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Coulomb repulsion in multiply charged ions: a computational study of the effective dielectric constants of organic spacer groups

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Abstract

Using dication and dianion models, effective dielectric constants have been calculated for several organic spacer groups (alkyl, poly-ether, and poly-ketone). Specifically, ab initio calculations at the MP2/6-31+G(d,p)//HF/6-31+G(d) level were used to estimate the ΔH_{acid} and the proton affinity (PA) values of a series of diammonium and dialkoxide ions, respectively. The variation in these values as a function of the distance between charges leads to the effective dielectric constant (ϵ) of the organic spacer group. For all the spacer groups, effective dielectric constants near unity were obtained indicating that the spacer group does not reduce the Coulomb repulsion in the doubly charged ion (relative to a vacuum). The values obtained in this study are all slightly less than unity (~ 0.85) because the definition of the charge separation as the distance between the formal charge centers (N or O) neglects delocalization and overestimates the true charge separation. For similar reasons, ϵ values slightly less than unity are also appropriate for zwitterionic systems. (Int J Mass Spectrom 185/186/187 (1999) 351–357) © 1999 Elsevier Science B.V.

Keywords: Coulomb explosion; Multiply charged ions; Ab initio calculations; Dielectric constants

1. Introduction

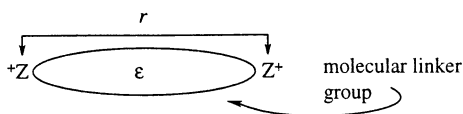
The development of electrospray ionization has allowed chemists to efficiently and selectively generate multiply charged ions in the gas phase [1–4]. Access to multiply charged ions has been particularly valuable in the study of polymeric materials (synthetic or biochemical) because high charge states reduce the mass-to-charge ratio and allow large molecules to be brought into workable mass ranges for conventional

instruments. Beyond simple mass analysis, there has been interest in how multiple charges can affect the structure and conformation of a substrate. For example, protein structures have been probed in the gas phase as a function of charge state and it has been observed that increasing charge leads to unfolding of the protein [5–9]. In addition, there has been interest in how multiple charges affect the reactivity of the ionized functional groups in a substrate. For example, several studies have been reported on the proton transfer behavior of multiply charged ions [10–21].

Of course the price of placing more than one charge on a substrate is the development of internal electrostatic repulsions. These can be very significant

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Dedicated to Professor Michael Bowers on the occasion of his 60th birthday.



Scheme 1.

and at short distances are greater than covalent bond strengths. For example, at a charge separation of 1.5 Å, the electrostatic repulsion (in a vacuum) is over 200 kcal mol⁻¹ or about twice the strength of a typical C–C bond. The electrostatic repulsion is inversely proportional to the charge separation and drops to much more manageable levels at longer distances, but it should play an important role in all multiply charged species. Electrostatic repulsion limits the number of charges that a substrate can bear [14, 16–18], it affects the conformational properties of the substrate [5–9,21], and it modifies the physical properties (i.e. acidity, basicity, etc.) [10–20] and reactivity of the substrate [22,23]. As a result, a reasonable estimate of the electrostatic repulsion is of critical importance in the study of multiply charged ions.

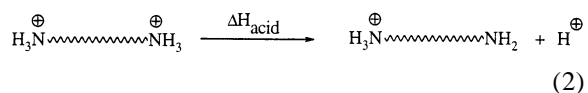
For the situation outlined in Scheme 1, the electrostatic repulsion between the two charges can be modeled with a simple Coulomb potential:

$$E_{\text{rep}} = q^2/\epsilon r \quad (1)$$

where r is the distance between the two charges and ϵ is the dielectric constant of the medium between the charges. However, application of this equation to molecular systems is problematic because ϵ and r are difficult to define in this environment. To a first approximation, r can be defined as the distance between the atoms bearing the formal charges, however, this is a somewhat simplistic view because charge is usually spread over several atoms either through resonance or polarization. As a result, there is some inherent uncertainty in this definition of r . The dielectric constant presents a problem because it is a bulk rather than a molecular property so no direct analogy is possible. One could assume that the molecular fragment between the charges has no effect on the Coulomb potential and use an effective dielectric of unity (vacuum dielectric). Conversely, one could

treat the intervening molecular fragment with a microsolvation approach and model it with the dielectric constant of an analogous, bulk solvent ($\epsilon = \sim 2\text{--}50$ depending on the functional groups). Even the lowest ϵ values in this range would lead to a dramatic reduction (at least a factor of 2) in the calculated electrostatic repulsion (as compared to a vacuum). In gas phase work, an ϵ value of 1 has been assumed in some cases [15,20], but models of proteins in aqueous solution generally point to ϵ values in the range from 2–5 for the protein interior [24]. In addition, an ϵ value of 2.0 has been reported for cytochrome *c* in the gas phase [16] although values closer to unity have been determined for other systems using the same approach [17,18]. Clearly, an accurate estimate of ϵ is required in order to calculate electrostatic repulsions in a meaningful way because varying assumptions about ϵ lead to huge variations in the calculated E_{rep} .

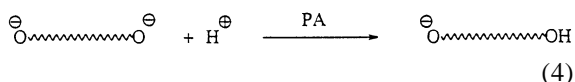
One approach for estimating the ϵ value of organic spacer groups is to investigate the physical properties of doubly charged ions as a function of the distance between the charges. Acid/base behavior is an ideal property to examine because it involves a charge separation process and therefore, the electrostatic repulsion is released in the reaction. For example, when the following dication acts as an acid, the ΔH_{acid} value can be modeled by combining the inherent acidity of the functional group with the electrostatic repulsion that is released (Coulomb potential)



$$\begin{aligned} \Delta H_{\text{acid}} &= \Delta H_{\text{acid}}(\text{model}) - E_{\text{rep}} \\ &= \Delta H_{\text{acid}}(\text{model}) - q^2/\epsilon r \end{aligned} \quad (3)$$

$\Delta H_{\text{acid}}(\text{model})$ in this equation represents the acidity of a singly charged (monofunctional) analog (i.e. RNH₃⁺). It should be noted that approximations related to Eq. (3) have been presented in the past by others [15–21]. If a series of homologous dications with different r values is considered, a plot of ΔH_{acid} versus $1/r$ has a slope of $-q^2/\epsilon$ and an intercept of

$\Delta H_{\text{acid}}(\text{model})$. A similar set of equations can be developed for the proton affinity (PA) of a dianion



$$\text{PA} = \text{PA}(\text{model}) + E_{\text{rep}}$$

$$= \text{PA}(\text{model}) + q^2/\epsilon r \quad (5)$$

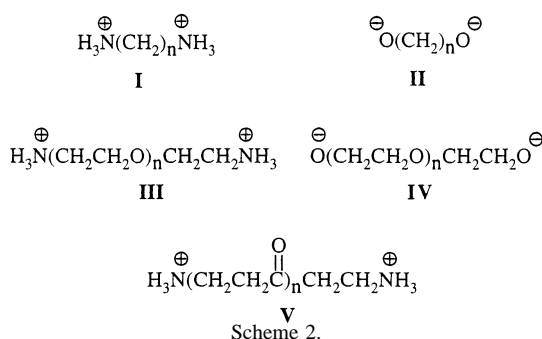
The main difference is that the slope is $+q^2/\epsilon$ because PA is defined as the $-\Delta H$ of the process in Eq.(4). A requirement of this treatment is that the singly charged products of Eqs. (2) and (4) must be restricted to a conformation that does not allow for a hydrogen-bonding interaction between the two ends because this is a stabilizing effect that is not available to a monofunctional analog.

Unfortunately, it is very difficult to experimentally probe the thermodynamics of the acid/base behavior of doubly charged ions. Although proton transfers involving singly charged species typically have negligible barriers, there are large kinetic barriers when doubly charged ions are involved [25]. For example, any attempt to establish the equilibrium in Eq. (6) (where B is a neutral base) would suffer from a large, reverse activation barrier for bringing together two cations



Kinetic methods for estimating the energetics of the reaction in Eq. (6) are also complicated by the presence of the reverse activation barrier. Specifically, to convert from kinetic to thermodynamic values, one must also measure the reverse activation barrier (by kinetic energy release determinations) and have an estimate of the Coulomb energy already released at the dissociative transition state [25]. Williams and co-workers have attempted to use kinetic acidities to estimate effective ϵ values in several species, but their analysis of the data contains a flaw [16–18]. A detailed discussion of this problem has been presented elsewhere [25].

In the absence of a suitable experimental technique, computational chemistry becomes an attractive



alternative. Modern theoretical methods yield good values for acidities (basicities) and should be particularly accurate in the present context because the ϵ values are derived from the relative acidities (basicities) of a series of homologues. This will allow for an extensive cancellation of errors. In addition, the computational approach has the advantage that geometries are determined in the process of calculating acidities (basicities) so that r can easily be extracted from the data.

In the present study, a range of doubly charged ions have been explored (Scheme 2). Diammonium ions have been used as an example of a cationic system and dialkoxides have been used as an example of an anionic system. Three types of organic spacer groups have been used. A simple alkyl chain has been used as a nonpolar spacer and poly-ethers and ketones have been used as polar spacers. On the basis of the dielectrics of analogous solvents (hexane, diethyl ether, and acetone), these functional groups cover a wide range of polarities (ϵ values from 1.9–21). As a result, this data set should provide a good foundation for exploring the effects of spacer groups on observed properties such as acidity and basicity.

2. Methods

All the calculations were completed with the GAUSSIAN 94 suite of programs developed by Pople and co-workers [26]. The singly and doubly charged species were locked into all-trans (extended) conformations and optimized at the HF/6–31+G(d) level of theory. These geometries were then used for single

point calculations at the MP2/6–31+G(*d*, *p*) level. This approach includes correlation as well diffuse functions on the nonhydrogen atoms. It is capable of giving reasonably accurate values for acidities and basicities. For example, this theoretical model (including corrections for zero-point and thermal energies) predicts a PA for CH₃NH₂ that is very close to the literature value (215.3 [25] versus 214.9 kcal mol⁻¹ [27]). For the purposes of determining ϵ values, zero-point and thermal energy corrections have not been calculated for every case because they should be nearly constant across a series and are computationally expensive. Instead, the corrections have been calculated for the smallest homologue in each series and that value has been applied uniformly across the series. The validity of this approach has been tested in a few cases and it appears that it introduces a trivial error (<0.1 kcal mol⁻¹).

3. Results

3.1. Alkyl spacer

The ΔH_{acid} values for the alkyl diammoniums (I) are listed in Table 1. As expected, the values increase with increasing chain length because less Coulomb energy is released when the dication loses a proton. In Fig. 1, the ΔH_{acid} values are plotted versus $1/r$ where r is the N–N distance in the optimized structure of the dication. An excellent correlation is obtained and the linearity of the plot confirms the validity of the model expressed in Eq. 3. The slope of the line indicates an effective dielectric constant of 0.82 for this series. The intercept (222.2 kcal mol⁻¹) gives a very reasonable value for ΔH_{acid} (model). For example, the ΔH_{acid} value of CH₃(CH₂)₅NH₃⁺ is 221.7 kcal mol⁻¹ [27]. Williams and co-workers have studied some of the same diammonium ions experimentally [18]. When converted to ΔH_{acid} values, their data suggests that the diammoniums are much more acidic (by 10–20 kcal mol⁻¹) because they overcorrected for the reverse activation barrier [25]. However, they do obtain an effective dielectric constant of approximately 1

Table 1
Acidities of diammonium ions^a

Structure	<i>n</i>	ΔH_{acid}	<i>r</i>	
⁺ H ₃ N(CH ₂) _{<i>n</i>} NH ₃ ⁺	4	158.0	6.33	
	5	168.2	7.56	
	6	175.8	8.87	
	7	181.7	10.11	
	8	186.4	11.41	
	9	190.1	12.66	
	10	193.2	13.95	
	⁺ H ₃ N(CH ₂ CH ₂ O) _{<i>n</i>} CH ₂ CH ₂ NH ₃ ⁺	1	162.0	7.32
		2	179.3	10.80
		3	188.6	14.33
4		194.3	17.85	
5		198.0	21.36	
⁺ H ₃ N(CH ₂ CH ₂ C(O)) _{<i>n</i>} CH ₂ CH ₂ NH ₃ ⁺	1	164.8	7.61	
	2	182.2	11.41	
	3	191.4	15.20	

^aEnergies in kcal mol⁻¹ and distances in Å. Values refer to formation of monocation in extended conformation. Distance is ⁺N–N⁺ separation in dication.

because of a fortuitous cancellation of errors in their analysis.

The data (Table 2) for the alkyl dialkoxides (II) are also plotted in Fig. 1. Once again, an excellent correlation is seen. The slope leads to an effective dielectric constant of 0.86 and the intercept gives a PA (model) of 376.3 kcal mol⁻¹. For comparison, the PA of CH₃(CH₂)₅O⁻ is 373.1 kcal mol⁻¹ [28,29].

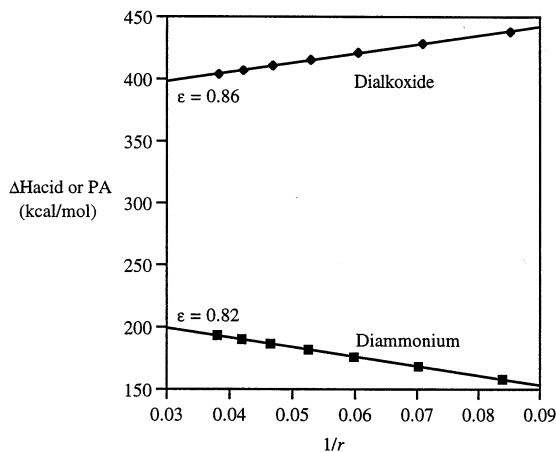


Fig. 1. Plots of ΔH_{acid} and PA versus $1/r$ for diammonium and dialkoxides ions with alkyl spacer groups; r is in bohr.

Table 2
Proton affinities (PA) of dialkoxides^a

Structure	<i>n</i>	PA	<i>r</i>
⁻ O(CH ₂) _{<i>n</i>} O ⁻	4	438.1	6.24
	5	428.4	7.49
	6	421.1	8.78
	7	415.3	10.04
	8	410.7	11.33
	9	406.9	12.59
⁻ O(CH ₂ CH ₂) _{<i>n</i>} CH ₂ CH ₂ O ⁻	10	403.9	13.87
	1	427.5	7.18
	2	408.8	10.71
	3	398.8	14.20
4	392.8	17.74	

^aEnergies in kcal mol⁻¹ and distances in Å. Values refer to formation of monoanion in extended conformation. Distance is ⁻O–O⁻ separation in dianion.

3.2. Poly-ether spacer

Data for the poly-ethers are listed in the tables and plotted in Fig. 2. For both the diammonium (III) and dialkoxide (IV) series, good correlations are seen. The effective dielectrics obtained from the plots are 0.83 and 0.80 for III and IV, respectively. The intercept for the diammonium series is 216.7 kcal mol⁻¹. For comparison, CH₃OCH₂CH₂NH₃⁺ has a ΔH_{acid} value of 221.9 kcal mol⁻¹ [27]. The dialkoxide series gives an intercept of 369.4 kcal mol⁻¹. For comparison, the

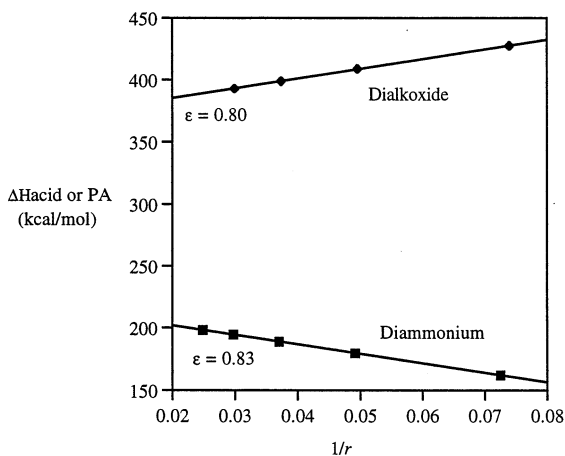


Fig. 2. Plots of ΔH_{acid} and PA versus $1/r$ for diammonium and dialkoxides ions with poly-ether spacer groups; *r* is in bohr.

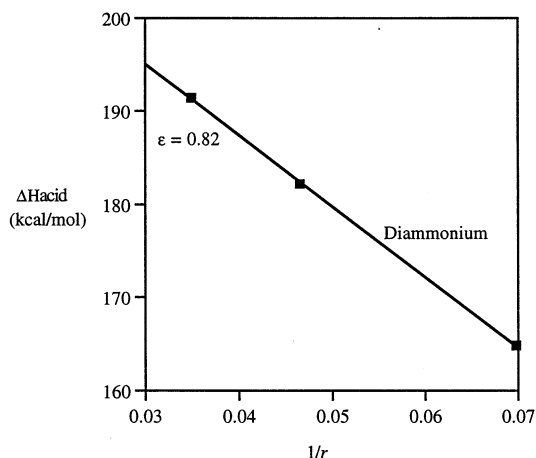


Fig. 3. Plot of ΔH_{acid} versus $1/r$ for diammonium ions with poly-ketone spacer groups; *r* is in bohr.

PA of CH₃OCH₂CH₂O⁻ is 375.6 kcal mol⁻¹ [28–30]. The differences between the intercepts and the model values are probably a result of using a simple ether to model an infinite poly-ether chain (intercept value). In addition, the experimental values also include contributions from internal hydrogen bonding.

3.3. Poly-ketone spacer

For the poly-ketones, only the diammonium series was considered and the data is in Table 1. The plot in Fig. 3 exhibits a good correlation and the slope indicates an effective dielectric of 0.82. The intercept gives a $\Delta H_{\text{acid}}(\text{model})$ of 217.8 kcal mol⁻¹. Unfortunately, there are no amino ketones available for comparison.

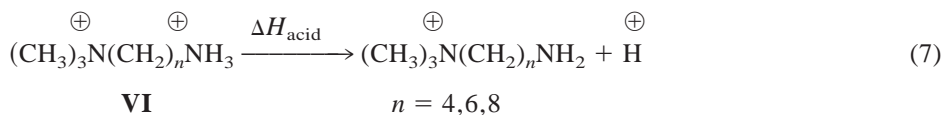
4. Discussion

The linearity of the plots in Figs. 1–3 provide a strong validation of the models presented in Eqs. (3) and (5). Further support comes from the sensible intercepts in the plots. The most striking feature of the data is the insensitivity of the effective dielectric to the nature of the organic spacer or the polarity of the charge. In each case, an ϵ value near unity is indi-

cated. In short, the organic spacers provide a dielectric medium that is best modeled by a vacuum ($\epsilon = 1$). This is not surprising because the region between the two charges experiences a relatively uniform electric field. As a result, there is little to be gained by polarizing the electron density of the spacer and the Coulomb potential is unaffected (i.e. $\epsilon = 1$). In an earlier paper, Fenselau and co-workers [15] used a similar argument to justify using an ϵ value of unity in their analysis. Although Gauss' law is fundamentally not applicable to molecular systems, it does help explain the ineffectiveness of spacer groups in stabilizing doubly charged ions. An outcome of Gauss' law is that in a uniform medium, excess charge will concentrate at the extrema of the medium. Of course, a molecule is not a uniform medium, but polarization of the spacer group would effectively result in shifting charge towards the center of the chain (i.e. a $[\delta^- \delta^+ \delta^- +]$ charge distribution for a dication) and would violate the principles of Gauss' law. The only way to reduce the electrostatic repulsion is to increase the distance between the charged centers. Consequently, it is not necessarily the dielectric of the medium between the like charges that is important; it is also the dielectric of the medium surrounding the system that mediates the electrostatic repulsion. For example, solvation of the end groups can effectively increase the charge separation and reduce the electrostatic repulsion. This type of behavior may play an important role in peptide systems where internal solvation

of the ionized groups (by other residues) could effectively stretch the charge separation and decrease the observed Coulomb repulsion. Of course, this effect is limited to small increases in the effective r because a large increase would imply the actual transfer of the charge to another functional group (residue).

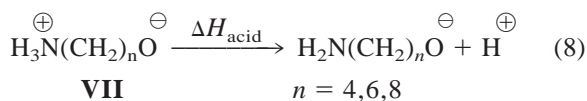
The other interesting feature of the data for the doubly charged ions is that all of the effective dielectric constants are less than unity. This is most likely a result of the way in which r is defined. As noted above, it is well known that charge is delocalized over several atoms in the gas phase either through resonance or polarization. For example, this is why CH_3NH_2 is much more basic than NH_3 in the gas phase (in CH_3NH_3^+ charge is delocalized onto the methyl group via polarization). In the diammoniums and dialkoxides this type of delocalization would be diminished because it effectively reduces the charge separation and therefore increases the Coulomb repulsion. However, it is likely that the charge is partially delocalized onto the adjacent carbons and therefore r is slightly less than the distance between the formal charge centers (N or O). Because ϵ is multiplied by r in Eqs. (3) and (5), an overestimation of r naturally leads to an underestimation of ϵ . Curvature in the plots versus $1/r$ is also expected, but the effect would be too subtle to detect at these distances. To test this rationalization, a system with a more symmetric ionic site was studied: **VI**



In the trimethylammonium group, charge should be more evenly delocalized onto each of the four carbons and therefore the locus of charge should be more closely centered on the nitrogen (i.e. r is more representative of the true charge separation). A plot of ΔH_{acid} versus $1/r$ leads to an ϵ value that is much closer to unity (0.94). This result suggests that charge delocalization is responsible for the small ϵ values that are observed in the other doubly charged systems.

Finally, a similar situation is expected for zwitterions. First, an effective dielectric greater than unity is not logical because a reduction of the Coulomb potential (i.e. polarization of the spacer) would decrease the stability of the system (the Coulomb potential is stabilizing in a zwitterion). Second, significant charge delocalization into the spacer is likely because a reduction in the effective r increases the Coulomb potential and stabilizes the system. As an

example, a plot of ΔH_{acid} versus $1/r$ for a zwitterion (VII) leads to an effective dielectric value of 0.90



5. Conclusion

In the region between ionized groups, organic spacer groups provide no stabilization and an effective dielectric of unity is appropriate for modeling doubly charged systems. This is independent of the nature of the spacer group. In practice, ϵ values slightly less than unity are observed because using the distance between the formal charges to define r tends to overestimate the true charge separation. Similar results are observed for zwitterionic systems.

Acknowledgements

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