

An analysis of complex alkyl-substituent effects in the water-catalyzed hydrolysis of 1-acyl-1,2,4-triazoles[#]

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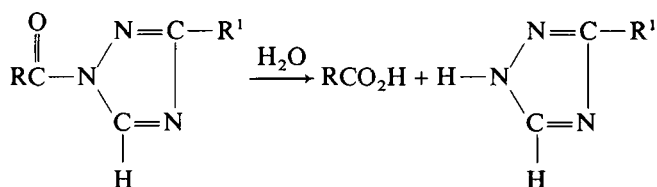
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Abstract. Pseudo-first-order rate constants and thermodynamic activation parameters have been determined for the water-catalyzed hydrolysis of the 1-acyl-1,2,4-triazoles **1-9** in water and in aqueous acetonitrile [$x(\text{H}_2\text{O}) = 0.80$]. The reaction occurs via water-catalyzed nucleophilic attack of water at the amide carbonyl group. Variation of the alkyl group in the acyl part of the substrate led to the sequence of reactivities (in water): $\text{R} = t\text{-Bu} > i\text{-Pr} > \text{Et} > \text{Me} > n\text{-Pr} > s\text{-Bu} > i\text{-Pent} > \text{neo-Pent}$. This complex behavior strongly suggests the operation of a composite steric effect most likely involving contributions from conformational preference (*SE1*), change of coordination number at carbonyl carbon (*SE2*), steric repulsion between O^2 and the alkyl group (*SE3*), and steric inhibition of solvation (*SE4*). Modelling of the relative rates in water in terms of the expanded branching equation gave satisfactory results. Two possible transition states are proposed for the neutral hydrolysis, one involving intramolecular hydrogen bonding between the second water molecule and N^2 of the 1,2,4-triazole ring. The different sequence of reactivities for neutral hydrolysis in aqueous acetonitrile as well as the rates for hydroxide-ion-catalyzed hydrolysis in water ($B_{\text{Ac}2}$ mechanism) support the analysis of substituent effects.

Introduction

1-Acyl-1,2,4-triazoles belong to a class of activated amides which undergoes hydrolysis under mild (pH, temperature) conditions¹. The rates of hydrolysis are pH-independent in the pH range ca. 3-6. Under these conditions the hydrolysis involves water-catalyzed nucleophilic attack of water on the amide carbonyl group. The process proceeds via a transition state containing two water molecules and in which three protons are in flight^{2,3}. Clearly, the nucleophilic attack is assisted by a second water molecule acting as a general base.



The hydrolysis of 1-acyl-1,2,4-triazoles is an excellent model reaction for the study of hydrophobic effects on chemical reactivity in water-rich mixed aqueous solvent systems^{4,5}. In addition, the reaction has been employed as a model process in studies of catalytic and inhibitory effects of micelles⁶, micelle-polymer complexes⁷ and of reactions in hydrophobic microdomains within water-soluble polymers⁸. Therefore, it is of great importance to understand the relative reactivities in a series of 1-acyl-1,2,4-triazoles as a function of the substituents R and R¹. In previous studies, variation of R and R¹ has been used to vary the hydrophobicity of the substrate⁴⁻⁸.

Herein we report an analysis of the relative rate constants for the neutral hydrolysis of a series of 1-acyl-1,2,4-triazoles (**1-9**; R¹ = H) in water as a function of the alkyl substituent R. The results are quite surprising (highest reactivity for R = *t*-Bu). The analysis is couched in terms of the expanded branching equation and provides evidence for the operation of a composite steric effect.

[#] Dedicated to Professor G. J. M. van der Kerk on the occasion of his 75th birthday.

Table I Pseudo-first-order rate constants and thermodynamic activation parameters for the neutral hydrolysis of the 1-acyl-1,2,4-triazoles 1-9 in H₂O and D₂O at 25°C^a.

Compd.	R	10 ⁴ × k _{obs} (s ⁻¹)		k(H ₂ O)/k(D ₂ O)	ΔG [#] (kJ·mol ⁻¹)	ΔH [#] (kJ·mol ⁻¹)	ΔS [#] (J·mol ⁻¹ ·K ⁻¹)
		H ₂ O	D ₂ O				
1	(CH ₃) ₃ C	33.7	11.0	3.26	86.3	38.2	-164
2 ^b	(CH ₃) ₂ CH	33.4	9.87	3.38	87.2	35.1	-175
3 ^b	CH ₃ CH ₂	29.7	9.40	3.16	87.4	41.4	-156
4 ^b	CH ₃	20.9	6.86	3.04	88.3	43.1	-152
5 ^b	CH ₃ CH ₂ CH ₂	17.4	5.26	3.31	88.8	38.1	-170
6	CH ₃ CH ₂ CH(CH ₃)	9.80	2.96	3.34	90.2	36.3	-181
7	(CH ₃) ₂ CHCH ₂	4.19			92.3	39.0	-179
8	(CH ₃ CH ₂) ₂ CH	0.941			96.0	42.4	-180
9	(CH ₃) ₃ CCH ₂	0.427	0.103	4.15	98.0	43.1	-184

^a pH (pD) ca. 4.2. ^b Data from ref. 2.

Results and discussion

Pseudo-first-order rate constants (k_{obs}) and thermodynamic activation parameters for the neutral hydrolysis of 1-9 in water are listed in Table I. Kinetic solvent deuterium isotope effects were determined for hydrolysis of 1-6 and 9 and indicate that the substrates react via the same mechanism. The enthalpies and entropies of activation exhibit a complex compensatory behavior as a function of substituent which is a usual feature for organic reactions in water⁹.

Large solvation changes during the activation process are indicated by the strongly negative entropies of activation. The k_{obs} values decrease in the series R = *t*-Bu > *i*-Pr > Et > Me > *n*-Pr > *s*-Bu > *i*-Bu > *i*-Pent > *neo*-Pent. Quite unexpectedly, the most rapid hydrolysis is found for the sterically much hindered substrate 1 (R = *t*-Bu). There is no significant correlation between $\log k_{\text{obs}}$ and carbonyl stretching frequencies [$\nu(\text{C}=\text{O})$]¹⁰, Taft's steric substituent constants (E_s)¹¹, Rekker's hydrophobic fragmental constants (f_i)¹², Charton's steric substituent constants for S_N2 reactions (ν')¹³, polarisabilities (P) of the alkyl moieties¹⁴, or inductive substituent constants (σ_I)¹⁵ (Table II).

Table II Carbonyl stretching frequencies and alkyl substituent constants for the 1-acyl-1,2,4-triazoles 1-9.

Compd.	$\nu(\text{C}=\text{O})$ (cm ⁻¹)	E_s	f_i	ν'	P	σ_I
1	1739	1.54	2.26	1.23	8.5	0.300
2	1754	0.47	1.64	0.62	6.5	0.200
3	1756	0.07	1.23	0.38	3.8	0.056
4	1759	0	0.70	0.35	0.0	0.046
5	1755	0.36	1.76	0.42	5.6	0.061
6	1753	1.13	2.17			0.210
7	1756	0.93	2.17	0.55		0.125
8	1752	1.98	2.70			0.286
9	1751	1.74	2.79		8.2	0.229

The relative reactivities within the series 1-9 will be analyzed in terms of primarily steric effects, assuming that the localized (field and/or inductive) and the delocalized (resonance) electrical effects of the alkyl (R) groups are constant¹⁶⁻¹⁸. Alkyl groups can therefore exert only steric and polarizability effects. Usually, steric effects cannot be analyzed using a single steric parameter. A major reason is, that steric effects are conformationally dependent¹⁹. However, in previous work it has been shown that steric effects

of alkyl groups are well modelled by the expanded branching (XB) equation¹⁹

$$Q = \sum_{i=1}^m \sum_{j=1}^3 a_{ij}n_{ij} + a_{00}$$

in which Q is the quantity to be correlated, m is the total number of carbon atoms in the longest chain of the alkyl group minus one, j the number of branches and n_{ij} the number of branches at the labelled carbon atom i . The branching parameters n_{ij} are obtained for an alkyl group by first numbering the group as shown in Fig. 1, starting with the carbon atom bonded to the rest of the molecule. The second digit indicates whether it is the first, second, or third branch at the carbon atom to which it is bonded. Hydrogen atoms are ignored. The parameter n_{ij} is equal to the number of atoms designated ($i + 1, j$).

The polarizability of an alkyl group is a linear function of the number of carbon atoms (n_c) in the group²⁰. It is therefore possible to represent the overall effect of an alkyl group by the expression

$$Q = \sum_{i=1}^m \sum_{j=1}^3 a_{ij}n_{ij} + a_c n_c + a_{00}$$

Correlation of the k_{obs} values for hydrolysis of 1-9 in water gave as the best correlation equation:

$$\log(k_{\text{obs}}/\text{s}^{-1}) = -0.676(\pm 0.145)n_{21} - 1.20(\pm 0.244)n_{23} + 1.51(\pm 0.107) \quad (1)$$

For this correlation the value of $100R^2$ (the percent of the variance of the data accounted for by the correlation equation) is 92.24, whereas $F = 35.67$, $S = 0.226$, $n = 9$ and $r_{21,23} = 0.177$ (for the meaning of these symbols see ref. 13). Similar results were obtained for hydrolysis of seven substrates in D₂O, the best correlation equation is ($100R^2 = 98.91$, $F = 91.00$, $S = 0.106$, $n = 7$, $r_{11,21} = 0.354$, $r_{11,23} = 0.16$, $r_{21,23} = 0.471$):

$$\log(k_{\text{obs}}(\text{D}_2\text{O})/\text{s}^{-1}) = 0.167(\pm 0.122)n_{11} - 0.407(\pm 0.0967)n_{21} - 1.58(\pm 0.130)n_{23} + 0.836(\pm 0.106) \quad (2)$$

Using a recently developed technique, the Zeta method²¹, we may combine the data in water and in D₂O into a single data set. The Zeta method makes use of internal parameterization to account for some variable of interest. It is very useful for combining small data sets measured under condi-

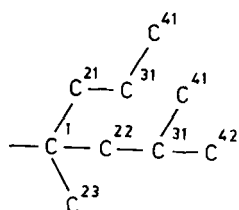


Fig. 1. Branching parameters $n_{11} = 1$, $n_{12} = 1$, $n_{13} = 1$, $n_{21} = 2$, $n_{22} = 0$, $n_{23} = 0$, $n_{31} = 2$, $n_{32} = 1$, $n_{33} = 0$.

tions such that some variable is held constant throughout the set but varies from one set to another. In this case it is necessary to account for the solvent effect of D_2O and of water. The method requires that values of Q measured under the same conditions as the members of the data sets be available for the same substituent in both solvents. As the solvent parameter Zeta we have chosen values of $\log 10^4 k$ for the neutral hydrolysis of 1-benzoyl-1,2,4-triazole in water and in D_2O ($k_{obs} = 20.9$ and 7.91 respectively). The data were then correlated with the equation

$$\log(10^4 k_{obs}/s^{-1}) = Z \zeta + a_{11}n_{11} + a_{21}n_{21} + a_{23}n_{23} + a_{00} \quad (3)$$

giving:

$$\log(10^4 k_{obs}/s^{-1}) = 1.06(\pm 0.233)\zeta + 0.222(\pm 0.154)n_{11} - 0.642(\pm 0.0878)n_{21} - 1.34(\pm 0.151)n_{23} - 0.970(\pm 0.292) \quad (4)$$

$100R^2 = 94.69$; $F = 49.05$; $S = 0.190$; $n = 16$.

As a_{11} is not significant we may exclude n_{11} as a variable. We then obtain

$$\log(10^4 k_{obs}/s^{-1}) = 1.05(\pm 0.243)\zeta - 0.601(\pm 0.0868)n_{21} - 1.33(\pm 0.157)n_{23} + 0.0788(\pm 0.276) \quad (5)$$

$100R^2 = 93.69$; $F = 59.39$; $S = 0.190$; $n = 16$

$r_{\zeta,21} = 0.194$; $r_{\zeta,23} = 0.048$; $r_{21,23} = 0.271$

These results clearly confirm those obtained in the separate correlations of the data sets in water and in D_2O . With 16 data points and only three parameters equation 5 provides strong evidence for significant steric retardation at C^2 and little or no steric effect at C^1 .

For the 1-acyl-1,2,4-triazoles **1**, **3**, **4**, **6**, and **7** k_{obs} values were also determined in aqueous acetonitrile [Table III, mole fraction of water, $x(H_2O) = 0.800$]²². Because of the

Table III Pseudo-first-order rate constants for the neutral hydrolysis of some 1-acyl-1,2,4-triazoles in acetonitrile-water mixtures [$x(H_2O) = 0.800$]^{a,b} at $25^\circ C$.

Compd.	$10^4 \times k_{obs}$	$k(H_2O)/k(MeCN-H_2O)$
1	1.28	27
3	2.42	12.3
4	2.22	9.4
6	0.553	17
7	0.292	14

^a $x(H_2O)$ = mole fraction of water. ^b pH ca. 4.2.

limited number of data, the results of the correlation are less certain and can only be considered as indicative. The

best equation ($100R^2 = 93.79$, $F = 15.10$, $S = 0.140$, $n = 5$, $r_{11,23} = 0.408$) is:

$$\log(k_{obs}/s^{-1}) = -0.258(\pm 0.171)n_{13} - 0.761(\pm 0.140)n_{21} + 0.366(\pm 0.0989) \quad (6)$$

It is clear that the sequence of reactivities is quite solvent dependent. However, in all three media there is a significant decremental effect due to the first branch at C^2 . In both water and deuterium oxide there is also evidence for a significant decremental effect due to the third branch at C^2 . No substrates with a third branch at C^2 have been studied in aqueous acetonitrile.

In none of the media studied is there a significant dependence on the second branch at C^2 . This pattern suggests a composite steric effect. No dependence on branching at C^1 is observed in water. A possible small incremental effect of the first branch at C^1 is found in D_2O , and a possible small decremental effect is observed for the third branch at C^1 in aqueous acetonitrile.

Overall, the results show that there is little or no dependence on branching at C^1 and significant decremental steric effects due to branching at C^2 . These conclusions are best accounted for by a combination of incremental and decremental steric effects. No dependence on polarizability was observed but such a dependence cannot be excluded as n_C is significantly linear in some of the n_{ij} .

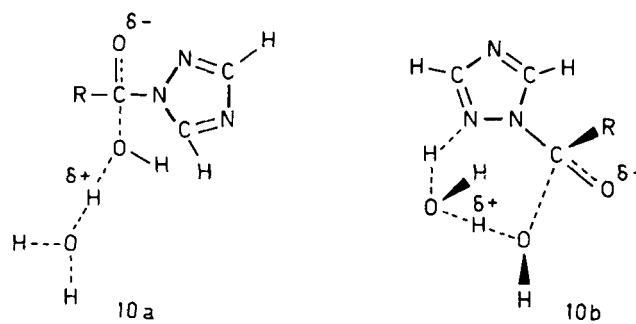


Fig. 2. Schematic representation of two possible transition states for the neutral hydrolysis of **1-9**.

The above results can be reconciled (Fig. 2) with two slightly different transition states **10a** (proposed previously)² and **10b**²³, for the neutral hydrolysis of **1-9**. Both can account for the observed deuterium isotope effects², the proton inventory², and the large negative entropies of activation². The composite steric effects may then be explained by considering contributions of four separate processes. They are:

- (1) *Conformational preference.* Some delocalization of π electrons must occur in **1-9** resulting in an amide NC bond order greater than one²⁴. Thus, there should be a planar conformation (interplanar angle $\theta = 0$) and a noncoplanar conformation ($\theta \neq 0$). Branching at C^1 should cause an increase in the population of the noncoplanar conformation. As this is the conformation required for the transition state, there will be an incremental effect of branching at C^1 on the rate constant.
- (2) *Change of coordination number (and hybridization) of the carbonyl carbon atom.* The increase in coordination number in the transition state as compared with the reactant should result in a decremental effect of branching at both C^1 and C^2 of the alkyl group on the rate constant.
- (3) *Steric repulsion of O^2 (second water) by the alkyl group.*

Branching at C¹ should have little influence, branching at C² may induce a decremental effect on the rate constant (10b).

(4) *Steric inhibition of solvation* of the developing charge on the carbonyl oxygen in the transition state²⁵.

These effects are designated *SE1*, *SE2*, *SE3* and *SE4*, respectively. The observed substituent effect will be the sum of contributions from individual steric effects. Thus, we may describe *SE1* using the XB equation:

$$SE1 = \sum_{i=1}^m \sum_{j=1}^3 a_{ij(1)} n_{ij(1)} + a_{00(1)}$$

In general, for the *k*th steric effect:

$$SEk = \sum_{i=1}^m \sum_{j=1}^3 a_{ij(k)} n_{ij(k)} + a_{00(k)}$$

The overall steric effect, which is the observed substituent effect, will then be given by:

$$\Sigma SE = \sum_{i=1}^m \sum_{j=1}^3 \sum_{k=1}^4 a_{ij(k)} n_{ij(k)} + a_{000}$$

The incremental effect of branching in *SE1* and the decremental effect in *SE2* apparently are of the same magnitude and roughly cancel out, resulting in a significant steric effect only from branching at C². The mechanism proposed by Hogg et al.^{23a} cannot easily account for the steric effects. Their cyclic transition state containing a large ring with four water molecules^{23a} does not require a noncoplanar conformation. However, one point needs further comment. In transition state 10b (Fig. 2), hydrogen bonding occurs at N² rather than at N⁴ although the latter is the more basic nitrogen atom. We note that in aqueous solution the lone pairs on both N² and N⁴ will be hydrogen-bonded to water molecules. The greater ease and higher probability that two water molecules will form the ring in transition state 10b as compared with that of four water molecules closing the ring in the transition state proposed by Hogg et al.^{23a} may well more than make up for the difference in basicity. Only if the transition state were to involve proton transfer to nitrogen (which is not the case), would the difference in basicity of N² and N⁴ be of major importance.

The operation of *SE4* is indicated by the change in the sequence of reactivities going from water to MeCN-H₂O [*x*(H₂O) = 0.80, Table III]. Steric hindrance of solvation is increased and the ratio of rate constants *k*(H₂O)/*k*(MeCN-H₂O) (Table III) is roughly that expected on the basis of *E_s*.

That the substituent effects labelled as *SE2* and *SE4* should be decremental with regard to branching at C¹ is supported by the second-order rate constants [*k*(OH)] for the hydroxide-ion-catalyzed hydrolysis (25°C) of the 1-acyl-1,2,4-triazoles 1 [*k*(OH) = 0.577 × 10⁻³ l·mol⁻¹·s⁻¹], 4 [*k*(OH) = 2.44 × 10⁻³ l·mol⁻¹·s⁻¹], and 9 [*k*(OH) =

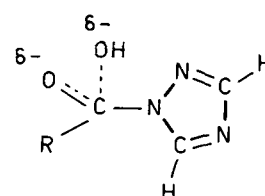


Fig. 3. Schematic representation of the transition state for hydroxide-ion-catalyzed hydrolysis of 1-9.

1.04 × 10⁻³ l·mol⁻¹·s⁻¹]. This reaction most likely occurs via a B_{AC}2 mechanism involving a transition state shown in Figure 3. Now both R = *t*-Bu (1) and R = *neo*-Pent (9) exhibit decremental steric effects, that of the former, which is entirely due to branching at C¹, being larger than that of the latter. Apparently, the average decremental branching effect at C¹ is about three times that at C².

Experimental

Infrared spectra were obtained using a Perkin Elmer Grating Spectrophotometer (model 125). Ultraviolet spectra were recorded on a Perkin Elmer Lambda 5 uv/vis spectrophotometer (at 25°C) coupled to a Perkin Elmer 3600 data station. The ¹H NMR spectra were taken on a Hitachi Perkin Elmer R-24B instrument, using CDCl₃ as the solvent and TMS (δ 0 ppm) as internal standard.

Materials

The 1-acyl-1,2,4-triazoles 2-5 have been prepared previously². The new substrates 1 and 6-9 were synthesized according to the following general procedure. A suspension of 1,2,4-triazole (1.38 g, 20 mmol) and pyridine (1.58 g, 20 mmol) in benzene (20 ml) was added during ½ h to the appropriate acyl chloride (20 mmol) in benzene (20 ml). After stirring for 24 h, pyr·HCl was filtered off and the solvent was removed *in vacuo*. The remaining material was distilled twice to yield the desired 1-acyl-1,2,4-triazoles in yields of 30-50%. Physical properties which support the structural assignments are listed in Table IV. The observation of two different ring-proton chemical shifts excludes the formation of 4-acyl-1,2,4-triazoles. No accurate elemental analyses could be obtained because of rapid hydrolysis. The presence of small amounts of hydrolysis products could be ascertained by ¹H NMR spectroscopy, and were found to have no effect on the observed rate constants.

Solutions

The water used in the kinetic experiments was demineralized and distilled twice in an all-quartz distillation unit. D₂O (99.75%) was obtained from Merck and used as such. Acetonitrile (Aldrich) was the best grade available and was used as such. All solutions for neutral hydrolysis were acidified with HCl (DCI) to pH (pD) around 4.2 to suppress catalysis by OH⁻ (OD⁻). Hydroxide-ion-catalyzed reactions were studied in NaOH solutions prepared from Merck Titrisol. Rates were determined at at least three OH⁻ concentrations (0.005, 0.02, 0.05 M), which were high enough to provide pseudo-first-order kinetics.

Table IV Physical data of the new 1-acyl-1,2,4-triazoles.

Compd.	B.p. (°C/torr)	λ _{max} (nm)		¹ H NMR
		MeCN	H ₂ O	
1	77/15	224	219	1.52 (9H), 7.98 (1H), 8.92 (1H)
6	88-89/16	223	219	1.22 (6H), 1.68 (2H), 3.58 (1H), 7.95 (1H), 8.87 (1H)
7	91-92/15	225	218	1.06 (6H), 2.33 (1H), 3.02 (2H), 8.02 (1H), 8.92 (1H)
8	95-96/16	224	219	0.92 (6H), 1.74 (4H), 8.02 (1H), 8.95 (1H)
9	97-98/18	223	219	1.10 (9H), 3.04 (2H), 8.02 (1H), 8.97 (1H)

Kinetic measurements

Pseudo-first-order rate constants (k_{obs}) were determined by following the change of absorbance at 225 nm. The reactions were carried out in 1.00-cm quartz cuvettes placed in the thermostated ($\pm 0.05^\circ\text{C}$) cell holders of a Varian Cary 210 uv/vis spectrophotometer (connected to an Apple computer) or a Perkin Elmer Lambda 5 uv/vis spectrophotometer (coupled to a Perkin Elmer 3600 data station). The hydrolyses were followed for at least 10 half-lives. Rate constants (calculated by computer) were reproducible to within 2%.

Thermodynamic activation parameters (Eyring equation) were obtained from rate constants at four different temperatures in the range 20–40°C. Estimated errors are 0.2 kJ·mol⁻¹ in ΔG^\ddagger , 0.8 kJ·mol⁻¹ in ΔH^\ddagger , and 2 J·mol⁻¹·K⁻¹ in ΔS^\ddagger .

Second-order rate constants [$k(\text{OH}^-)$] for hydroxide-ion catalyzed hydrolysis were measured with an Aminco-Morrow stopped-flow apparatus equipped with a single beam monochromator and a data acquisition storage and retrieval (DASAR) system. Temperatures were measured with a thermocouple and were constant within $\pm 0.05^\circ\text{C}$. The $k(\text{OH}^-)$ values (estimated error 3%) were obtained from the linear plots of $\log k_{\text{obs}}$ vs. $[\text{OH}^-]$.

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- ²² This mixture can be characterized as a typically non-aqueous solution and does not show large deviations from thermodynamically ideal behavior. See: *F. Franks* in "Water. A Comprehensive Treatise", *F. Franks*, Ed.; Plenum Press: New York, 1973; Vol. 2, Chapter 1.
- ²³ Cyclic transition states have been proposed previously for water-catalyzed hydrolysis reactions:
 - ^a *J. F. Patterson*, *W. P. Huskey* and *J. L. Hogg*, *J. Org. Chem.* **45**, 4675 (1980);
 - ^b *W. P. Huskey*, *C. T. Warren* and *J. L. Hogg*, *J. Org. Chem.* **46**, 59 (1981);
 - ^c *G. Gopalakrishna* and *J. L. Hogg*, *J. Org. Chem.* **49**, 3161 (1984). For the hydrolysis of **1–9** a transition state may be envisioned containing three water molecules in the ring. However, this structure is less likely, mainly in view of the results of the proton inventory².
- ²⁴ *J. Elguero*, *C. Marzin* and *L. Pappalardo*, *Bull. Soc. Chim. Fr.* 1137 (1974).
- ²⁵ For an early study of steric hindrance to solvation, see: *W. M. Schubert*, *J. M. Craven*, *R. G. Minton* and *R. B. Murphy*, *Tetrahedron* **5**, 194 (1959).