Pergamon

TETRAHEDRON

Tetrahedron 58 (2002) 1745–1749

The aqueous salt-promoted Diels–Alder reaction of anthracene-9-carbinol with *N*-ethylmaleimide

Anil Kumar* and Sanjay S. Pawar

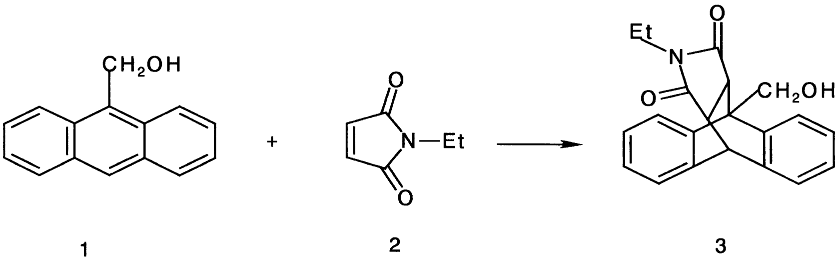
Physical Chemistry Division, National Chemical Laboratory, Pune 411008, India

Received 22 September 2001; accepted 10 January 2002

Abstract—The Diels–Alder reaction of anthracene-9-carbinol with *N*-ethylmaleimide has been investigated in several aqueous salt solutions of different concentrations. The enhancement in reaction rates in the presence of LiCl, NaCl, KCl, $MgCl_2$, Na_2SO_4 and Gn_2SO_4 are attributed to the salting-out effect. On the other hand, $LiClO_4$, $NaClO_4$, GnCl, GnBr, CH_3COOGn and $GnClO_4$ inhibit the rate owing to the salting-in effect. The variations in rate data can be explained using the experimental solubility data and computed salting coefficients.

1. Introduction

Rideout and Breslow discovered the special effect of water in enhancing the rates of Diels–Alder reactions.[1] They attributed the rate enhancement to the hydrophobic packing of diene and dienophile in water. Later, Breslow and coworkers demonstrated that ionic solutes like LiCl promoted the reaction rates, while $LiClO_4$ and guanidinium chloride (GnCl) inhibited the progress of these reactions.[2] Effects of salt solutions on kinetics of these reactions has recently been reviewed from this laboratory.[3] Breslow and Rizzo[4] described the ability of LiCl, $LiClO_4$, GnCl and $GnClO_4$ in diagnosing the hydrophobic effects on the basis of the reaction of anthracene-9-carbinol **1** with *N*-ethylmaleimide **2** (Scheme 1). Later, Rizzo[5] carried out this reaction in 2 M solutions of aqueous sodium and guanidinium salts and concluded that the reaction rates followed the Hofmeister series.[6] The degree of hydrophobic effect at different concentration of salts cannot be understood from the available experimental data, as the reaction was not carried out in different concentrations of a variety of salts. As a part of continuing efforts from this laboratory,[7] it would be desirable to investigate the reaction in different concentrations of several types of salt solutions, which could offer information useful in delineating the origin of forces responsible for such remarkable rate variations. The reaction selected was noted to be slower in methanol (a polar solvent) than in 2,2,4-trimethylpentane (a nonpolar solvent).[4] These findings can also be supported on the basis of excellent work of Schneider and Sangwan, where a solvophobicity parameter was first applied quantitatively to support the role of solvophobicity or hydrophobicity in Diels–Alder reactions.[8] The present paper describes: (1) reaction rates of the title reaction in different salt concentrations of aqueous LiCl, NaCl, KCl, $MgCl_2$, Na_2SO_4, Gn_2SO_4, $LiClO_4$, $NaClO_4$, GnCl, GnBr, CH_3COOGn and $GnClO_4$; (2) solubilities of **1** in different salt solutions to support the rate profiles; (3) salting coefficients and a



Scheme 1.

Keywords: Diels–Alder reaction; anthracene-9-carbinol; salting coefficients.

* Corresponding author. Fax: +91-20-5893-044; e-mail: akumar@ems.ncl.res.in

Table 1. Concentration dependence of rates, *k*, for the reaction of **1** and **2** in the rate-promoting salts; *k* in water=$232\pm6\times10^{-3}$ M^{-1} s^{-1}

LiCl		NaCl		KCl		$MgCl_2$		Na_2SO_4		Gn_2SO_4	
[Salt] (mol L^{-1})	*k* (10^3 M^{-1} s^{-1})	[Salt] (mol L^{-1})	*k* (10^3 M^{-1} s^{-1})	[Salt] (mol L^{-1})	*k* (10^3 M^{-1} s^{-1})	[Salt] (mol L^{-1})	*k* (10^3 M^{-1} s^{-1})	[Salt] (mol L^{-1})	*k* (10^3 M^{-1} s^{-1})	[Salt] (mol L^{-1})	*k* (10^3 M^{-1} s^{-1})
0.55	277	0.43	257	0.51	253	0.52	285	0.48	260	0.42	243
1.25	309	1.38	291	1.11	268	1.11	328	0.98	276	0.95	257
2.13	401	2.15	307	2.04	271	1.65	371	1.51	304	1.22	264
3.35	452	3.50	392	3.08	296	2.17	417	2.11	331	1.74	275
4.50	541	4.6	434	4.11	309	3.11	484			2.08	281
5.20	600	5.4	475								

discussion of their relationship with rate data and (4) comment on anomalous behaviour of Gn_2SO_4 on the rate data as compared to other guanidinium salts.

2. Experimental

The commercially available AR grade LiCl, NaCl, KCl, $MgCl_2$, Na_2SO_4, $LiClO_4$, $NaClO_4$, GnCl and Gn_2SO_4 purchased from Aldrich were recrystallized from water and dried under vacuum. GnBr, CH_3COOGn and $GnClO_4$ were prepared by the procedure outlined elsewhere.[9,10] The salt solutions were prepared in de-ionised water. Both **1** and **2** were procured from Aldrich.

For a typical reaction, solutions of 0.025 mM of **1** and 150 mM of **2** were prepared. 3.0 mL of **1** was measured with a volumetric pipette and placed in a 4 mL cuvette and incubated for 30 min in a thermostatted cell maintained at 45±0.01°C. Then, 25 μL of solution of *N*-ethylmaleimide was added and absorbance was measured over time between 10 and 12 h (at least 7 half lives). The rates were determined under pseudo-first order conditions with about a 40-fold excess of **2**. The progress of reaction was monitored by following the decrease in absorbance of **1** at 247 nm using a Carry 50 UV–visible spectrophotometer.[4,5] The absorbance was measured every 6 min and the reaction rates were calculated using the kinetics software supplied by the manufacturer. The rate constants were precise to within 1.6% as calculated from triplicate measurements.

Solubilities of **1** were determined by measuring the optical densities of a solution saturated with **1** in both pure water and salt solutions with a Carry 50 UV spectrophotometer (Varian) at 247 nm. The changes in the ionic concentrations produced negligible changes in the absorptivity of **1**. An average of three readings was considered as a final value. All the measurements were made at 45±0.1°C using a constant temperature water bath supplied by Julabo.

3. Results and discussion

The experimental rate data collected in this study show that LiCl, NaCl, KCl, $MgCl_2$ and Gn_2SO_4 act as rate-promoting salts (Table 1). Contrary to these salts, $LiClO_4$, $NaClO_4$, GnCl, GnBr, $GnClO_4$ and CH_3COOGn are observed to inhibit the reaction rates (Table 2). The dependence of the relative rate constant, k_{rel} (*k* in salt solution/*k* in water) on the salt concentration, [salt] is shown in Fig. 1(a) for different rate-promoting salts. For instance, the reaction rates are increased by about 40, 30, 15, 10 and 6% in 1 M solution each of $MgCl_2$, LiCl, NaCl, KCl and Gn_2SO_4, respectively. Similar plots for the rate-inhibiting salts are presented in Fig. 1(b). The rate drops by 7, 13, 22, 28, 32 and 41% in 1 M solution of $NaClO_4$, $LiClO_4$, CH_3COOGn, GnCl, GnBr and $GnClO_4$, respectively. The steep slopes ($\partial k/\partial M$) noted for $MgCl_2$ and $GnClO_4$ in Fig. 1(a) and (b) demonstrate the powers of these salts in enhancing or decreasing the reaction rates.

Guanidinium salts have been noted to have interesting effects on the reaction rates. From the kinetic study of this reaction in 2 M solution by Rizzo[5] GnCl, GnBr, $GnBF_4$, GnSCN and $GnClO_4$ have been reported to be rate-inhibiting salts, which is further confirmed by the concentration-dependent rate data collected in this work. However, one notes that another guanidinium salt, namely, Gn_2SO_4 acts in an entirely opposite manner by enhancing the reaction rates by 20% in its 1 M solution. The anomalous behaviour of Gn_2SO_4 as compared to other guanidinium salts is an important observation of this work. In order to assess the effect of SO_4^{2-} on the kinetic progress of the reaction, a few reactions were carried out in Na_2SO_4. The reaction rate was noted to increase in Na_2SO_4.

Table 2. Concentration dependence of rates, *k*, for the reaction of **1** and **2** in the rate-inhibiting salts; *k* in water=$232\pm6\times10^{-3}$ M^{-1} s^{-1}

$LiClO_4$		$NaClO_4$		GnCl		GnBr		CH_3COOGn		$GnClO_4$	
[Salt] (mol L^{-1})	*k* (10^3 M^{-1} s^{-1})	[Salt] (mol L^{-1})	*k* (10^3 M^{-1} s^{-1})	[Salt] (mol L^{-1})	*k* (10^3 M^{-1} s^{-1})	[Salt] (mol L^{-1})	*k* (10^3 M^{-1} s^{-1})	[Salt] (mol L^{-1})	*k* (10^3 M^{-1} s^{-1})	[Salt] (mol L^{-1})	*k* (10^3 M^{-1} s^{-1})
0.60	211	0.45	223	0.51	195	0.50	186	0.42	211	0.36	176
1.20	192	1.20	214	1.05	167	0.56	130	0.92	184	0.91	141
2.03	184	2.01	205	1.93	129	0.69	160	1.55	174	1.25	125
3.05	168	2.63	200	3.05	106	2.07	116	2.11	151	1.69	101
3.55	164	3.46	194	4.14	86					2.10	84
4.07	157			4.8	72						

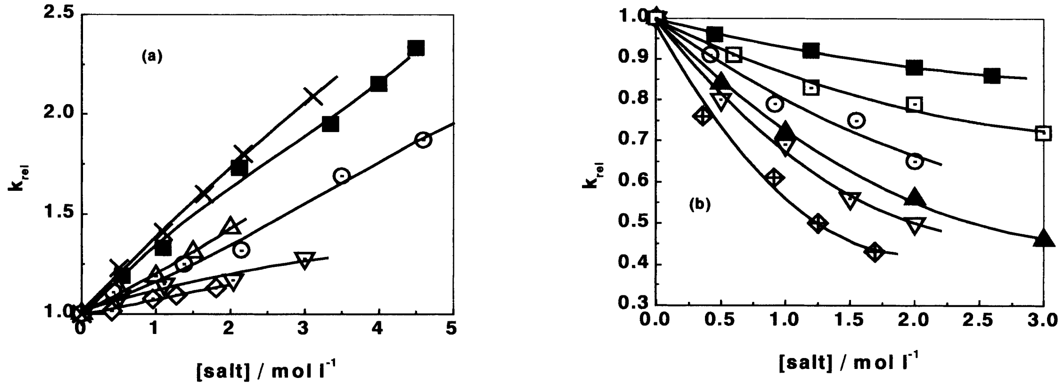


Figure 1. k_{rel} as a function of salt concentration for the reaction of **1** with **2**; (a) (×) $MgCl_2$; (■) LiCl; (△) Na_2SO_4; (○) NaCl; (▽) KCl; (◇) Gn_2SO_4. (b) (■) $NaClO_4$; (□) $LiClO_4$; (○) CH_3COOGn; (▲) GnCl; (▽) GnBr; (⊕) $GnClO_4$.

Rate enhancement of Diels–Alder reaction in an aqueous medium has been attributed to an increased hydrophobic effect. In terms of Breslow's explanation, LiCl, NaCl, KCl, $MgCl_2$ and Na_2SO_4 can be termed as pro-hydrophobic salts, as they increase the hydrophobic effect favourable for the above reaction. The rate-inhibiting salts, like $NaClO_4$, GnCl, GnBr, $GnClO_4$ and CH_3COOGn decrease the hydrophobic effect and are known as anti-hydrophobic salts. Thus, the rate-promoting salts facilitate the hydrophobic packing of diene and dienophile, while the reverse is expected in the case of rate-inhibiting salts. The qualitative studies by Rideout and Breslow[1] and later the experiments and calculations from this laboratory[7c] showed that the striking variations in the reaction rates and the (*endo*/*exo*) ratios can be attributed to the salting-out (S-O) and salting-in (S-I) phenomena.[11] Thus, salts such as LiCl, NaCl, KCl, $MgCl_2$ and Na_2SO_4 are S-O agents, while $NaClO_4$, GnCl, GnBr, $GnClO_4$ and CH_3COOGn S-I agents. With this criterion, Gn_2SO_4 is the only S-O salt out of several guanidinium salts examined here for their effect on reaction rates.

The S-O and S-I effects in the reaction can be determined by two methods: (a) by measuring solubility of a reactant in salt solution with respect to that in water and (b) by calculating S-O and S-I coefficients from knowledge of molecular properties of diene and dienophile and physico-chemical properties of salt solutions. First, in Fig. 2, the salt concentration dependence of relative solubilities of **1**, i.e. $(S/S_o)_1$ (S and S_o are the solubilities of **1** in the salt solution and water, respectively), in aqueous LiCl, $MgCl_2$, Gn_2SO_4, $NaClO_4$, GnCl and CH_3COOGn solutions are shown.[12] It is clear from Fig. 2 that LiCl, $MgCl_2$ and Gn_2SO_4 decrease the solubilities of **1** indicating the S-O behaviour of these salts. The increased solubilitites of **1**, on the other hand, in $NaClO_4$, GnCl and CH_3COOGn solution suggest the S-I effect by these salts. The decreased solubilities of **1** in Gn_2SO_4 should be noted. Fig. 3 depicts a linear correlation between $k_{2,rel}$ and $(S_{MA}/S_o)_1$ in different salt solutions of 1 M concentration. The plot with steep slope indicates the effective role of the increase or decrease in solubilities of the reactants or S-O or S-I phenomena on the reaction rates.

The salting coefficients, κ_s can be calculated by using the scaled particle theory, as described by Shoor and Gubbins.[13a] According to this theory, the salting coefficient, κ_s is calculated by combining the contributions due to the cavity formation, κ_a and the introduction of an organic molecule to the cavity, κ_b. The number density of solution species is given by κ_c. The input parameters for computing κ_a values for the guanidinium salts are the ionic radii and the diameter of water molecule taken from the compilation of Marcus.[14] The values of partial molar volumes at infinite dilutions, V^0 required in the calculations are obtained from the literature.[15] The κ_c is estimated from V^0 of the individual salts in water. The κ_s values for each salt listed in Table 3 indicate the expected trend in the salting coefficients. The negative κ_s values are obtained for all the rate-inhibiting salts, while a positive κ_s for the rate-promoting ones, including Gn_2SO_4. The effects arising due to κ_a and κ_b compete

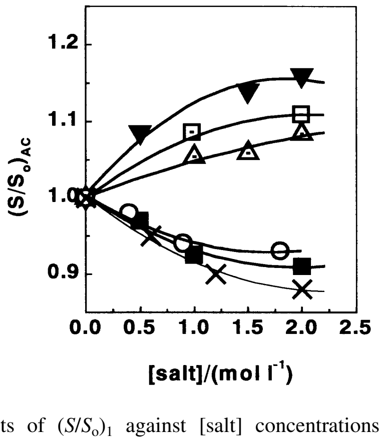


Figure 2. Plots of $(S/S_o)_1$ against [salt] concentrations (▼) $NaClO_4$; (□) GnCl; (△) CH_3COOGn; (○) Gn_2SO_4; (■) LiCl; (×) $MgCl_2$.

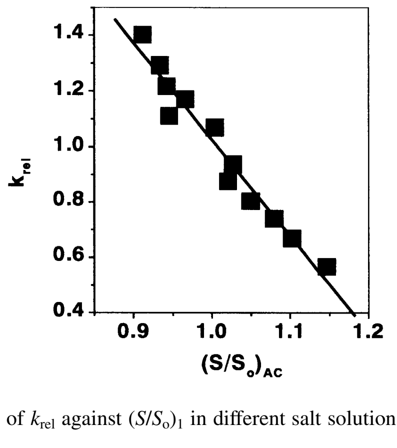


Figure 3. Plot of k_{rel} against $(S/S_o)_1$ in different salt solutions.

Table 3. The contribution of κ_a, κ_b and κ_c terms to salting coefficient, κ_S

Salt	κ_a	κ_b	κ_c	κ_S
LiCl	0.506	−0.064	0.009	0.451
NaCl	0.445	−0.052	0.008	0.401
KCl	0.211	−0.041	0.006	0.176
$MgCl_2$	0.648	−0.098	0.025	0.575
Na_2SO_4	0.554	−0.078	0.016	0.492
Gn_2SO_4	0.220	−0.030	0.027	0.217
$LiClO_4$	0.185	−0.281	−0.079	−0.175
$NaClO_4$	0.195	−0.219	−0.057	−0.081
GnCl	0.118	−0.489	−0.044	−0.415
GnBr	0.101	−0.456	−0.080	−0.435
CH_3COOGn	0.111	−0.368	−0.085	−0.342
$GnClO_4$	0.006	−0.338	−0.104	−0.436

each other to yield the total salting coefficient. With regard to $LiClO_4$, $NaClO_4$, CH_3COOGn, GnCl, GnBr and $GnClO_4$, higher negative values indicate strong solute–solvent interactions, i.e. solvation of hydrocarbons. The higher negative κ_b values outcompete the small positive κ_a values leading to the phenomena of solvation of hydrocarbons by the rate-retarding salts. On the contrary, a high positive κ_a value is obtained for LiCl, NaCl, KCl, $MgCl_2$, Na_2SO_4 and Gn_2SO_4 suggesting the high cost of cavitation. The surface tension data of these salts also support these observations.[16]

The guanidinium salts with SCN^-, Cl^- and CH_3COO^- ions are known to be potential destabilisers of proteins. On the other hand, Gn_2SO_4 was noted to enhance the transition temperature of the proteins thus acting as a stabiliser unlike other guanidinium salts. It is suggested that though the effect of guanidinium cation is to decrease the transition temperature, the overall effect of the salt on the system depend on the constituent anion of the guanidinium salts.[17] The contrasting effect of Gn_2SO_4 was also noted during the investigation of efficacy of various protein denaturants (guanidinium salts) as hydrophobic bond breakers.[18] It was observed that GnSCN showed a strong disruptive effect and increased the critical micelle concentration by several orders of magnitude, while Gn_2SO_4 stabilised the micelles. On the other hand, the S-I anions like Cl^-, Br^-, SCN^-, ClO_4^-, etc. will further enhance the destabilising behaviour of their salts with the guanidinium ion. By comparing the results on proteins with this study, it is clear that these anions themselves increase the rate-retarding power of Gn^+, as these anions act as S-I species, which further support the S-I tendency of Gn^+.

Some further comments on the anomalous behaviour of Gn_2SO_4 are in order. Li^+, Na^+, K^+, Mg^{2+} and SO_4^{2-} species are S-O species in water, while Gn^+, Cl^-, Br^-, ClO_4^- and CH_3COO^-, the S-I ones. In Gn_2SO_4, a strong S-O anion, such as SO_4^{2-} will over compensate the S-I tendency of guanidinium ion, thus giving the overall S-O effect, whereas in Na_2SO_4 both Na^+ and SO_4^{2-} are the S-O species. This is the reason that the effect of Na_2SO_4 on the rates is more pronounced than Gn_2SO_4, as the effect of SO_4^{2-} in Gn_2SO_4 is reduced by Gn^+, while in the case of Na_2SO_4, both Na^+ and SO_4^{2-} being S-O ions combine to enhance the reaction profiles.

It should be noted that the rates obtained in the present investigation follow the Hofmeister series[6a] in a given salt concentration for all the salts (the rates–ionic radii plot are linear with correlation coefficient being 0.9985) except Na_2SO_4 and Gn_2SO_4. The presence of ion pairing in these salts might be a reason for their not obeying the Hofmeister series.

Diels–Alder reactions are usually accompanied with negative activation volumes, suggesting compact transition states.[19] The activation volume of a Diels–Alder reaction is often suggested to be solvent independent. The activation volume for this reaction in different salt solutions calculated from the density measurements,[20] and by the method suggested by McCabe et al.[21] was -23.1 cm^3 mol^{-1} at the reaction temperature and did not vary significantly in any salt solutions (maximum variation 5%).

In summary, the above investigation shows that the enhancement and inhibition of the rates in different salt solutions are the result of salting-out and -in effects. The abnormal effect of Gn_2SO_4 compared to other guanidinium salts is another notable observation from this study.

Acknowledgements

The authors acknowledge a grant-in-aid (No. SP/S1/G-19/99) from Department of Science and Technology, New Delhi for carrying out this work.

References

1. Rideout, D. C.; Breslow, R. *J. Am. Chem. Soc.* **1980**, *102*, 7816.
2. (a) Breslow, R.; Maitra, U.; Rideout, D. C. *Tetrahedron Lett.* **1983**, *24*, 1901. (b) Breslow, R.; Maitra, U. *Tetrahedron Lett.* **1984**, *25*, 1239. (c) Breslow, R.; Guo, T. *J. Am. Chem. Soc.* **1988**, *110*, 5612. (d) Breslow, R. *Acc. Chem. Res.* **1991**, *24*, 159 and references cited therein.
3. Kumar, A. *Chem. Rev.* **2001**, *101*, 1.
4. Breslow, R.; Rizzo, C. A. *J. Am. Chem. Soc.* **1991**, *113*, 4340.
5. Rizzo, C. A. *J. Org. Chem.* **1992**, *57*, 6382.
6. (a) Hofmeister, F. *Ach. Exptl. Pathol. Pharmakol.* **1888**, *24*, 247. For details see (b) Collins, K. D.; Washabaugh, M. W. *Quart. Rev. Biophys.* **1985**, *18*, 323.
7. (a) Kumar, A.; Phalgune, U. D.; Pawar, S. S. *J. Phys. Org. Chem.* **2001**, *14*, 577. (b) Kumar, A.; Phalgune, U. D.; Pawar, S. S. *J. Phys. Org. Chem.* **2000**, *13*, 555. (c) Pawar, S. S.; Phalgune, U. D.; Kumar, A. *J. Org. Chem.* **1999**, *64*, 7055. (d) Kumar, A. *Pure and Appl. Chem.* **1998**, *70*, 615. (e) Kumar, A. *J. Phys. Org. Chem.* **1996**, *9*, 287. (f) Kumar, A. *J. Org. Chem.* **1994**, *59*, 4612. (g) Kumar, A. *J. Org. Chem.* **1994**, *59*, 230.
8. (a) Schneider, H.-J.; Sangwan, N. K. *J. Chem. Soc., Chem. Commun.* **1986**, 1787. (b) Schneider, H.-J.; Sangwan, N. K. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 896. (c) Schneider, H.-J.; Sangwan, N. K. *J. Chem. Soc., Perkin Trans. 2* **1989**, 1223.
9. Bonner, O. D. *J. Chem. Thermodyn.* **1976**, *8*, 1167.
10. Kumar, A. *J. Solution Chem.* **2001**, *30*, 281.
11. (a) Debye, P.; McAulay, J. *Phys. Z.* **1925**, *26*, 22. (b) Long, F. A.; McDevitt, F. W. *Chem. Rev.* **1952**, *52*, 119.

(c) McDevitt, F. W.; Long, F. A. *J. Am. Chem. Soc.* **1952**, *74*, 1773.

12. Though the solubilities of **1** were measured in all the salt solutions, they are shown in Fig. 2 only for few systems for the sake of clarity.
13. For working equations see: (a) Shoor, S. K.; Gubbins, K. E. *J. Phys. Chem.* **1969**, *73*, 498. (b) Pierotti, R. A. *Chem. Rev.* **1976**, *76*, 717. For appropriate mixing rule see: (c) Kumar, A. *J. Am. Chem. Soc.* **1993**, *115*, 9243. (d) For application to organic reactions see: Ref. 7c.
14. Marcus, Y. *Ion Solvation*; Wiley: New York, 1986.
15. Millero, F. J. In *Water and Aqueous Solutions*; Horne, R. A., Ed.; Wiley: New York, 1972.
16. (a) Horvath, A. L. *Handbook of Aqueous Electrolyte Solutions*; Wiley: Chichester, UK, 1985. (b) Breslow, R.; Guo, T. *Proc. Natl Acad. Sci. USA* **1990**, *87*, 167.
17. (a) von Hippel, P. H.; Wong, K.-Y. *Science* **1964**, *145*, 577. Also see: (b) von Hippel, P. H.; Wong, K.-Y. *J. Biol. Chem.* **1965**, *240*, 3909. (c) von Hippel, P. H.; Schleich, T. *Acc. Chem. Res.* **1969**, *9*, 257. (d) Castellino, F. J.; Barker, R. *Biochemistry* **1968**, *7*, 4135. (e) Castellino, F. J.; Barker, R. *Biochemistry* **1968**, *7*, 3439.
18. Gratzer, W. B.; Beaven, G. H. *J. Phys. Chem.* **1969**, *73*, 2270.
19. (a) Drljaca, A.; Hubbard, C. D.; van Aldik, R.; Asono, T.; Basilevsk, M. V.; Le Noble, W. J. *Chem. Rev.* **1998**, *98*, 2167. (b) van Eldik, R.; Asono, T.; LeNoble, W. J. *Chem. Rev.* **1989**, *89*, 549. (c) Le Noble, W. J. *Progress in Physical and Organic Chemistry*, Vol. 5; Interscience: New York, 1967; p 207.
20. Densities were determined using a digital densitometer (Metler Paar) with an accuracy of 10×10^{-6} g cm^{-3}.
21. McCabe, J. R.; Grieger, R. A.; Eckert, C. A. *Ind. Engng Chem. Fundam.* **1970**, *9*, 156.