A narrative about the dissolution of aromatic diisocyanates into aqueous environments

Patrick M. Plehiers - ORCID 0000-0002-4630-5016

Introduction

It is simple, isn't it? According to the text books, a diisocyanate reacts with water to form the corresponding diamine.

Well, this single sentence includes two half-truths that are a frequent source of confusion and misinterpretation.

First and foremost, the isocyanate groups are converted one at a time (*Figure 1*). Second, all aromatic diisocyanates are very poorly soluble in water. While quantitative conversion to the diamine is correct at sub-micromolar concentrations (Neuland et al., 2022), with increasing loading, the diamine becomes minor and polyurea constitutes the bulk of the hydrolysis products (Yakabe et al., 1999).

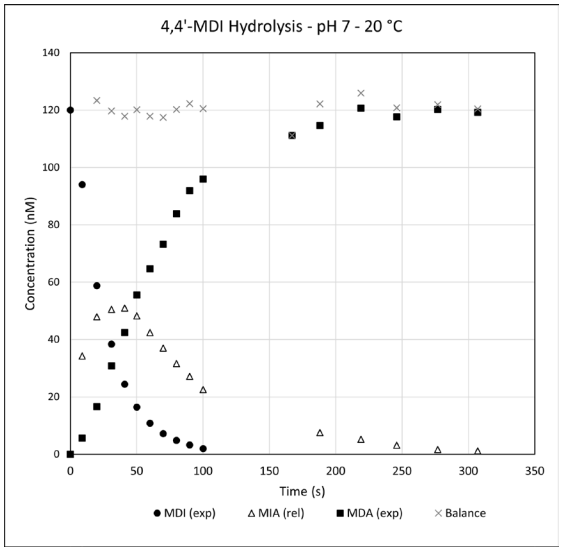

Figure 1 - Two-step hydrolysis of MDI in water.

Symbols and abbreviations

C	concentration
D	distribution coefficient
k	reaction rate constant
K_{OW}	octanol-water partition coefficient
GSH	glutathione
MDA	methylene dianiline
MDI	methylene diphenyl diisocyanate
MIA	methylene diphenyl amino-isocyanate
pMDI	polymeric MDI
TDI	toluene diisocyanate

Subscripts

AA	diamine
IA	amino-isocyanate
II	diisocyanate
U	urea; urea formation
W	water; hydrolysis

Superscripts

I	at interface
O	in organic phase or boundary layer
W	in water phase or boundary layer

Amines are much stronger nucleophiles than water; correspondingly, the rate constant for amine+isocyanate reactions is much larger than for the water+isocyanate reaction (Ekberg and Nilsson, 1976).

Back to dissolution. What mechanism lies behind the fact that only 2.5 mg/L of MDA are formed when 10,000 mg/L of pMDI are

mixed into water? And how to explain that diamine formation stops before complete conversion of the diisocyanate (Yakabe et al., 1999)? To find the answers to these questions, let's dig into the details.

While this narrative is necessarily simplified, it does reflect the results of three decades of research as well as rigorous computer modeling of the process. Also, while MDI is used as an example, the same principles apply to TDI as well.

Hydrolysis in the organic phase

Two characteristics are important when considering the hydrolysis reaction in the organic (i.e., diisocyanate) phase.

First, the solubility of water in aromatic diisocyanates is low. Interpolation based on log K_{OW} or calculation using COSMO-RS (BioVia, San Diego, CA, USA) give solubility estimates between 100-400 mg/kg, in the order of magnitude of 10 mM. Applying the steady-state approximation allows obtaining an order of magnitude for the respective concentrations of the amino-isocyanate (*ca*. 25 mg/kg) and the diamine (*ca*. 2 µg/kg) in the bulk of the organic phase (*Inset 1*). With the water solubility of MDA being 1 g/L at neutral pH (Macnab, 1999), the aqueous concentration in equilibrium with a 10^{-8} M concentration in the organic phase would be just 10 ng/L.

Conclusion: the presence of diamine in the aqueous phase does NOT originate from leaching of diamine from the organic phase.

Second, the concentration of the diisocyanate is large. Consequently, the amine+isocyanate reaction is strongly favored and, as already mentioned, polyurea is the main reaction product. In other words, as time proceeds, the organic phase is gradually converted into a quasi-insoluble and (eco)-toxicologically inert urea particle (Neuhahn et al., 2020; Sendijarevič et al., 2004).

Inset 1

Balancing the rate of the formation and the main disappearance reactions of the amino-isocyanate:

$$2\ k_W\ C_{II}\ C_W \approx 2\ k_U\ C_{II}\ C_{IA}$$

$$C_{IA} \approx (k_W/k_U)\ C_W$$

$$\approx 10^{-2} \times 10^{-2} = 10^{-4}\ (ca.\ 25\ mg/kg)$$

For the diamine:

$$k_W\ C_{IA}\ C_W \approx 4\ k_U\ C_{II}\ C_{AA}$$

$$C_{AA} \approx \tfrac{1}{4}\ (k_W/k_U)^2\ C_W^2/C_{II}$$

$$\approx 10^{-4} \times 10^{-4} = 10^{-8}\ (ca.\ 2\ \mu g/kg)$$

k_W/k_U based on Ekberg and Nilsson (1976) at high organic content.

What happens at the organic-water interface?

At the very interface between the organic and aqueous phases, the extremes meet and purely organic material comes into contact with 55 M water. While being a very strong approximation, applying the same methodology as in *Inset 1* provides some prime insight. The concentration of the amino-isocyanate would increase to about 0.5 M, which is about 10% of the concentration of pure diisocyanate. In other words, at the interface, significant depletion of the diisocyanate occurs and much urea is formed. In the next section, the effect thereof on the diffusion processes in the organic phase will be discussed. Thereafter, migration into the aqueous phase will be considered.

Diffusion processes in the organic phase

Ureas – The mono-ureas of MDI and MDA are poorly soluble in water (Neuhahn et al., 2020) and, hence, will mostly migrate back into the organic phase where they continue to polymerize.

Amino-isocyanate and diamine – Both are present at the interface in concentrations higher than those in the bulk organic phase. Maybe counterintuitively, they will, in part, diffuse back from the interface into the bulk organic phase and add to the formation of polyurea.

Diisocyanate – The depletion of the diisocyanate at the edge of the boundary layer creates a strong concentration gradient between the bulk organic phase and the organic interface. Consequently, according to Fick's law of diffusion there will be an important flux of diisocyanate from the bulk organic phase to the interface.

Figure 2 provides a graphical overview of these diffusion processes and of the urea formation (broad arrow).

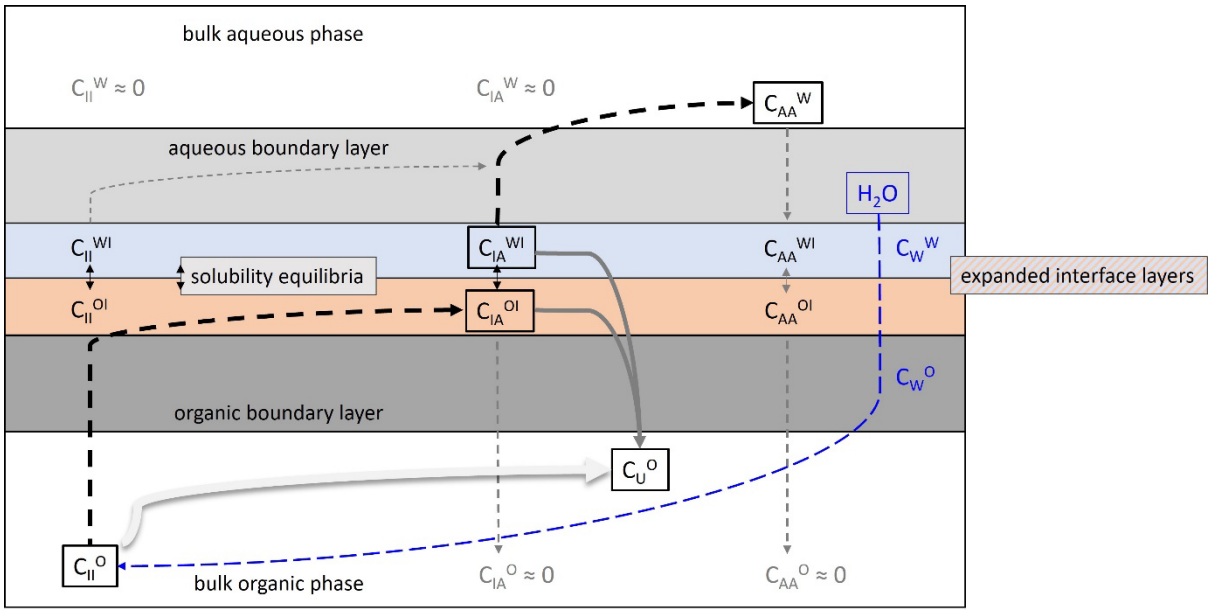

Figure 2 - Schematic representation of the main processes taking place at the water-organic interface.

Solubility equilibria and migration into the aqueous boundary layer

As mentioned above, the solubility of MDA in water is 1 g/L at neutral conditions (Macnab, 1999). The only experimental estimate of the water solubility of MDI is 30 µg/L (Yakabe, 1997). Since the amino-isocyanate is only a transient species, no experimental data are available. However, a good estimate of its solubility can be obtained from the geometric average of the values for MDI and MDA. That value is 5.6 mg/L. This assumes that each amino group (-1.5 log K_{OW} units each) has a similar effect (a factor of *ca*. 200) on solubility.

Migration into the aqueous boundary layer takes place in two steps. First, equilibrium between the two interface layers is rapidly established (Brunner, 1904; Nernst, 1904). Subsequently, diffusion through the aqueous boundary layer occurs (Hamlin et al., 1965; Southworth et al., 1983). Given the similarity in molecular weights, the

diffusion constants that form the basis for the mass transfer rate constants are nearly the same for MDI, MIA, and MDA. This means that the overall rate of transfer is proportional to the concentration in the aqueous phase that is in equilibrium with that in the organic phase (*Inset 2*).

Inset 2

For MDI, an upper-end value for its concentration is ca. 5 M, as can be calculated from its molecular weight and pure substance density (Allport et al., 2003).

For MIA, the interface concentration was shown to be >10% thereof. This remains so as conversion of the diisocyanate increases with time.

Relative dissolution rates:

MDI < 5 / 5 x 0.03 = 0.03

MIA > 0.5 / 5 x 5.6 = 0.28

Conclusion: interestingly, dissolution of the diisocyanate into water occurs almost exclusively post-reaction via the more soluble amino-isocyanate.

Initially, the diamine may contribute to the dissolution process as well. However, this process rapidly reverses as the concentration of the diamine in the bulk aqueous phase exceeds the concentration in equilibrium with the organic phase (*Figure 2*).

In the aqueous boundary layer, the migrating amino-isocyanate and diisocyanate are hydrolyzed to the diamine. While these reactions are generally complete within the boundary layer, they do not lead to a significant acceleration of the mass transfer process (analysis based on Froment and Bischoff, 1979; pp. 310-313).

Further support for reactive dissolution

Extractability of prepolymers based on aliphatic diisocyanates correlates with log D of the diamine rather than with log K_{OW} (West et al., 2024), because protonation of the aliphatic amino groups leads to increased solubility of the amino-isocyanate.

Time-course of diamine formation

Two phenomena reduce the rate of dissolution and the subsequent formation of diamine in the aqueous phase. As conversion of the diisocyanate in the organic phase proceeds, the concentration gradient to the reactive interface is reduced. In addition, the gradual conversion of the organic particle into polyurea creates additional resistance against diffusion. Both factors combined lead to the observation that diamine formation stops prior to complete conversion of the diisocyanate (Yakabe et al., 1999).

A brief word on biological media

In biological media like broncho-alveolar lining fluid, glutathione (GSH) is the most important anti-oxidant. Its sulfur group in deprotonated form is extremely reactive (Schupp and Plehiers, 2022). With a log K_{OW} of -6, GSH also has much greater solubilizing power than the conversion of an isocyanate into an amino group. By the same mechanism as described above, "dissolution" of diisocyanates in biological media can be considered to take place exclusively via GSH-adducts, making the diisocyanate moiety itself not systemically available.

References

Allport, D. C., Gilbert, D. S., and Outterside, S. M. (2003). MDI and TDI: safety, health and the environment. A source book and practical guide. *Wiley, Chichester, UK.* (ISBN 0-471-95812-3).

Brunner, E. (1904). Reaktionsgeschwindigkeit in heterogenen Systemen. *Z Phys Chem*, **47U**, (1), 56-102.

Ekberg, G. and Nilsson, I. (1976). The reaction of phenyl isocyanate in dioxane-water mixtures. *Acta Pharm Suec*, **13**, 251-60.

Froment, G. F., and Bischoff, K. B. (1979). Chemical reactor analysis and design. *Wiley, New York*. (ISBN 0-471-02447-3).

Hamlin, W. E., Northam, J. I., and Wagner, J. G. (1965). Relationships between *in vitro* dissolution rates and solubilities of numerous compounds representative of various chemical species. *J Pharm Sci*, **54**, (11), 1651-1653.

Macnab, J. I. (1999). Determination of physical properties of 4,4'-MDA. International Isocyanate Institute, Manchester, UK.

Nernst, W. (1904). Theorie der Reaktionsgeschwindigkeit in heterogenen Systemen. *Z Phys Chem*, **47U**, (1), 52-55.

Neuhahn, A., Neuland, M., and Sadler, T. (2020). Mono-ureas of MDA and MDI: determination of physico-chemical properties, biodegradability, and acute aquatic toxicity. International Isocyanate Institute, Boonton, NJ, USA.

Neuland, M., Allmendinger, H., Pirkl, H.-G., West, R. J., and Plehiers, P. M. (2022). Homogeneous hydrolysis of 4,4'-methylenediphenyl diisocyanate (MDI) in water. *Toxicol Environ Chem*, **104**, (1), 55-66.

Schupp, T., and Plehiers, P. M. (2022). Absorption, distribution, metabolism, and excretion of methylene diphenyl diisocyanate and toluene diisocyanate: Many similarities and few differences. *Toxicol Ind Health*, **38**, (9), 500-528.

Sendijarevič, V., Sendijarevič, A., Sendijarevič, I., Bailey, R. E., Pemberton, D., and Reimann, K. (2004). Hydrolytic stability of toluene diisocyanate and polymeric methylenediphenyl diisocyanate based polyureas under environmental conditions. *Environ Sci Technol*, **38**, (4), 1066-72.

Southworth, G. R., Herbes, S. E., and Allen, C. P. (1983). Evaluating a mass transfer model for the dissolution of organics from oil films to water. *Water Res*, **17**, (11), 1647-1651.

West, R. J., Jarrom, R., Kelly, M., Simon, G. S., and Snyder, S. (2024). Exploring structure-property relationships to health and environmental hazards of polymeric polyisocyanate prepolymer substances-3. Aquatic exposure and hazard of aliphatic diisocyanate-based prepolymers. Submitted for publication.

Yakabe, Y. (1997). Determination of Log Pow values of MDI and TDI. International Isocyanate Institute, Manchester, UK.

Yakabe, Y., Henderson, K. M., Thompson, W. C., Pemberton, D., Tury, B., and Bailey, R. E. (1999). Fate of methylenediphenyl diisocyanate and toluene diisocyanate in the aquatic environment. *Environ Sci Technol*, **33**, (15), 2579-83.

The referenced III Reports are available from: https://www.bl.uk/onlinegallery/