-0.53$ ), an equivalent amount of DMSO added to water changes greatly the decarboxylation rate constant (i.e., for a 0.5 molar fraction  $\log k$  is equal to  $+0.67$ ).

**Use of the Decarboxylation Process as an Environmental Probe.** According to Smid et al.,<sup>24</sup> poly(4-vinylbenzo-18-crown-6) catalyzes the decarboxylation of 6-nitrobenzoxazole-3-carboxylate in water. The process involves the formation of a complex between the polymer and the anion. In this situation, the decarboxylation of 6-nitrobenzoxazole takes place at a rate similar to that observed in benzene (i.e.,  $9.3 \times 10^7$  times greater than in the gas phase).

In the presence of cation-binding crown polymers, the rate of the process increases dramatically (by a factor up to  $5.7 \times 10^8$  relative to the gas phase). The effect can be ascribed to the formation of tight ion pairs within the polymer core, where the distance between pairs increases, as does the activity of carboxylate ion, the active species,



**Figure 4.** Plot of  $\log k$  values for the decarboxylation rate of the tetramethylguanidinium salt of 3-carboxy-6-nitrobenzoxazole versus the values predicted by eq 9 corresponding to 24 pure solvents and 36 binary mixtures of DMSO.

as a result. The net effect is that the decarboxylation rate is much greater than that for the tetramethylguanidinium salts, which form ion pairs, but similar to the values found in nonprotic dipolar solvents.

The use of this kinetics to derive information about the environment of the process and the factors that influence it have been discussed by several authors.<sup>25,32,35</sup>

In any case, from eq 9 it follows that the rate constant depends qualitatively and quantitatively differently on SA, SPP, and SB, which hinders its use as an environmental probe. Thus, although the most influential parameter is SPP, its effect is appreciably modulated by the basicity.

Acidity has the opposite effect, consistent with its sequestering action on carboxylate ion (the active species).<sup>10,24,35</sup> In summary, the interpretation of  $k$  values, the sole experimental data for the reaction, rests on three parameters that vary with the particular environment. A deeper, more comprehensive description of the decarboxylation process requires the knowledge of the presence and sign of charges in the biochemical environment that triggers the reaction.

However, the fact that eq 9 applies to both pure solvents and solvent mixtures could help to explain the catalytic mechanism for a reaction and/or boosting the efficiency of existing biochemical sites.

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