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Review

Factors affecting selectivity of inorganic anions in capillary electrophoresis

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Abstract

Capillary zone electrophoretic separations of inorganic anions are largely governed by the intrinsic (infinite dilution) mobility of the anion. This in turn is a function of the hydrodynamic friction caused by the size of the ion and the dielectric friction caused by the charge density of the anion re-orienting the surrounding solvent. The influence of these factors on the mobility of anions is examined in both water and nonaqueous solvents. The influence of other experimental parameters, such as ionic strength, ion association, electroosmotic flow modifier concentration, and the addition of complexing agents such as polymeric cations, cyclodextrins, crown ethers and cryptands are also reviewed. From this discussion, some rules of thumb as to when different approaches will be most effective are drawn. © 1999 Elsevier Science B.V. All rights reserved.

Keywords: Buffer composition; Complexation; Non-aqueous capillary electrophoresis; Reviews; Selectivity; Inorganic anions

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1. Introduction

In recent years there has been great interest in capillary electrophoretic separations of inorganic ions. This interest is in large part because the selectivities offered by capillary electrophoresis are complementary to those of ion chromatography [1–4]. In chromatography separation selectivity is based on ion-exchange equilibria, whereas in capillary electrophoresis separations result from differences in ion mobilities. Thus for instance, F^- and acetate are both weakly retained on anion exchange columns and so difficult to separate using that technique. However they have significantly different mobilities and so can easily be separated by capillary zone electrophoresis (CZE).

Recent exhaustive reviews provide guidance as to how to control selectivity in separations of metal species by capillary electrophoresis [5,6]. Timerbaev points out that efficient separations based solely on differences in ionic mobility can only be achieved for some alkali, alkaline earth and a limited number of other group cations. Other metal groups such as the transition metals and lanthanides cannot be separated based on their native ionic mobilities. Such separations are best achieved using partial complexation with a suitable ligand. Common ligand systems include α -hydroxyisobutyric acid (HIBA) [7–10], lactic acid [11], 8-hydroxyquinoline-5-sulfonic acid (HQS) [12], Arsenazo I [13], Arsenazo III [14] and crown ethers [15–17]. Alternatively, metal ions can be irreversibly complexed prior to separation with ligands such as *trans*-cyclohexanediaminetetraacetic acid (CDTA) [18,19], 8-hydroxyquinoline-5-sulfonic acid (HQS) [20], 4-(2-pyridylazo)resorcinol (PAR) [21] and Arsenazo III [21].

However, for anionic species it is generally not possible to use complexation to modify selectivity. As a result, anion separations are much more dependent upon the intrinsic ionic mobilities of the anions. These mobilities can be subtly influenced by a

number of experimental parameters. Thus, this report will focus on the fundamental factors governing the ionic mobility of ions and the influence of experimental parameters such as solvent type, buffer counter-ion and ionic strength, and buffer additives on the mobility.

2. Electrophoretic mobility of anions

The mobility of an anion is a function of its charge (z) and a frictional drag (f):

$$\mu \propto \frac{z}{f} \quad (1)$$

The most common hydrodynamic model for mobility is related to the Stokes–Einstein diffusion model, and is known as the Hückel equation:

$$\mu_0 = \frac{q}{6\pi\eta r_s} \quad (2)$$

In this model, the solute mobility at infinite dilution (μ_0) is related to the charge q , the radius of an idealized spherical ion (r_s) and the solvent viscosity η . It is important to appreciate that the Hückel equation (Eq. (2)) refers to the infinite dilution where the ionic strength and ion pairing effects are minimized. The influence of these effects are discussed in Sections 4.2 and 4.3 below. The infinite dilution mobility can also be related to the ionic equivalent conductance (λ_0) by the expression:

$$\mu_0 = \frac{\lambda_0}{|z|F} \quad (3)$$

where F is the Faraday constant. Eq. (2) can also be rearranged to yield the Stokes' radius of an ion (r_s). Indeed, the observed mobility of anions has been related to the Stokes' radius [24]. However, the Stokes' radius is often erroneously also referred to as the hydrated radius of the ion (r_h). While the two are related, they are not the same [22]. The hydrated radius of an ion is comprised of the central ion plus

its waters of hydration, and so is always larger than the crystallographic radius of the ion (r_i). However, mobility is truly governed by the crystallographic radius of the ion, as will be discussed in Section 2.1. Therefore, Table 1 presents crystallographic radii (r_i) and infinite dilution mobilities (μ_0) for common anions [23].

The mobility of univalent anions in CZE separations have been found to relate to the hydrated ionic radius (r_s) [24] or the ionic equivalent conductance (λ_0) [25] of the anion (Fig. 1). However as can be seen in Fig. 1, multi-valent anions (Fig. 1A) deviate from the monovalent ion behavior. While not shown, hydrophilic anions such as SCN^- and ClO_4^- also deviated from the idealized behavior [25]. To understand the general trend in Fig. 1, as well as the deviations, it is necessary to have a fundamental understanding of the factors governing the ionic mobility. These factors will be discussed in the next section.

2.1. Factors governing the intrinsic mobility of anions

In Fig. 1 there is a general trend of longer migration times with decreasing equivalent ionic conductance. Equally obvious is the lack of correlation in Table 1 between the crystallographic ionic radius (r_i) and the ionic mobility. This lack of correlation is due in part to the ionic mobility being a function of two frictional terms, rather than the single frictional term suggested by Eqs. (1) and (2):

$$\mu_0 = \frac{q}{f_h + f_{di}} \quad (4)$$

where f_h is the hydrodynamic friction as described by the Hückel equation (Eq. (2)) and f_{di} is the dielectric friction. In essence, this dielectric friction is a charge induced frictional term. Such frictional effects are typically attributed to the increased hydration number (and thus hydrated radius) of small highly charged ions. However, hydration numbers cannot be calculated a priori, are difficult to quantify, and show distinct differences depending on the manner in which they are generated [26].

Dielectric friction results from the interaction between the moving ion and the adjacent solvent

dipoles. As an ion migrates through the solvent, it causes the adjacent solvent dipoles to orient. After passage, the solvent dipoles relax to their normal random orientation. However this relaxation takes a finite period of time (τ), and so imposes a retarding force on the migrating ion. In essence, the dielectric friction can be considered as an effective increase in the local viscosity around the ion.

To accurately predict the effect of dielectric friction on ion mobility, it is necessary to account for the molecularity of the solvent [27,28]. However, such models are too complex to express simply. Alternatively, the classical theories of Zwanzig [28] and Hubbard–Onsager [28–30] use the approximation of hard ions moving through a continuum solvent. These models capture many of the key dependencies of ionic mobilities, and so will be used herein. Both the Zwanzig and the Hubbard–Onsager models reduce to the general ‘stick’ form [28]:

$$\mu_0 = \frac{ze}{6\pi\eta r_i + \left(\frac{B'}{r_i^3}\right)} \quad (5)$$

where z is the valence number of the ion charge, e is the charge on the electron, η is the solvent viscosity and r_i is the crystallographic radius. The constant B' is:

$$B' = H(ze)^2\tau \cdot \frac{\epsilon_0 - \epsilon_\infty}{\epsilon_0^2} \quad (6)$$

where τ is the solvent dielectric relaxation time, and ϵ_0 and ϵ_∞ are the low- and high-frequency dielectric constants, respectively. The constant H is 3/8 for the Zwanzig model and 1/16.5 for the Hubbard–Onsager model. Similar expressions can be written assuming ‘slip’ conditions.

Thus, it is the combined effects of the hydrodynamic and dielectric frictions that dictate the drag force opposing the electrostatic attraction of the ion to the applied voltage. In the next section, the influence of these two frictional forces on the mobility of anions will be illustrated with the ion behavior in nonaqueous solvents.

3. Intrinsic mobility in nonaqueous solvents

From an operational stand-point there are a number of properties that must be considered in choosing

Table 1
Physical parameters related to mobility of inorganic anions

Ion	Name of ion	Crystal radius ^a (pm)	Mobility ^b (25°C) cm ² /(V s)×10 ⁴	Ion-exchange relative selectivity for AG-1 resin ^c
Ag(CN) ₂ ⁻	Dicyanoargenate(I)	340	6.9	
At ⁻	Astatide	228	6.0	
Au(CN) ₂ ⁻	Dicyanoaurate(I)	320	5.39	
B(C ₆ H ₅) ₄ ⁻	Tetraphenylborate	421	2.06	
Br ⁻	Bromide	196	8.09	50
Br ₃ ⁻	Tribromide	400	4.5	
BrO ₃ ⁻	Bromate	191	5.77	27
BrO ₄ ⁻	Perbromate	250	5.9	
Cl ⁻	Chloride	181	7.92	22
ClO ⁻	Hypochlorite	210	4.4	
ClO ₂ ⁻	Chlorite	250	5.4	
ClO ₃ ⁻	Chlorate	200	6.70	74
ClO ₄ ⁻	Perchlorate	240	6.99	
CN ⁻	Cyanide	191	8.5	28
CNO ⁻	Cyanate	203	6.70	
Co(CN) ₆ ³⁻	Hexacyanocobaltate(III)	430	10.52	
CO ₃ ²⁻	Carbonate	178	7.182	
CrO ₄ ²⁻	Chromate	240	8.60	
F ⁻	Fluoride	133	5.74	1.6
Fe(CN) ₆ ³⁻	Hexacyanoferrate(III)	440	11.24	
Fe(CN) ₆ ⁴⁻	Hexacyanoferrate(II)	450	10.5	
H ₂ AsO ₄ ⁻	Dihydrogenarsenate		3.5	
H ₂ PO ₄ ⁻	Dihydrogenphosphate		3.4	5
HCO ₃ ⁻	Hydrogencarbonate		4.61	6
HF ₂ ⁻	Hydrogendifluoride		7.8	
HPO ₄ ²⁻	Hydrogenphosphate		3.4	
HS ⁻	Hydrogensulfide	207	6.74	
HSe ⁻	Hydrogenselenide	205	7.3	
HSO ₃ ⁻	Hydrogensulfite	170	5.2	27
HSO ₄ ⁻	Hydrogensulfate	190	5.2	85
I ⁻	Iodide	220	7.92	175
I ₃ ⁻	Triiodide	470	4.40	
IO ₃ ⁻	Iodate	181	4.20	5.5
IO ₄ ⁻	Periodate	249	5.66	
MnO ₄ ⁻	Permanganate	240	6.3	
MoO ₄ ²⁻	Molybdate	254	7.72	
N ₃ ⁻	Azide	195	7.2	
Ni(CN) ₄ ²⁻	Tetracyanonickelate(II)	360	10.26	
NO ₂ ⁻	Nitrite	192	7.44	24
NO ₃ ⁻	Nitrate	179	7.41	65
O ₂ ⁻	Superoxide	158	6.2	
OH ⁻	Hydroxide	133	20.55	
P ₂ O ₇ ⁴⁻	Diphosphate	300	9.95	
PF ₆ ⁻	Hexafluorophosphate	245	5.90	
PO ₄ ³⁻	Phosphate	238	7.15	
ReO ₄ ⁻	Rhenate	260	5.69	

Table 1 (continued)

Ion	Name of ion	Crystal radius ^a (pm)	Mobility ^b (25°C) cm ² /(V s) × 10 ⁴	Ion-exchange relative selectivity for AG-1 resin ^c
S ²⁻	Sulfide	184	19.80	
S ₂ O ₃ ²⁻	Thiosulfate	250	8.799	
S ₂ O ₃ ²⁻	Dithionite	260	6.89	
S ₂ O ₆ ²⁻	Dithionate	280	9.64	
S ₂ O ₈ ²⁻	Tetrathionate	290	8.19	
SCN ⁻	Thiocyanide	213	6.8	
Se ²⁻	Selenide	198	16.48	
SeCN ⁻	Selenocyanide	225	6.71	
SeO ₄ ²⁻	Selenate	243	7.846	
SO ₃ ²⁻	Sulfite	200	8.281	
SO ₄ ²⁻	Sulfate	230	8.29	
WO ₄ ²⁻	Tungstate	270	8.60	
HCOO ⁻	Formate	204	5.66	4.6
CH ₃ COO ⁻	Acetate	232	4.24	3.2
CH ₃ CH ₂ OO ⁻	Propanoate		3.71	2.6
C ₆ H ₅ COO ⁻	Benzoate		3.36	
C ₆ H ₂ (NO ₂) ₂ O ⁻	Picrate		3.15	
NH ₂ SO ₃ ⁻	Sulfamate	255	5.01	
CH ₃ SO ₃ ⁻	Methylsulfonate		4.76	
C ₆ H ₅ SO ₃ ⁻	Benzenesulfonate		3.6	500

^a From Ref. [72].^b From Ref. [23].^c From Ref. [73].

an organic solvent for CZE. These include the solvent's volatility, its ability to dissolve suitable electrolytes, its dielectric constant, its boiling point and its viscosity [31,32]. A low viscosity is desirable as it will increase ionic mobilities (Eq. (2)) and the electroosmotic flow (EOF), and thus decrease the analysis time. A high dielectric constant for the solvent is desirable as it gives improved electrical properties. However, it is the ratio of dielectric constant to viscosity (ϵ/η) that is the best predictor of the magnitude of the electroosmotic flow [32,33], although the zeta potential (ζ) must also be considered in organic–aqueous solvent mixtures [34,38].

However, while such parameters govern how fast ions will migrate in nonaqueous solvents, they do not address the issue of selectivity. One of the key variables that may be altered upon using a nonaqueous solvent is the analyte acid–base properties. Amphiprotic solvents with acidic character enhance solute basicity and reduce analyte acidity, whereas amphiprotic basic solvents, such as formamide, *N*-methylformamide, and *N,N*-dimethylformamide,

have the opposite effect [32]. Thus, the degree of solute deprotonation can be altered by changing the solvent. However such behavior is not expected to have significant effects with inorganic anions, which are by-and-large the salts of strong acids.

In the discussion below, the issue of selectivity for separating inorganic anions will be addressed from the perspectives of fundamental electrolyte theory and experimental CZE results.

3.1. Theoretical predictions

The emphasis on ϵ/η traditionally used to select organic solvents for CZE implicitly assumes that only hydrodynamic friction governs the ionic mobility of anions. If solvent mobility were strictly a function of hydrodynamic friction, then the product of the ionic mobility (or more traditionally the equivalent conductivity) times the solvent viscosity should be constant, independent of the solvent used. Further, if this 'Walden' product ($\eta\mu$) were plotted versus the reciprocal of the crystallographic radius

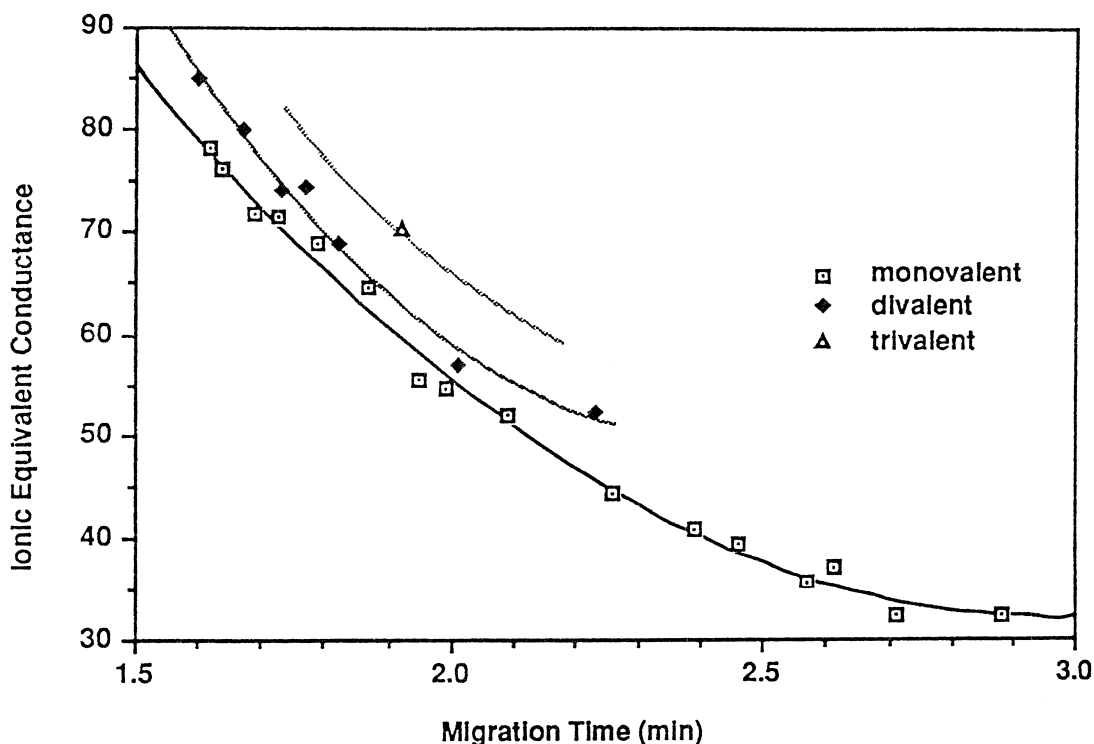


Fig. 1. Relationship between migration times for anions in CZE versus the ionic equivalent conductance of the individual ions. Experimental conditions: capillary, 60 cm (52 cm to detector) \times 50 μ m; electrolyte, 5 mM chromate and 0.5 mM tetradecyltrimethylammonium bromide adjusted to pH 8.0; voltage, 30 000 V; detection, indirect at 254 nm; injection, electrokinetic at 1 kV for 15 s (reproduced with permission from Ref. [25]).

($1/r_i$) a linear plot should result. In Fig. 2, the linear line represents mobilities predicted based solely on hydrodynamic friction (Hückel equation, Eq. (2)). It has often been noted that the 'stick' assumption that leads to the '6' in the denominator of Eq. (2) underestimates the mobility of small ions. Therefore, a line correlating to the other extreme assumption of 'slip' (constant in denominator of Eq. (2) becomes '4') is included in Fig. 2.

If only hydrodynamic friction were operative, all ions in all solvents would follow the linear behavior predicted by the Hückel equation. Instead, an almost parabolic relationship between the Walden product ($\eta\mu$) and the reciprocal radii is observed. For large ions, such as $B(C_6H_5)_4^-$, the mobility is determined almost exclusively by the hydrodynamic friction. This evidenced by all of the solvents displaying approximately the same mobility for this ion. Taking

water (\diamond) for an example, the ionic mobilities first increase as the crystallographic radius decreases ($1/r_i$ increases), reaches a maximum at around Br^- , and then decreases again for small ions such as F^- . The nonlinearity of the mobility behavior is due to the dielectric friction.

The influence of now going to nonaqueous solvents is described by Eqs. (5) and (6). The hydrodynamic friction is strictly a function of the solvent viscosity (η) and the crystallographic radii of the ion (r_i). However, additional parameters are needed to account for dielectric friction upon the anions – the solvent dielectric relaxation time, and the low- and high-frequency dielectric constants. The high-frequency dielectric constant (ϵ_∞) has a very limited range, from 1.9 to 5.7 for many polar liquids [35]. Further, it is very small compared to the low-frequency dielectric constant (ϵ_0). Thus, in this discus-

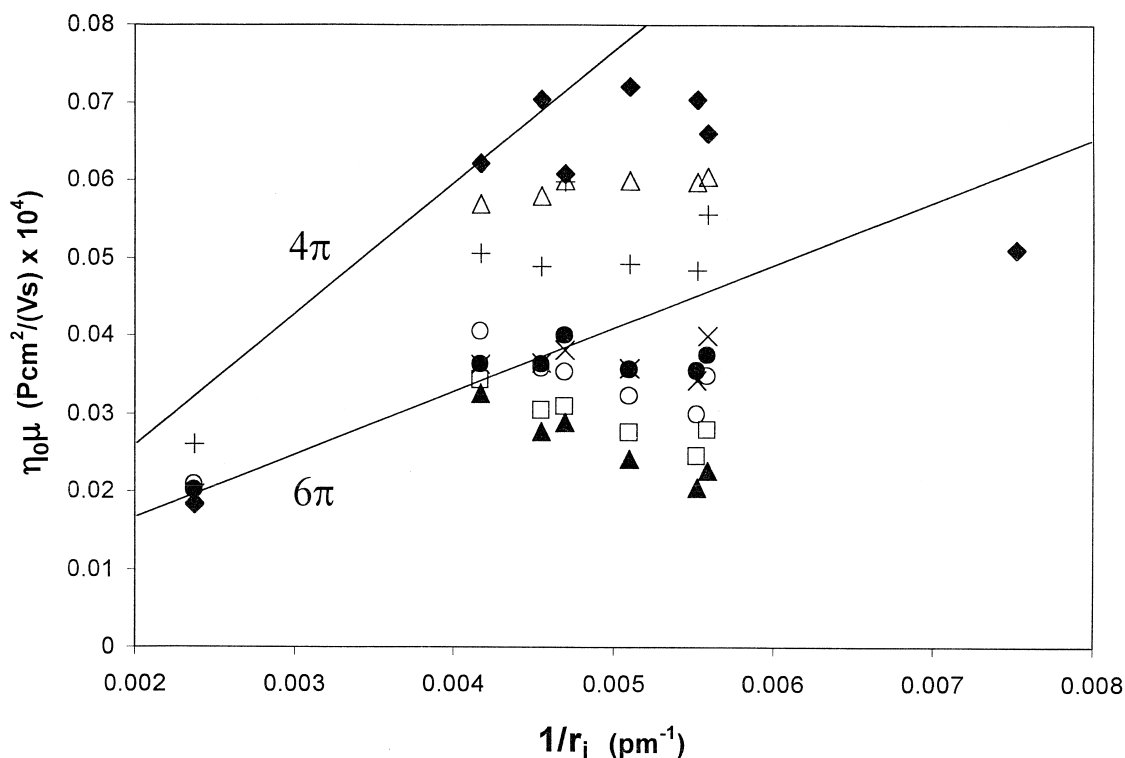


Fig. 2. Walden plot for anions in non-aqueous solvents at 25°C. (♦) Water; (Δ) formamide; (+) dimethylsulfoxide; (●) acetonitrile; (×) acetone; (○) methanol; (□) ethanol; (▲) propanol. Data from Ref. [71].

sion the high-frequency dielectric constant will be ignored.

Ignoring the high frequency dielectric constant, the magnitude of the hydrodynamic friction relative to the dielectric friction can be expressed in the following manner:

$$\frac{f_h}{f_{di}} \propto \frac{\eta}{B'} \propto \frac{\eta \epsilon_0}{\tau} \quad (7)$$

Table 2 summarizes the relevant parameters related to ionic mobility for a number of solvents at 25°C [36], and gives the ratio expressed by Eq. (7).

One of the most striking observations from Table 2 is that water has amongst the highest values of $\eta \epsilon_0 / \tau$. This suggests that ionic mobilities in water are governed more by hydrodynamic friction than in almost any other solvent. This behavior is evident in Fig. 2. For water (♦), the highest mobility is

observed for bromide. In contrast for methanol (○), which has a much lower value for $\eta \epsilon_0 / \tau$, the large perchlorate ion has the fastest mobility. This indicates that the dielectric friction is much stronger in methanol than in water. Other solvents, whose $\eta \epsilon_0 / \tau$ range between that of water (7×10^{12}) and methanol (0.34×10^{12}), range in behavior between these two solvents. Thus, in Table 2 as one descends down the solvents, one would expect to see mobilities that are increasingly governed by dielectric rather than hydrodynamic friction.

However, while the concept of dielectric friction explains the general trend to be expected for spherical ions (halides, ClO_4^-), significant deviations from the general behavior are observed for non-spherical ions such as SCN^- and NO_3^- . For instance, SCN^- is distinctly slower than ClO_4^- in water, but much faster than ClO_4^- in DMSO. Thus, while the concept of hydrodynamic and dielectric friction explains

Table 2
Solvent properties related to hydrodynamic and dielectric friction^a

Solvent	Viscosity (cP)	ϵ_0	ϵ_∞	τ (ps)	$\eta/(\tau/\epsilon_0) \times 10^{10}$
<i>N</i> -Methylformamide	1.65	182.4		24	1300
Water	0.8903	78.36	5	10	700
Ethylene glycol	17.712	37.7	2.04	106	630
Dimethylsulfoxide (DMSO)	1.991	46.45	5.7	21	440
Formamide	3.302	111	3	108	340
Acetonitrile	0.341	35.94	2	5	250
Acetone	0.3029	20.56	1.9	3	210
<i>N,N</i> -Dimethylformamide	0.802	36.71		15	200
Tetrahydrofuran	0.46	7.58		3	120
Methanol	0.5513	32.66	5.6	53	34
Ethanol	1.0826	24.55		143	19
2-Propanol	2.0436	19.92		292	14
1-Propanol	1.943	20.45		430	9
1-Butanol	2.571	17.51	2.95	668	7

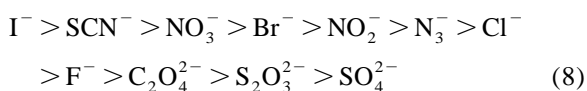
^a Data from Ref. [36].

some of the general trends underlying ionic mobilities in nonaqueous solvents, it cannot account for the molecularity effects that can significantly alter mobilities of non-spherical anions. Such effects can only be studied experimentally.

3.2. Experimental observations

There have been few studies of the effect of organic solvents on the mobility of inorganic anions. Buchberger and Haddad [37] investigated the effect of up to 30% of methanol, acetonitrile, tetrahydrofuran, acetone or ethylene glycol on anion mobilities in a chromate electrolyte containing tetradecyltrimethylammonium bromide (TTAB) as an EOF modifier. A few trends were observed for all of these organic modifiers. Firstly, the mobility of sulfate decreased relative to all monoanions, such that by 30% organic modifier the sulfate–nitrate migration order was reversed. It should be noted, however that the other di-anion studied, thiosulfate, did not show a similar dramatic loss in mobility. Secondly, the resolution between thiosulfate, bromide and chloride tended to degrade as organic modifier was added. Thirdly, the relative migration time for nitrite tends to increase with organic modifier, eventually reversing the migration order of nitrite and nitrate. Finally, the addition of organic modifiers tended to increase the migration times of all of the anions.

Salimi-Moosavi and Cassidy evaluated methanol and dimethylformamide for the separation of inorganic anions [38]. They noted some significant changes in separation order relative to aqueous systems, with some instances in reversal of order of migration. For instance, SCN^- was the slowest ion studied in water, but became the second fastest migrating ion in 98% methanol. Conversely, $\text{S}_2\text{O}_3^{2-}$ was the fastest ion in water, and became the second slowest ion in methanol. In 98% methanol using 0.01 *M* potassium hydrogenphthalate with 0.02 *M* *n*-butylamine as buffer, the migration order was:



This is in agreement with the infinite dilution mobilities shown in Fig. 2 for methanol. Thus, the selectivities observed in methanol were reflective of the intrinsic mobilities within that solvent. This is important since changes in selectivity due to changes in the counter-ion were observed for dimethylformamide. Greater discussion of this effect is given in Section 4.3.

Mobilities for 25 and 50% methanol in water were lower than those in pure water or methanol. This is consistent with the higher viscosity of methanol–water mixtures. The selectivities observed in methanol–water mixtures was intermediate between those

of the pure solvents. However, given the slower mobilities of the anions in methanol–water mixtures, the overall mobility range was attenuated compared to either pure solvent.

3.3. Rule of thumb

At this time, the theoretical treatments of mobility of inorganic ions can explain only the grossest of trends. Further, only limited studies of the use of nonaqueous solvents for CZE of inorganic ions have been made [37–39]. Nonetheless, a rule of thumb regarding when the use of nonaqueous solvents can be put forward.

If two anions of equal charge co-migrate, then the total friction arising from the hydrodynamic and dielectric friction (Eq. (4)) must be the same. However, the relative contributions of dielectric and hydrodynamic friction change with solvent type (Table 2). Thus, if the two co-migrating ions are similar in size, then the changes in hydrodynamic and dielectric friction will affect them similarly, and little improvement in selectivity would be expected. However, if the co-migrating ions have distinctly different crystallographic radii (r_i), then it is unlikely that the two ions will co-migrate in a second solvent. This rule-of-thumb is illustrated in Fig. 3. In Fig. 3a an aqueous buffer fails to separate iodide ($r_i=220$ pm) from chloride ($r_i=181$ pm), and perchlorate ($r_i=240$ pm) from azide ($r_i=195$ pm). Addition of 15% methanol significantly alters the balance of hydrodynamic and dielectric friction within the buffer, resulting in separation of all anions, as shown in Fig. 3b.

In summary, the rule-of-thumb is that nonaqueous solvents will be most effective when the crystallographic radii (Table 1) of the co-migrating ions are distinctly different.

4. Electrolyte effects

The discussion above referred to fundamental factors that influence the intrinsic mobility of an anion at infinite dilution (no buffer). Addition of a buffer electrolyte alters the mobility of anions in a myriad of ways. These include alteration of the ion charge due to acid dissociation, alteration of the

effective size of the anion by complexation, and alteration of its mobility due to interaction with other buffer additives.

In the following sections, each of these effects will be discussed individually. However, in a true buffer system the behavior is more complex, as many of these factors act in concert.

4.1. Acid–base equilibria

Changes in the electrophoretic mobility of an anion are most dramatic at or near the pK_a of the ion. Smith and Khaledi [40] demonstrated that the effective mobility (μ_{eff}) of a weakly acidic anion is governed by:

$$\mu_{\text{eff}} = \mu_{\text{A}^-} \cdot \frac{K_a}{[\text{H}^+] + K_a} \quad (9)$$

where μ_{A^-} is the mobility of the full deprotonated anion, and K_a is the acid dissociation constant of the anion. Smith and Khaledi verified this behavior using phenols, as have others [41]. In co-EOF separations using chromate as the indirect detection anion and a cationic surfactant such as TTAB to reverse the EOF, the pH range is limited to about 8–13 [42]. Above pH 13, the baseline is very noisy. Below pH 8, the background electrolyte becomes cloudy due to formation of a sparingly soluble chromate-TTAB species [42]. Of the standard anions, only carbonate ($pK_{a_2}=10.329$) and borate ($pK_a=9.236$) have acid dissociation constants in the center of the pH 8–13 region (Table 3). Thus, these anions show the most dramatic change in selectivity when the pH of the chromate buffer is adjusted [25]. Phosphate has pK_a on the edges of this pH range. Thus, some selectivity changes were noted for phosphate as well [25]. At pH 8, some resolution was observed between phosphate and fluoride, with fluoride migrating slightly faster. Between pH 9.5 and 11.5, the two co-migrate. Finally, above pH 11.5, the third pK_a of phosphate is approached, and so phosphate migrates slightly faster than fluoride.

Harakuwe and Haddad demonstrated that greater resolution between phosphate and fluoride could be achieved if the pH of the chromate-TTAB buffer were reduced below 8 [42]. Addition of 7.5% 1-butanol to a background electrolyte of 5 mM chro-

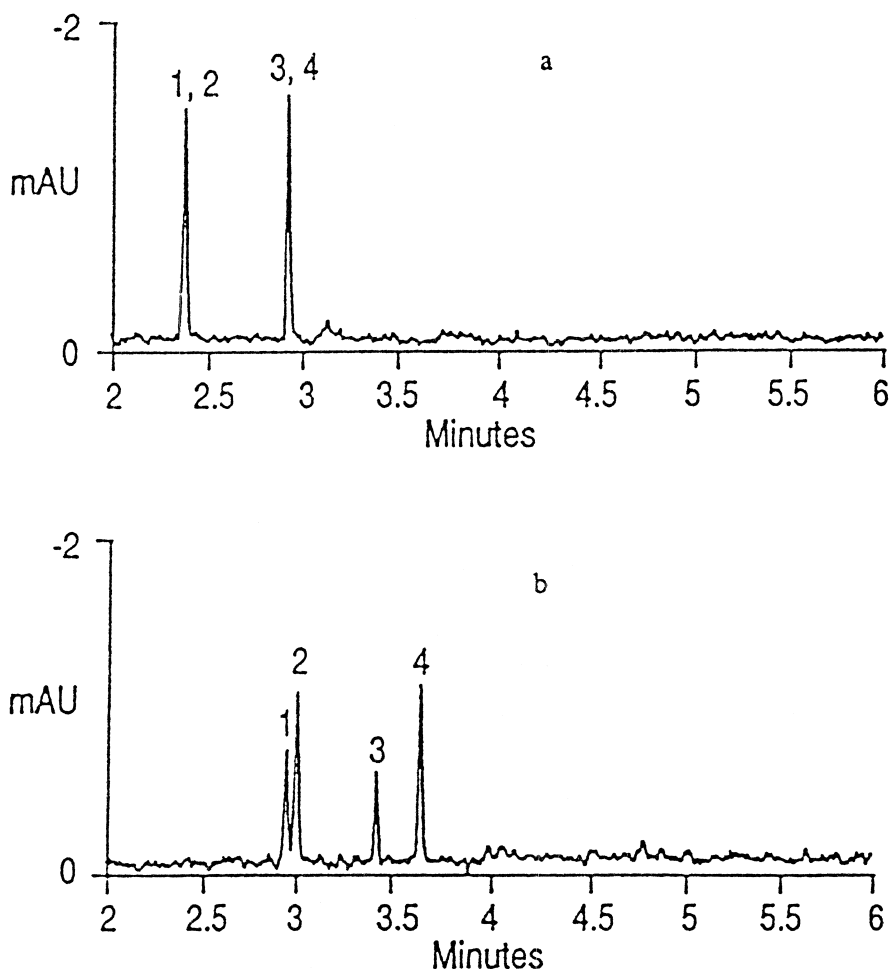


Fig. 3. Effect of nonaqueous solvent on separation of anions. (a) Aqueous electrolyte of 2.5 mM pyromellitic acid, 6.5 mM NaOH, 0.75 mM hexamethonium hydroxide, 1.6 mM triethanolamine (pH 7.7). (b) Electrolyte as in (a) but with 15% methanol. Experimental conditions: capillary 50 cm \times 50 μ m I.D. voltage, 30 000 V; detection, indirect at 250 nm; injection, gravity at 100 mm for 20 s. Peaks: (1) iodide (5.0 mg/l); (2) chloride (2.5 mg/l); (3) perchlorate (2.5 mg/l); (4) azide (2.5 mg/l) (reproduced with permission from Ref. [39]).

mate and 2.5 mM TTAB stabilized the buffer down to pH 7. Lowering the pH to 7 caused increased protonation of the hydrogenphosphate, causing it to migrate slower than the fluoride, and thus greatly improved resolution. Additional experiments demonstrated that the 1-butanol did not directly affect the selectivity between phosphate and fluoride.

Similarly dramatic changes in the relative migration time of carbonate relative to carboxylic acids were observed when the background electrolyte is changed: in pH 5.9 phthalate, carbonate elutes after butyrate; in pH 8.0 chromate, carbonate appears

before acetate; and in pH 10.9 naphthalene dicarboxylate buffer, carbonate appears before formate [43].

Thus, extensive studies have investigated the pH range 7–13 where the mobility of borate, carbonate and phosphate are varied. Surprisingly, few studies have investigated lower pH ranges, where the selectivity of numerous other anions (Table 3) could be altered. Separations of anionic chloro complexes of gold(III) and platinum group elements at pH 1–2.4 has been studied [44–46]. For these species the acidic conditions were necessary to minimize hydrolysis of the complexes. As a result, the focus of

Table 3
Acid dissociation constants for inorganic anions^a

Acid name	Structure	pK _a
Acetic acid	CH ₃ COOH	4.757
Arsenic acid	H ₃ AsO ₄	2.24, 6.96, 11.50
Arsenous acid	H ₃ AsO ₃	9.29
Boric acid	H ₃ BO ₃	9.236
Carbonic acid	H ₂ CO ₃	6.352, 10.329
Chlorous acid	HClO ₂	1.95
Chromic acid	H ₂ CrO ₄	pK _{a2} = 6.51
Hydrogen azide	HN ₃	4.65
Hydrogen cyanate	HCNO	3.48
Hydrogen cyanide	HCN	9.21
Hydrogen-fluoride	HF	3.17
Hydrogen hypophosphite	H ₃ PO ₂	1.23
Hydrogen iodate	HIO ₃	0.77
Hydrogen sulfide	H ₂ S	7.02, 13.9
Hydrogen thiocyanate	HSCN	0.9
Hydrogen thiosulfate	H ₂ S ₂ O ₃	0.6, 1.6
Hypobromous acid	HOBr	8.63
Hypochlorous acid	HOCl	7.53
Hypoiodous acid	HOI	10.64
Phosphoric acid	H ₃ PO ₄	2.148, 7.199, 12.15
Phosphorous acid	H ₃ PO ₃	1.5, 6.79
Sulfurous acid	H ₂ SO ₃	1.91, 7.18
Sulfuric acid	H ₂ SO ₄	pK _{a2} = 1.99

^a Data from Ref. [50].

the studies was on hydrolytic degradation, rather than the effect of pH on mobility. Thus, of these and other anions such as F⁻, Br⁻, NO₃⁻, IO₄⁻, IO₃⁻ investigated, only HFe(CN)₆³⁻ and HCrO₄⁻ had pK_a in the pH range studied. Unfortunately, their acid dissociation behavior was not followed up. Amran et al. [47] studied the effect of pH from 2 to 8 on the migration behavior of bromide, bromate, iodide, iodate, nitrite, nitrate, and selenite. Of these anions, only nitrite and selenite had pK_a in the range studied (3.37 and 2.46, respectively). The retardation of nitrite is first noticeable at pH 4, while selenite was not appreciably slower until pH 3. By pH 3 both of these ions migrated more slowly than iodate [47]. Takayanagi et al. also saw improvements in the separation of nitrite and nitrate at low pH values (monochloroacetate buffer with pH about 3) [48].

4.2. Ionic strength

4.2.1. Theoretical treatment

Numerous studies have noted subtle changes in CZE separations of inorganic anions due to the

buffer concentration [37,39]. Much of this discussion has focussed on optimization of the buffer concentration with respect to Joule heating and electrodispersion [39]. However, selectivity changes have also been observed [37]. However, until recently no fundamental explanation of the effect of ionic strength on selectivity had been made. Li et al. recently demonstrated that the Pitts equation successfully described the influence of ionic strength on the mobility of singly and multiply charged carboxylates and sulfonates [49]. The Pitts equation assumes that an anion of finite size is surrounded by an ionic atmosphere of an equal cationic charge. These assumptions are analogous to those in the Debye–Hückel extended law for ionic activity. The simplified version of the resultant expression for water at 25°C is [48]:

$$\begin{aligned} \mu &\approx \mu_0 - 4.31 \\ &\times 10^{-4} z_- \frac{\sqrt{I}}{1 + a(0.329A^{\sigma-1}M^{-1/2})\sqrt{I}} \\ &\approx \mu_0 - 4.31 \times 10^{-4} z_- \frac{\sqrt{I}}{1 + \sqrt{I}} \text{ (cm}^2/\text{V s)} \end{aligned} \quad (10)$$

where a is the ionic size parameter. This size parameter tends to be greater than the crystallographic radii of an ion (Table 1), but less than the hydrated radius of the ion. Tables of these ion size parameters are presented in standard analytical chemistry texts in discussions of ionic activity [50,51]. For many inorganic anions, the ion size parameter (a) is about 3 Å. Thus, the denominator term can be approximated as ~ 1 , giving the right-hand equality.

The Pitts equation has not yet been validated for inorganic anion mobility in CZE, only for organic anions [49]. However, the expression has been validated for equivalent ion conductance of inorganic ions [52]. Thus, it should provide reliable guidance for the effect of ionic strength on the mobility of inorganic anions in CZE.

4.2.2. Experimental behavior

Fig. 4 illustrates the effect that ionic strength has on selectivity [53]. Fig. 4a is a co-EOF separation of anions using a dilute chromate buffer and indirect detection. The ionic strength of this buffer is about

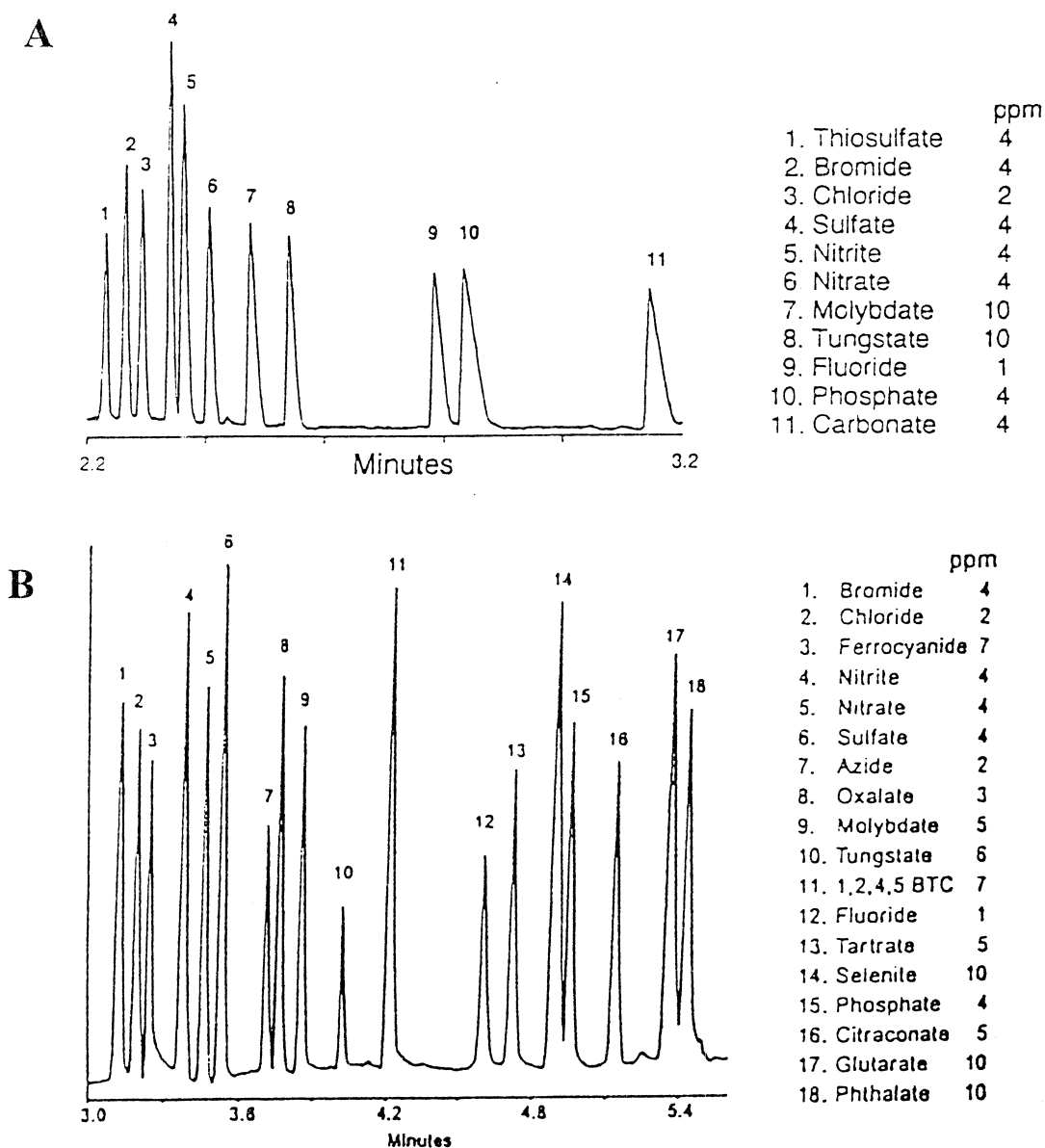


Fig. 4. Effect of ionic strength on anion selectivity of sulfate (SO_4^{2-}) relative to univalent anions: (A) 5 mM sodium chromate and 0.5 mM CIA-Pak OFM Anion-BT at pH 8.0 (ionic strength, $I=0.017\text{ M}$) monitored by indirect absorbance; (B) 50 mM CHES, 20 mM LiOH, 0.03% (w/w) Triton X-100 at a natural pH of 9.2 ($I=0.052\text{ M}$) monitored by direct conductivity. See Ref. [53] for complete recipes for separations (reproduced with permission from Ref. [52]).

0.017 M. Fig. 4b is a co-EOF separation of anions using a more concentrated 2-(*N*-cyclohexylamino)ethanesulfonic acid (CHES) buffer (ionic strength $\sim 0.052\text{ M}$) and direct conductivity detection. In both of these figures the selectivity between

univalent anions remains the same. This is consistent with predictions based on Eq. (10), which states that ions of the same charge will be affected similarly by ionic strength. This is also why the observed migration times of monovalent anions in Fig. 1 are

monotonically related to the ionic equivalent conductance at infinite dilution.

In contrast, the multiply charged anions in Fig. 1 are shifted to later migration times. Similarly, in Fig. 4 the chloride-sulfate and fluoride-phosphate selectivity significantly increases in going from the dilute chromate buffer (Fig. 4a) to the more concentrated CHES buffer (Fig. 4b). The difference in buffer pH is not believed to have altered the fluoride-phosphate selectivity, as previous studies saw no selectivity change over this pH range [42]. Rather in both the $\text{Cl}^-/\text{SO}_4^{2-}$ and $\text{F}^-/\text{HPO}_4^{2-}$ cases the migration rate of the multicharged anion (sulfate and phosphate) slowed relative to that of the surrounding monovalent anions. This observation is consistent with those of Jones and Jandik [25] and Buchberger and Haddad [37], who noted that the relative migration rate of divalent anions decreased as the concentration of chromate buffer increases. A similar trend is noted in Fig. 1.

These behaviors are consistent with Eq. (10), which states that the mobility of multiply charged will be more significantly affected by ionic strength. Thus the impact of changes in the ionic strength of the buffer are directly related to the charge on the anion.

4.2.3. Rule of thumb

A subsequent rule-of-thumb is that selectivity changes related to changing the buffer concentration (ionic strength) will be effective only if the two co-migrating anions differ in charge.

4.3. Ion association

4.3.1. Background electrolyte

For the sake of this discussion, ion association or ion pairing refers to when counter-ions move together as a single physically associated entity, with a lifetime sufficiently long to survive several collisions before dissociating. The ion association equilibrium can be written as:



With the corresponding equilibrium constant (K_{ass}):

$$K_{\text{ass}} = \frac{[\text{C}^+ \text{A}^{n-}]}{[\text{C}^+][\text{A}^{n-}]} \quad (12)$$

Classical conductometric studies have been used to study ion association in strong electrolytes [54]. Table 4 presents an abbreviated listing of ion association constants for inorganic anions from these studies. For a more complete listing, readers are referred to reference [55]. Ion association between alkali metals and univalent anions is minimal. With nitrates, chlorates, bromates, and iodates there is some ion association with alkali metals, with the heavier alkali metals displaying stronger association.

With multivalent anions there is generally stronger ion association. A rule of thumb is that for an increase of one in the valency of the anion, there will be a factor of ten increase in the association constant ($\log K_{\text{ass}}$ increases by 1). In keeping with this trend, ion association is common with alkaline earth metals, even in dilute solutions.

Thus, given the dilute buffers used in CZE of inorganic anions and the ion association constants in Table 4, it can be inferred that when alkali metals (Li^+ , Na^+ , K^+) are used as the buffer counter-ion, ion association could only affect selectivity between anions of different charge. Alternatively, if alkaline earth cations are used, much more dramatic selectivity changes may be observed. For example, under typical chromate buffer conditions nitrate and oxalate are only partially resolved. Addition of 4 ppm calcium to the chromate buffer results in a retardation of the oxalate migration due to complexation between this bidentate carboxylate ligand and the calcium [60]. As a result excellent resolution is achieved between nitrate and oxalate.

Similarly with organic compounds little selectivity change has been observed when the buffer cation is an alkali metal [49,56]. However the relative migration of aromatic anions has been significantly altered by the addition of quaternary amine cations [57,58]. This behavior is also evident with inorganic anions, as will be discussed in the next two sections.

Finally, it should be noted that ion association effects will be much stronger in low dielectric solvents and aprotic solvents. For instance, no ion association behavior was noted in 98% methanol, whereas the anion selectivity in dimethylformamide strongly depended on the buffer cation [38].

Table 4
Ion association between inorganic anions and buffer cations^a

Ion	Name of ion	log K_{ass}				
		Li ⁺	Na ⁺	K ⁺	Mg ²⁺	Ca ²⁺
Br ⁻	Bromide				ne ^b	
Br ₃ ⁻	Tribromide					
BrO ₃ ⁻	Bromate		-0.50	-0.4		
Cl ⁻	Chloride	ne	ne	ne	ne	ne
ClO ₃ ⁻	Chlorate		-0.50	-0.1		
ClO ₄ ⁻	Perchlorate			-0.5		
F ⁻	Fluoride				1.82	<1.0
Fe(CN) ₆ ³⁻	Hexacyanoferrate(III)			2.3	3.87	3.77
Fe(CN) ₆ ⁴⁻	Hexacyanoferrate(II)				2.79	2.83
HPO ₄ ²⁻	Hydrogen phosphate				2.5	2.7
IO ₃ ⁻	Iodate		-0.50	-0.3	0.72	0.89
NO ₃ ⁻	Nitrate	ne	-0.60	-0.2	ne	0.28
ReO ₄ ⁻	Rhenate			0.7		
S ₂ O ₃ ²⁻	Thiosulfate		0.600	0.9	1.83	1.95
SO ₄ ²⁻	Sulfate	0.6	0.70	1	2.23	2.28
HCOO ⁻	Formate					0.8
CH ₃ COO ⁻	Acetate				0.78	0.77
⁻ OCCOO ⁻	Oxalate				3.43	3

^a Data from Ref. [55].

^b ne, no evidence.

4.3.2. Electroosmotic flow modification

Small inorganic anions migrate counter to the natural electroosmotic flow in fused-silica capillaries. Such counter-EOF migration results in very long migration times. Therefore typically EOF modifiers such as alkylammonium surfactants are added to the buffer to reverse the direction of the (EOF) [59]. Under such co-EOF conditions, rapid determinations of anions are achieved [25].

While the primary purpose of adding alkylammonium surfactants such as (TTAB) to the buffer is to reverse the EOF, their addition also affects the mobility of some anions [25,60]. Fig. 5 shows the dramatic decrease in the mobilities of Br⁻, SO₄²⁻ and NO₃⁻ that are observed when the concentration of the EOF modifier (an alkyl trimethyl ammonium surfactant) is increased. Similarly, highly polarizable anions, such as BF₄⁻, ClO₄⁻, SCN⁻ and I⁻ show even more dramatic reductions in mobility at low EOF modifier concentrations [61].

Studies of anion migration in micellar electrokinetic capillary chromatography (MECC) showed that anion migration was inhibited by the cationic micelles in the order: IO₃⁻ < BrO₃⁻ < Br⁻ < NO₃⁻ << I⁻ [62]. These studies demonstrated that anion

mobility is retarded by two processes. The first is the ion association equilibrium between the anion and the monomeric surfactant below its critical micelle concentration (CMC) [62]. The second mechanism which occurs above the CMC has been described as either partitioning of the anion into the micelle [62] or ion-pairing between the ion and the micelle in a manner reminiscent of polycations [63], as will be discussed in Section 4.3.3. The net result is that the migration order undergoes a transition from that predicted by the intrinsic ionic mobilities of the ions (Table 1) to that resembling in part that in ion-exchange chromatography [63]. As a rough guide, relative selectivities on Dowex AG-1 resin are included in Table 1.

Thus, the alteration in anion mobility with the concentration of the cationic surfactant EOF modifier is a facile means of optimizing CZE separations of anions. An interesting refinement to this technique is to use mixtures of cationic surfactants such as TTAB and dodecyltrimethylammonium bromide (DTAB). Altering the total concentration of the surfactant, altered the selectivity in the manner discussed above. However, subsequent variation in the ratio of the two surfactants allowed finetuning of the selectivity [63],

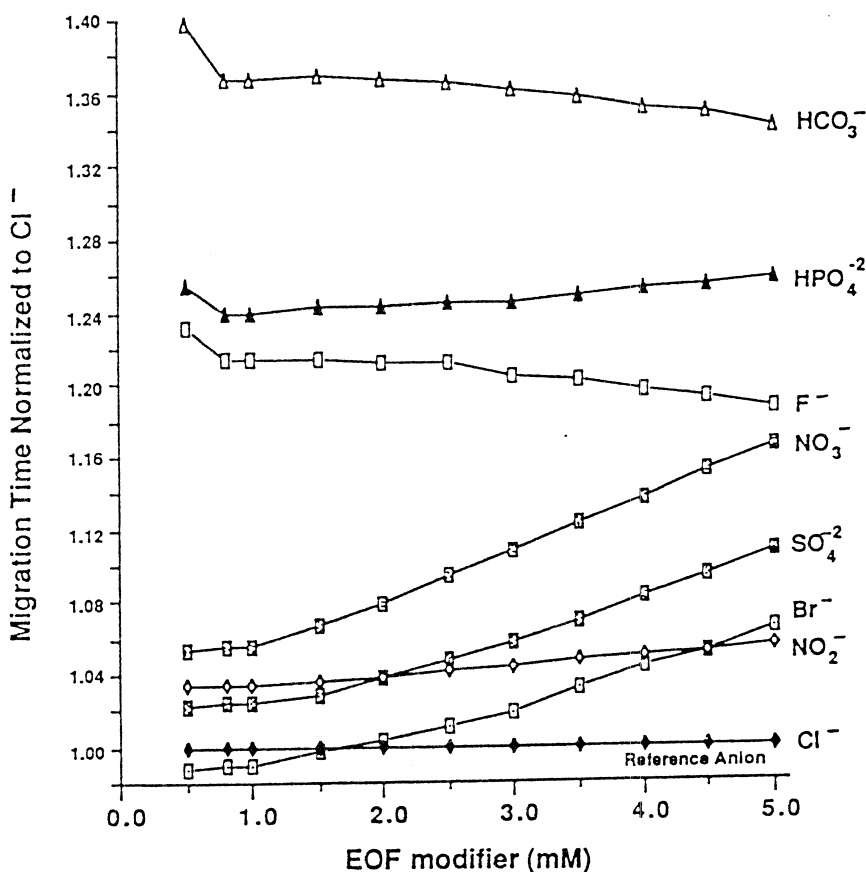


Fig. 5. Effect of increasing the alkyltrimethylammonium EOF modifier on the migration times relative to that of Cl⁻. Electrolyte: 5 mM chromate with EOF modifier (TTAB) adjusted to pH 8.0 (reproduced with permission from Ref. [25]).

presumably by varying the relative amounts of ion association with surfactant monomers and the micelles. As an example of the selectivity changes, with 2.6 mM DTAB no separation was observed between fluoride, phosphate and bromate in the 5 mM chromate (pH 8.8) electrolyte. If instead 1.3 mM of each surfactant were used phosphate was separated from the other two anions. Finally, use of 2.6 mM TTAB resulted in separation of all three anions. Such finetuning of the selectivities was used to optimize the separation of inorganic and organic anions in Bayer liquor [64].

Similarly, Yeung and Lucy demonstrated that both the reversed EOF and the selectivity for anionic separations could be finetuned using mixtures of a zwitterionic (Rewoteric CAS U) and a cationic surfactant (TTAB) [65]. Zwitterionic surfactant

alone yields essentially no EOF. Alternatively, cationic (TTAB) surfactant alone yields fully reversed EOF. If the two surfactants are mixed, the magnitude of the reversed EOF can be altered monotonically from near zero to fully reversed. However, more important for the present discussion, the addition of the zwitterionic surfactant resulted in alteration in the anionic selectivity, as shown in Fig. 6. In particular in going from 0.5 mM TTAB (Fig. 6A) to 0.5 mM of the zwitterionic CAS U, the selectivities for the bromide–chloride, sulfate–nitrite and nitrate–oxalate separations all improved.

Finally, a general rule of thumb is that altering anion selectivity through adjustment of the EOF modifier will be most effective if the co-migrating ions possess significantly different ion-exchange behavior (Table 1).

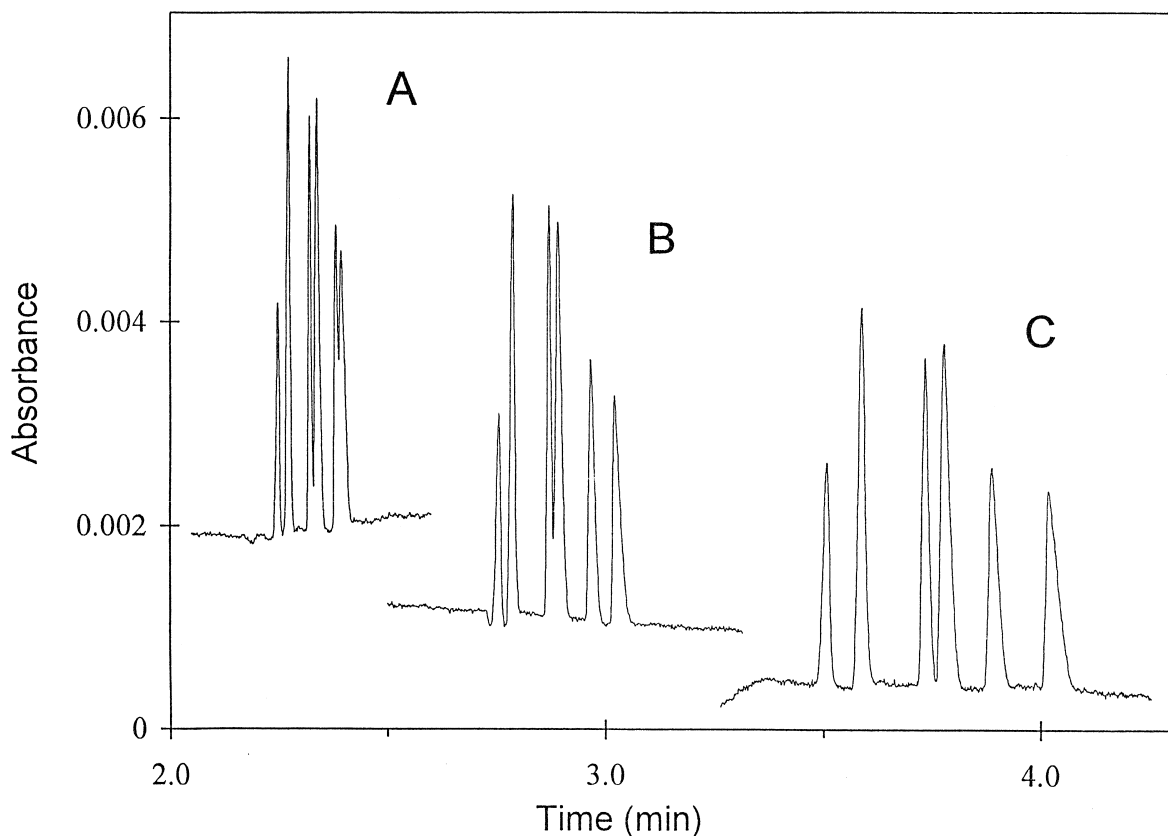


Fig. 6. Separation of six inorganic anions with various amounts of cationic (TTAB) to zwitterionic (CAS U) surfactant: (A) 0.5 mM TTAB; (B) 0.5 mM TTAB and 0.5 mM CAS U; and (C) 0.5 mM CAS U. Experimental conditions: applied voltage, -20 kV; capillary length, 57 cm, 50 cm to detector; indirect detection at 254 nm; buffer, 5.0 mM potassium chromate with pH adjusted to 8.0 using phosphoric acid; and sample, 5 ppm mixed anion solution. Anion migration order: bromide, chloride, sulfate, nitrite, nitrate and oxalate (reproduced with permission from Ref. [65]).

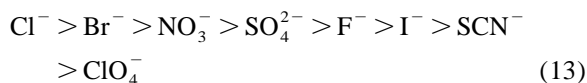
4.3.3. Polymeric cations

An alternative means of shifting the selectivity of CZE towards that achieved using ion exchange is to add a polycation [66]. Examples of such species are poly(1,1-dimethyl-3,5-dimethylenepiperidinium) (PDDPi) and poly(1,1-dimethyl-3,5-dimethylenepyrrrolidinium) (PDDPy) of molecular masses around 2×10^5 – 3×10^5 . Changes in the relative values of electrophoretic mobilities were a function of the polycation concentration, with the largest effects being for the divalent sulfate anion [26% for PDDPi over the concentration range 0.004–0.2% (w/w) and 16% for PDDPy over the concentration range 0.05–0.17% (w/w)] [66]. In most respects the selectivity changes are comparable to those achieved

by varying the concentration of the cationic surfactant EOF modifier (Section 4.3.2). The most notable examples of resolution enhancement being for bromide–chloride and phosphate–fluoride, as are also evident in Fig. 5. Also, the increase in migration time for sulfate was demonstrated to be useful in the analysis of sulfate in the presence of a large excess of nitrate and/or nitrite.

One unique advantage of polycations over concentrated EOF modifier is the ability to add organic solvents to further alter the selectivity. Use of methanol–water mixtures in combination with polycations such as PDDPi or PDDPy results in subtle selectivity changes between inorganic anions [67]. Alternatively, if acetonitrile–water mixtures are used

with these polycations, significant changes in selectivity are observed. For instance adding 35% acetonitrile to 0.1% (w/v) PDDPi in 5 mM chromate (pH) alters the selectivity from:



to



The difference in behavior of the polycations in methanol–water and acetonitrile–water solvent systems is believed to be related to methanol's ability to solvate anions [67]. Methanol is capable of H-bonding, whereas acetonitrile is aprotic.

Greater ion association in aprotic solvents is consistent with the behavior observed in nonaqueous CE [38]. As discussed in Section 3.2, the selectivities observed in methanolic electrolyte buffers were similar to the infinite dilution mobilities. Thus the presence of the counter-ion did not significantly alter selectivities. In contrast, in aprotic dimethylformamide the use of tetraethylammonium in place of tetrabutylammonium as the buffer cation caused significant changes in the migration order of SCN^- , N_3^- , I^- , NO_2^- and Cl^- [38].

4.4. Complexation

Whereas complexation is widely used for the alteration of the mobility of metal cations, there has been little work on the modification of inorganic anion selectivities. Stathakis and Cassidy [68] examined the control of anion selectivities in cyclodextrin-mediated CZE. As surfactants such as TTAB are complexed by cyclodextrins, polymeric cations were used in this work to reverse the EOF. The degree of complexation depended on the hydrophobicity of the inorganic anion and by size of the cyclodextrin. Complexation was greatest for hydrophobic anions such as iodide, thiocyanate and perchlorate. Significant complexation was only noted with α -cyclodextrins. No effects beyond bulk viscosity effects were observed with β - and γ -cyclodextrins, as would be expected given their larger cavity sizes. Addition of 20 mM α -cyclodextrins to a

5 mM sodium chromate (pH 8) buffer with 0.002% (w/v) PDDPi for EOF control yielded the following anion mobility order:



This is clearly altered from that predicted based on the infinite dilution mobilities in Table 1. Further, the separation efficiencies were between 50 000 and 400 000 indicating rapid equilibration between the inorganic anions and the α -cyclodextrin.

Crown ethers can be used to modify the selectivity of cation separations in CE [11] and to alter the EOF in anion separations [69]. However no selectivity changes were observed with 18-crown-6 complexes of Na^+ and K^+ were added to the electrolyte buffer. However, in contrast to crown ethers, cryptands are protonated in solution (at $\text{pH} \leq 7$ for cryptand-2.2 and $\text{pH} < 10$ for cryptand-2.2.2). Anions are electrostatically attracted to the protonated form of the cryptand. All of the inorganic anions studied (I^- , NO_3^- , SCN^- , CrO_4^{2-} , BrO_3^- , IO_3^-) displayed slower mobilities in the presence of cryptand-2.2 [70]. As the interaction between the anions and the cryptand- H_2^+ is believed to be primarily electrostatic, the selectivity changes would be expected to follow ion-exchange selectivities (Table 1). Thus, the addition 8 mM cryptand-2.2.2 slowed iodide relative to chloride such that baseline separation of the two could be achieved [69].

5. Conclusion

Anion separations in CZE are largely governed by the intrinsic mobility of the anion. This intrinsic mobility is a function of the charge of the ion balanced by frictional forces related to the size of the ion (hydrodynamic friction) and the charge density of the ion (dielectric friction). However, as has been discussed above, a number of approaches can be used to alter these selectivities. The use of nonaqueous solvents primarily alters the relative contributions of the hydrodynamic and dielectric frictions to the mobility on an anion. Thus, use of nonaqueous solvents will be most useful when the ions possess differing crystallographic radii. Altering the buffer

ionic strength alters the ionic screening. Thus it will be most effective when the co-migrating anions differ in charge. Ion association is fairly weak in aqueous solutions, and so will be most effective with multivalent cations added to alter the relative mobility of multivalent anions. A facile means of altering anion selectivities is to adjust the concentration of the cationic surfactant EOF modifier. This will be most effective when the co-migrating anions possess significantly different ion exchange selectivities.

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