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HI 6 dimethanesulfonate has better dissolution properties than HI 6 dichloride for application in dry/wet autoinjectors[1]

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Abstract

To oppose the rapid onset of cholinergic crisis after poisoning with highly toxic organophosphorus compounds, atropine in combination with a cholinesterase reactivator should be administered as early as possible. Due to its broader antidotal spectrum against nerve agents, the second-generation oxime HI 6 appears suitable to replace the marketed oximes, pralidoxime and obidoxime. To meet the requirement of prompt availability, even in the absence of a physician, autoinjectors for intramuscular injection are of advantage. Five hundred micrograms HI 6 dichloride has been considered an appropriate dose for human adults which has to be dissolved in a volume not exceeding 3 ml. Such a concentrated HI 6 solution (appr. 0.5 M) is too unstable for storage. Therefore, dry/wet autoinjectors have been developed in which the HI 6 powder is dissolved in an atropine solution by activating and shaking the device for 5 s immediately before use. However, absolute solubility of HI 6 dichloride is lower than the considered 0.5 M when the temperature is below 10°C. Moreover, the dissolution rate is markedly reduced when the absolute solubility is approached. In case of low ambient temperature, malfunctions of autoinjectors containing HI 6 dichloride may occur with plugging the cannula by undissolved HI 6 and failure in delivery of both antidotal components. Such an event would be particularly tragic if the life-saving atropine dose will not been administered. In contrast to HI 6 dichloride, HI 6 dimethanesulfonate, prepared from the dichloride by ion exchange, is much better soluble and its absolute water-solubility is two and five times higher at 20 and 5°C, respectively. To follow the dissolution kinetics on-line in the short time scale of interest, a method was developed for conductivity measurement of high salinities in a miniaturized assembly in order to be sparing with the valuable oximes. As a result, HI 6 dimethanesulfonate dissolves about 4 and 6 times faster than HI 6 dichloride at 20°C and 5°C, respectively. Thus, HI 6 dimethanesulfonate appears to meet the required specification of quick dissolution much better than the dichloride salt.

Keywords: HI 6; Solubility; Conductivity; Autoinjectors; Antidote; Organophosphate

1. Introduction

Poisoning with organophosphorus compounds, particularly with nerve agents, calls for adminis-

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[1] Some findings have briefly been summarized in a recent overview (Thiermann et al., 1995c).

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tration of antidotes as early as possible. Immediate injection of atropine in combination with an enzyme-reactivating oxime is regarded to be the most effective regimen (for review see Dawson, 1994). Because of the broader antidotal spectrum against nerve agents, the second generation oxime HI 6 (1-(((4-(aminocarbonyl)pyridinio)methoxy)-methyl)-2-((hydroxyimino)methyl) pyridinium dichloride monohydrate; CAS 34433-31-3) appears to be superior to the marketed oximes pralidoxime and obidoxime (Oldiges and Schoene, 1970; Clement, 1981, 1983; Wolthuis et al., 1981a; Wolthuis et al., 1981b; Boskovic et al., 1984; Clement et al., 1992; Lundy et al., 1992). Five hundred grams HI 6 is considered as an effective dose for human therapy (Kusic et al., 1985; Kusic et al., 1991; Clement et al., 1994) that should be administered together with 2 mg atropine as soon as feasible. To meet the requirement of prompt availability for self- and buddy-aid autoinjectors for intramuscular injection are of advantage. For this purpose, 500 mg HI 6 dichloride have to be dissolved in about 3 ml. Unfortunately, such a concentrated solution is unstable and cannot be stored for longer periods (shelf-life about 1 year at 20°C) (Eyer and Hell, 1985; Eyer et al., 1986, 1988, 1989; Fyhr et al., 1987). Therefore, dry/wet autoinjectors have been developed containing HI 6 as a powder which is dissolved in the atropine-containing solution immediately before i.m. injection.

Different types of dry/wet autoinjectors are commercially available, e.g. from Astra Tech (AB, S-43121 Mølndal/Sweden; AT) and STI International Ltd. (Frindsbury, Rochester, Kent ME2 4DP/England; BJ). The principle of the activation procedure consists of breaking the membrane between both compartments followed by shaking the device. Both manufactures claim that a shaking time of 5 s is sufficient for mixture. Schlager et al. (1991) showed that autoinjectors delivered about 500 mg (BJ) and 450 mg (AT) HI 6 dichloride and 2 mg atropine after shaking for 7 s; presumably, the investigation was performed at room temperature. However, a recent study on operational evaluation of dry/wet autoinjectors (Thiermann et al., 1994, 1995b) and on bioavailability of HI 6 dichloride and atropine in dogs (Spöhrer et al., 1994; Thiermann et al., 1995a) revealed that, in some cases, incomplete delivery from both autoinjector types had occurred, although the shaking procedure in our studies lasted 60 s to guarantee complete dissolution. It appeared to us that autoinjectors stored at low ambient temperature (4–8°C) are particularly prone to scattering delivery. Moreover, the aspect of the delivered quantity resembled a suspension rather than a clear solution. Therefore, the question arose whether HI 6 dissolves quickly enough at low temperature to meet the requirement of short shaking time. Considering the utmost stress in the case of recognized symptoms of organophosphate poisoning, even a well-trained soldier will hardly shake an autoinjector for periods longer than 10 s. Hence, rapid and complete dissolution of antidotes even under unfavorable conditions is of paramount importance. Admittedly, one may argue that an injected suspension will dissolve quickly in the warm musculature and must not be expected to produce additional harm. However, the sludge may plug the cannula and the spring force may not surmount the friction of the system that is probably enhanced in the cold. In the worst case, the life-saving atropine dose will not be delivered.

Since it is our firm belief that fool-proof functioning autoinjectors are required, we felt it urgent to evaluate the operational properties of the binary HI 6 autoinjectors also at low temperatures. We found that the limit of solubility of HI 6 dichloride monohydrate (500 mg in a final volume of about 3 ml, i.e. about 0.5 M) is reached at 10°C. To follow the rapid dissolution kinetics of the different HI 6 salts in a short time scale, we determined the increase in conductivity as measure of the increase in concentration during the dissolution process. The study showed that the dissolution rate of HI 6 dichloride was markedly retarded when the temperature was lowered.

Since HI 6 dimethanesulfonate was found to be a better soluble salt of HI 6 at 20°C (Eyer et al., 1992), we investigated also the dissolution properties of HI 6 dimethanesulfonate. This salt is five-times more soluble than the dichloride at 5°C and, more important, is quickly dissolved even at low temperatures.

2. Materials and methods

2.1. Chemicals

HI 6 dichloride monohydrate was a generous gift from Astra Tech AB, S-43121 Mølndal/Sweden. The atropine-containing solution was taken from commercially-available AT autoinjectors.

Methanesulfonic acid and Dowex ion exchange resin (1 × 2, 100–200 mesh, chloride form) were purchased from Aldrich Chemie, Steinheim, Germany; all other chemicals were from E. Merck, Darmstadt, Germany.

Sodium methanesulfonate: equimolar amounts of NaOH and methanesulfonic acid were mixed, followed be freeze drying. The crude material was mortared to give a fine powder.

NaH_2PO_4 monohydrate was mortared and sieved to a fraction between 0.2 and 0.3 mm and 0.4 and 0.6 mm, respectively.

One hundred grams of Dowex was washed with 5 l 1 M NaOH over a Büchner funnel until the eluate was chloride-free (argentometry). After extensive washings with water (eluate pH < 8), the resin was converted with 0.7 l 1 M methanesulfonic acid and washed with water until the eluate became neutral.

2.2. Preparation of HI 6 dimethanesulfonate from HI 6 dichloride by ion exchange chromatography

Fifty grams of HI 6 dichloride monohydrate was dissolved in 300 ml water. Half of the solution was applied to a column of 100 g Dowex in the methanesulfonate form (4 cm int. diam. × 17 cm). HI 6 was eluted with 0.5 mM methanesulfonic acid. The HI 6-containing fractions that were free from chloride (argentometry) were combined and lyophilized. The residue was dissolved in 15 ml water to give a solution of approximately 35 ml; 250 ml EtOH were slowly added during gentle shaking to avoid precipitation of HI 6 dimethanesulfonate. The solution was allowed to stand at 4°C overnight, whereupon HI 6 dimethanesulfonate crystallized (white needles). The crystals were suction-filtered and washed with EtOH. After drying the crystals at 0.01 Torr overnight, 25 g HI 6 dimethanesulfonate were obtained. After regeneration of the resin with 500 ml 1 M methanesulfonic acid and rinsing with 5 l distilled water, the second portion of HI 6 dichloride was converted. The combined mother liquid from the crystallization steps was evaporated, the residue dissolved in a small volume of water and treated with EtOH to obtain a second crop of some 10 g HI 6 dimethanesulfonate. There was a total yield of 60 g, i.e. 95% of theory.

The white crystals melted at 168–170°C (decomp.).

$C_{16}H_{22}N_4O_9S_2$ (478.5)

calc.: C 40.16 H 4.63 N 11.71 O 30.09 S 13.40

found: C 40.10 H 4.65 N 11.61 O 29.96 S 13.40

HPLC analysis of HI 6 dimethanesulfonate revealed that the compound was pure (> 99.7%, assuming similar molar absorption of the impurities at 254 and 300 nm, respectively). A minor product (< 0.3%) was suggested to be the deamination product of HI 6 (HI 6 acid (Eyer et al., 1986)).

The spectroscopic determination of HI 6 dimethanesulfonate at pH 2 exhibited a maximum at 300 nm $E = 12.09 \times 10^3\ M^{-1}\ cm^{-1}$ which agreed with HI 6 dichloride ($E_{300nm} = 12.15 \times 10^3\ M^{-1}\ cm^{-1}$).

2.3. Analytical procedures

2.3.1. HPLC

HPLC was performed with an L-6200A pump (Merck-Hitachi, Darmstadt, Germany) on LiChrosphere® 60 RP-select-B (5 μm; E. Merck, Darmstadt, Germany) at a flow rate of 1.2 ml/min. The mobile phase consisted of MeOH/ PIC-B7/PIC-A/H_2O (12:4:0.5:83.5% v/v; PIC-B7® and PIC-A® being ion-pairing reagents; Waters-Millipore, Eschborn, Germany). HI 6 was eluted after 5.4 min. The oxime was quantified with a UV/Vis, SPD-6AV detector (Shimadzu, Duisburg, Germany) and a D-2500 Chromato-Integrator (E. Merck, Darmstadt, Germany) calibrated with authentic standards. The detection wavelengths were 300 and 254 nm, respectively.

2.3.2. Photometric determination

Oxime concentrations were determined spectroscopically in 20 mM phosphoric acid, pH 2, with

a UV-265 spectrophotometer (Shimadzu, Duisburg, Germany). An extinction coefficient $E_{300\ nm} = 12.1 \times 10^3\ M^{-1}cm^{-1}$ was used for both HI 6 salts.

2.3.3. Sieve analysis

Weighed HI 6 dichloride and HI 6 dimethanesulfonate were sieved with a Kressner sieve (registered trademark 143046), sieve mesh number 4, 5, 6 and 7 (Deutsches Arzneibuch, 1968).

2.3.4. Determination of solubility

For determination of the solubility of HI 6 dichloride monohydrate and HI 6 dimethanesulfonate, both salts, in the presence of solid, were stirred with water at 1.5, 5, 10, 15 and 20°C ± 0.2°C for 8 h. The same procedure was used for dissolution of HI 6 dichloride in atropine-containing solution at 4°C. Thereafter, the oxime concentrations in the clear supernatant were determined photometrically.

2.3.5. Conductivity determination

In order to be sparing with the valuable oximes, the conductivity measurements of high salinities that usually require large volumes had to be scaled down. To this end, a small cylindrical plexiglass chamber (0.8 cm int. diam. × 1.5 cm) was constructed and fitted tightly to the glass cylinder of a commercially available hang-in conductivity cell by means of a silicon sealing ring. Both parts were compressed by three rubber bands (Fig. 1). A magnetic bar placed at the bottom of the plexiglass chamber allowed constant stirring of the solution. The whole assembly was immersed in a thermostated (± 0.2°C) water bath, and the tempered solution (usually 2.5 ml) was filled in with a syringe by means of a small Tygon®-tube inserted through an orifice at the upper part of the conductivity cell (Double Pt electrode 60910.120, Metrohm, Herisau, Switzerland). Conductivity was determined with a 712 Conductometer (Metrohm) and recorded by a Servogor 120 plotter (Metrawatt GmbH, Nürnberg, Germany). Calibration was performed with a KCl standard solution (0.1000 ± 0.0005 M; 11.67 mSi/cm at 20°C; Metrohm). The cell constant was 0.926 cm^{-1} and the scanning frequency set at 2.5 s^{-1}. All measurements were performed in stirred solutions.

The conductivity vs. concentration curves were fitted to an exponential association function that was found to satisfactorily fit the data:

$$C = A\,x\,(1 - e^{-k\,x\,X}) + E$$

where C is the actual conductivity, A the conductivity of a saturated solution, E the conductivity of water at the given temperature, k a factor that includes substance- and assembly-specific properties, and X the concentration of the salt.

The device was tested with sodium chloride and sodium methanesulfonate standard solutions at various temperatures. As shown in Fig. 2, the data for sodium chloride and sodium methanesulfonate are reasonably fitted by the curves. When

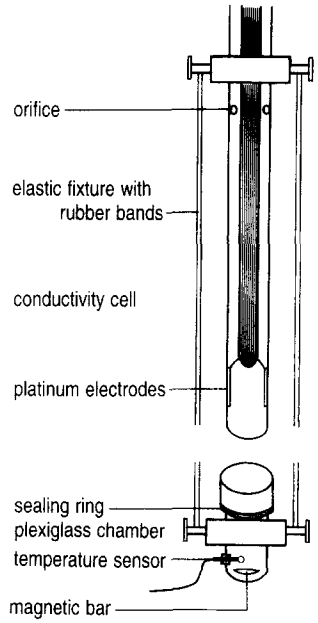

Fig. 1. Miniature assembly for measurement of conductivity. The conductivity cell was pressed on a sealing ring of a plexiglass chamber by rubber bands. Fluid was filled in through the orifice at the upper part and conductivity was measured by platinum electrodes, while being stirred. To follow dissolution kinetics, known amounts of solid were placed in the chamber prior to connection with the conductivity cell. Then water was instilled through the orifice with a syringe by means of a Tygon® tube and conductivity was measured on-line. Temperature was controlled with a small sensor during measurement of conductivity.

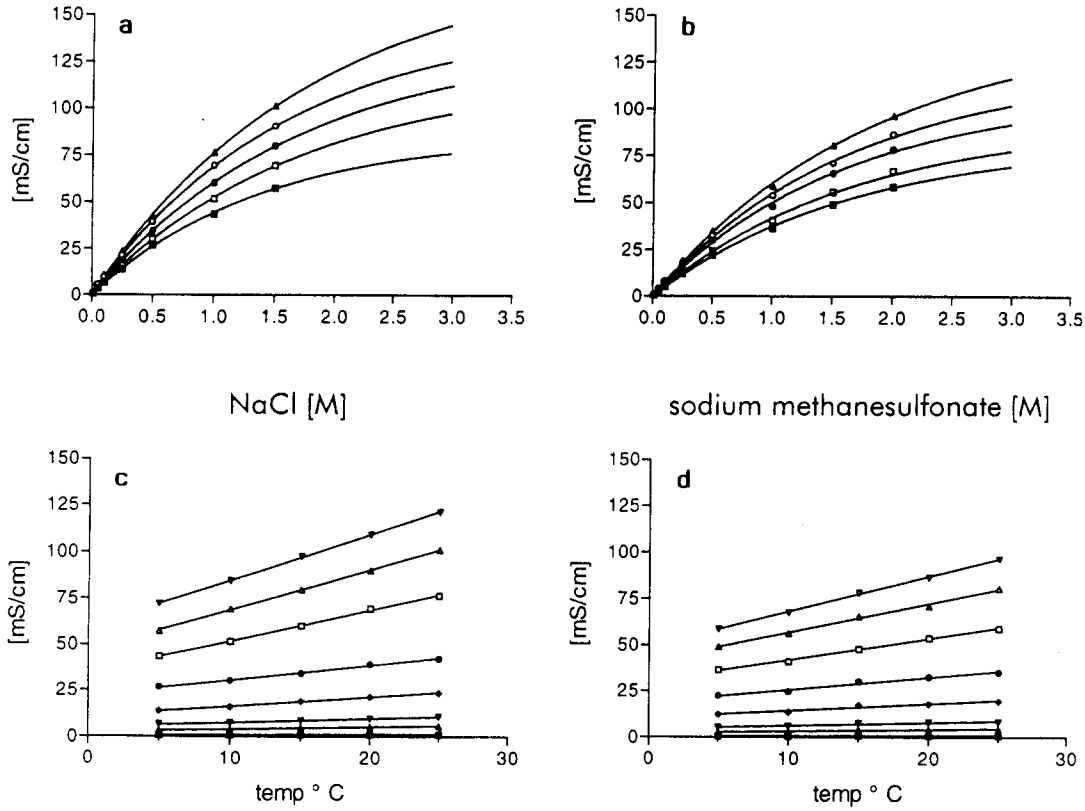

Fig. 2. (a) and (b) Dependence of conductivity on the concentration of NaCl and sodium methanesulfonate. Solution (2.5 ml) was filled into the assembly and conductivity was measured at different temperatures (▲ 25°C, ○ 20°C; ● 15°C, □ 10°C, ■ 5°C). The data were fitted to an exponential association function ($r^2 \geq 0.999$). (c) and (d) Temperature-dependent increase of conductivity of the different NaCl and sodium methanesulfonate concentrations (▽ 2.0 M, △ 1.5 M, □ 1.0 M, ● 0.5 M, ◆ 0.25 M, ▼ 0.1 M, ▲ 0.05 M, ■ 0.01 M). Linear regression was achieved with $r^2 = 1.00 \pm 0.01$ and 0.94 ± 0.05, respectively.

the temperature was elevated a linear increase in conductivity was observed. Independent of the salt used, conductivity increased 1.7-fold when the temperature was raised from 5 to 25°C. In order to test whether the curves extrapolated to higher salt concentrations were still valid, solutions of both salts (up to 5 M) were measured at 10°C. No deviation from the extrapolated curve was found (data not shown).

For determination of dissolution kinetics, known amounts of solids were placed in the plexiglass chamber. After fixing the assembly and temperature equilibration, tempered water (2.5 ml) was filled in while the magnetic stirrer (RMH, Gerhardt, Bonn, Germany) was set to maximal speed (1100 rpm) to allow vigorous stirring. Care was taken to place the tube delivering the solvent near the top of the solid and to avoid splashing onto the upper part of the conductivity cell. The introduction of the solvent was complete in less than 1.5 s.

The described assembly was not suitable for analysis of very rapid dissolution kinetics of easily soluble salts such as sodium chloride or sodium methanesulfonate, where dissolution (2 M) was complete within less than 3 s at room temperature. Such a trial was performed with sodium dihydrogenphosphate monohydrate which dissolves more slowly (Fig. 3). The measured conductivities were transformed into molarities by the

exponential association function determined for NaH_2PO_4 (data not shown). Two sieved fractions were analyzed and it became obvious that the dissolution rate increased markedly at decreasing particle size (Merkel, 1934). From these findings, it is evident that any precise curve description is thwarted by particles of uneven size. Nevertheless, the dissolution studies showed that parameters such as time for 90% dissolution can be determined with sufficient accuracy, e.g. 16 s with the small-size fraction and 32 s with the larger-size fraction of NaH_2PO_4.

2.3.6. Determination of heat of solution during the dilution process

A temperature sensor (PT 100) was fixed in the plexiglass chamber and both conductivity and temperature (Carry 219 spectrophotometer equipped for temperature recording, Varian, Darmstadt) were determined at 20° and 5°C when 0.5 M and 0.3 M HI 6 salts, respectively, were dissolved.

2.4. Statistics

The results are given as arithmetic means ± S.D., if not otherwise indicated. For calculation on a PC, a GraphPad Prism program (GraphPad 10855 Sorrento Valley Road, Suite 203, San Diego, CA 92121 USA) was used.

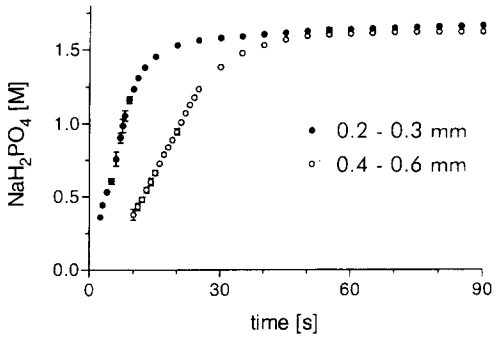

Fig. 3. Dissolution kinetics of NaH_2PO_4 monohydrate in water at 20°C. Weighed NaH_2PO_4 monohydrate (particle size: 0.2–0.3 mm and 0.4–0.6 mm, respectively) was whirled with water by a magnetic bar. Increase in concentration (1.6 M) was determined by recording the conductivity on-line. Means ± S.E., $n = 3$.

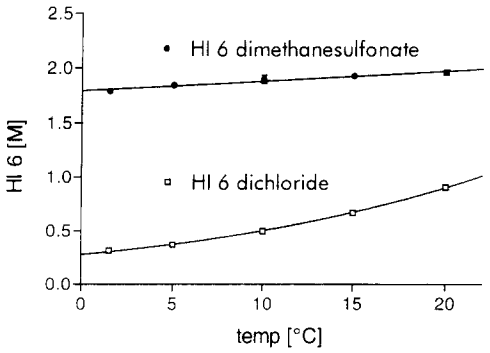

Fig. 4. Solubility of HI 6 dichloride monohydrate and HI 6 dimethanesulfonate at different temperatures. HI 6 concentrations at equilibrium (in the presence of solid) were determined spectrophotometrically after being stirred continuously for 8 h.

3. Results

3.1. Temperature-dependent solubilities of HI 6 dichloride monohydrate and HI 6 dimethanesulfonate

The solubility of HI 6 dichloride monohydrate increased exponentially ($r^2 = 1.00$) from 11.3 to 33.9 g per 100 ml when the temperature was raised from 1.5 to 20°C. There was no difference in solubility when HI 6 dichloride was incubated in water or in the atropine-containing diluent of the AT autoinjectors at 5°C. In contrast, the solubility of HI 6 dimethanesulfonate showed weak temperature dependence and appeared to increase linearly ($r^2 = 0.956$) from 86.1 to 95.7 g per 100 ml upon raising the temperature (Fig. 4). It should be noted that in all measurements, dissolved HI 6 was determined in the supernatant in the presence of solid.

3.2. Dissolution kinetics of HI 6 dichloride monohydrate and HI 6 dimethanesulfonate

The rates of dissolution were determined by conductivity measurements where the conductivities were transformed into molarities by means of the known exponential association function. Fig. 5a and 5b) shows that the conductivity data are reasonably fitted by the curves ($r^2 \leq 0.998$). As observed with NaCl and sodium methanesul-

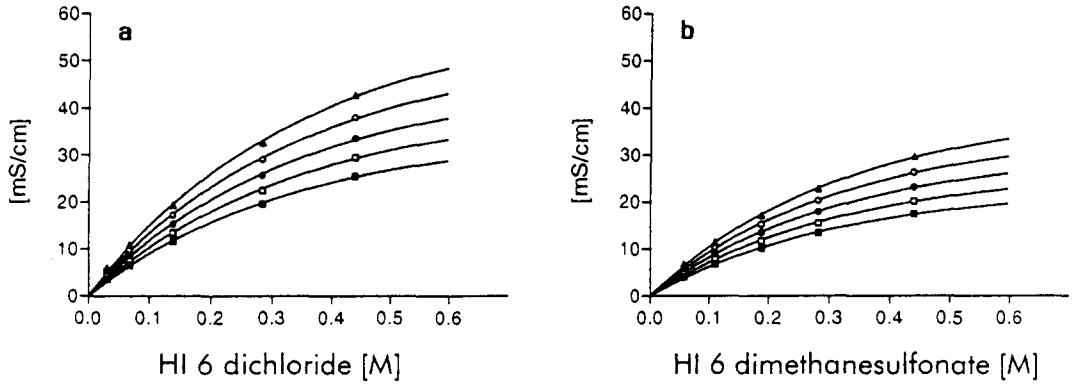

Fig. 5. (a) and (b) Dependence of conductivity on the concentration of HI 6 dichloride monohydrate and HI 6 dimethanesulfonate. Solution (2.5 ml) was filled in the assembly and conductivity was measured at the respective temperatures (▲ 25°C, ○ 20°C; ● 15°C, □ 10°C, ■ 5°C). The data were fitted to an exponential association function ($r^2 \geq 0.998$ each).

fonate the conductivity increased 1.7-fold when the temperature was raised from 5 to 25°C.

The particle size of both HI 6 preparations appeared not to be different, $^3/_4$ of the particles had a diameter between 0.5 and 0.1 mm. From probit analysis a mean of 0.15 mm was estimated.

The determination of the heat of solution (0.5 M, 20°C) revealed a decrease in temperature of about 3°C within 10 s (HI 6 dimethanesulfonate) and 3.8°C within 15 s (HI 6 dichloride), respectively. Since conductivity increased linearly with increasing temperature, the measured conductivities were corrected accordingly before calculating the concentrations. As shown in Fig. 6, HI 6 dimethanesulfonate was faster dissolved than HI 6 dichloride to give a final concentration of 0.5 M at 20°C. Ninety percent of HI 6 dimethanesulfonate was dissolved in 6 s, while 22 s were needed for HI 6 dichloride.

At 5°C the dissolution rate of HI 6 dichloride was slower than at room temperature, and it took 30 s for 90% dissolution (Fig. 6). To exclude that absolute solubility may become rate-limiting at 5°C, the amount of oximes to be dissolved was reduced to give a final concentration of 0.3 M. In contrast to HI 6 dichloride, HI 6 dimethanesulfonate was dissolved readily, 90% being dissolved within 5 s.

4. Discussion

As reported by Eyer et al. (1992), solubility of HI 6 dimethanesulfonate at 20°C exceeded that of HI 6 dichloride twice. This difference was even more prominent at lower temperatures, e.g. at 5°C, when the ratio reached 5:1. In autoinjectors, about 500 mg (Astra Tech) or 580 mg (Binaject) HI 6 dichloride are to be dissolved to give a final volume of 3.2 ml (Astra Tech) or 2.8 ml (Binaject), respectively (Thiermann et al., 1994, 1995a). Therefore, after complete dissolution, concentrations of 0.4 or 0.5 M are reached. This approaches the range of maximal solubility in water at less than 10°C (Fig. 4). Solubility of HI 6 dichloride in the atropine-containing solvent which was obtained directly from autoinjectors (AT) was not different from solubility in water. Therefore, problems of precipitation in autoinjectors at lower temperature cannot be ruled out. In contrast, solubility of HI 6 dimethanesulfonate was hardly affected by temperature and precipitation will occur at about 5 times higher concentration, even at 5°C.

In addition, the question whether the higher solubility would be reflected by a faster rate of dissolution had to be answered. Since the dissolution process in the autoinjectors is limited to small volumes (about 3 ml) and only some 10 gm of HI 6 dimethanesulfonate were available, a method was established to follow the dissolution rate in

small volumes. Miniaturization of the conductivity assembly resulted in the same values of conductivity for NaH_2PO_4 (0.01–2 M) and NaCl up to 0.5 M as published (Weast, 1973). At concentrations above 0.5 M NaCl, conductivity was smaller (11% at 1.0 M) in our miniature device. This difference became even more prominent at higher concentration (20% at 2.0 M) when conductivity reached about 110 mS/cm. As shown in Fig. 1, the platinum electrodes are plated on the inner wall of the glass tube, thereby confining the electric field. Additionally, the distance of the electrodes from the plain bottom was 1.5 cm only. Placing the conductivity cell in a beaker with a larger distance to the bottom increased conductivity (+5% at 1.0 M and +10% at 2 M, respectively). Therefore, geometrical properties of the miniature assembly were assumed to be responsible for the comparably lower conductivity measured at high salinities. At lower conductivity, e.g. below 50 mS/cm as observed in measurements with HI 6 salts, no deviation from literature data was found for NaCl and NaH_2PO_4.

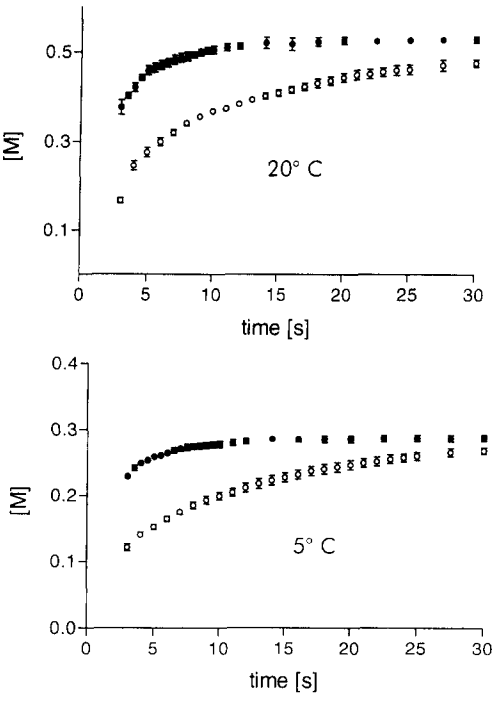

Fig. 6. Dissolution rate of HI 6 dichloride monohydrate (○) and HI 6 dimethanesulfonate (●) in water at 20°C and at 5°C. Weighed HI 6 powder was whirled with water by a magntic bar. Increase in concentration (0.5 M at 20°C, 0.3 M at 5°C) was determined by recording the conductivity on-line. Mean ± S.E., $n = 3$.

More important for the precise determination of the salt concentration from a conductivity calibration curve is the steepness of the curve in the region of interest. The 95% confidence interval in the determination of conductivity amounted to 3.0 ± 2.0% of the mean (between 0.01 and 0.5 M of the HI 6 salts, $n = 5$ each) and the concentrations could be calculated with an error ≤ 6%.

An additional viewpoint was the endothermic dissolution process. Remarkable lowering of temperature was recorded during the first 20 s of the dissolution process despite immersion of the whole assembly in a thermostated water bath. The increase in conductivity was linearly correlated with increasing temperature and amounted to 1.7 per 20°C, independent of the concentration (0.05–0.5 M). This is about the same magnitude as published for other electrolytes (H_2SO_4: 1.43, $MgSO_4$: 1.71; NaCl: 1.62, KCl: 1.56 (Rauen, 1956). Therefore, a reasonable correction of the measured conductivity values was feasible prior to calculation of the concentrations from the standard curves.

Minor persistent problems in determining fast dissolution kinetics arose from the miniaturization of the assembly: the small portion of the solvent standing above the platinum electrodes (Fig. 1) is not readily available for the dissolution process. Hence the volume of distribution for the solute is smaller than calculated at the very beginning. Such an effect is illustrated in Fig. 6 for HI 6 dimethanesulfonate. The concentration determined between 10 and 20 s exceeded the calculated ones by 5% then dropping slowly to the expected 0.5 M.

With regard to the dissolution kinetics of both HI 6 salts, the results are unambiguous: HI 6 dimethanesulfonate is dissolved about 4 times faster than HI 6 dichloride at 20°C and about 6 times faster at 5°C when the time for 90% dissolution is compared. Apart from substance-specific properties, dissolution is dependent on the concentration gradient between actual and saturation concentration (Merkel, 1934). This ratio amounts

to about 0.25 for HI 6 dimethanesulfonate but only to 0.5 for HI 6 dichloride at 20°C. At 5°C, the limit of solubility is reached at about 0.4 M HI 6 dichloride. Therefore at 5°C, dissolution kinetics of 0.3 M HI 6 salts were investigated to allow complete dissolution also for HI 6 dichloride.

Dissolution of 90% HI 6 dichloride at 20°C lasted for about 20 s. Schlager et al. (1991) reported that about 90% HI 6 dichloride were released from autoinjectors containing 500 mg HI 6 dichloride within 7 s. It may be conceded that manual shaking (2 shakes/s) may better whirl powder and water than a magnetic bar. In this study, however, it was not clarified whether the released HI 6 dichloride was completely dissolved. Adhering to the 5 s mixing time specification, we found that less than 60% of HI 6 dichloride (0.3 M final concentration) were dissolved at 5°C. Thus, the highly soluble HI 6 dimethanesulfonate is expected to meet the requirement of broad versatility much better.

The use of methanesulfonate as anion is common pharmaceutical practice, even in combination with oximes. While pralidoxime chloride is used in U.S.A. (Dawson, 1994), pralidoxime methanesulfonate is preferred in UK. Hence, disadvantages of the methanesulfonate regarding tolerance are unlikely. Thus, the replacement of the dichloride salt by the dimethanesulfonate salt appears to be reasonable.

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