

The Theoretical Description for Ag_2O_2 /Squaraine Dye – Metformin Electrochemical Determination

Volodymyr V. Tkach*^a, Marta V. Kushnir^a, Yana G. Ivanushko^{a,c}, Valentyna G. Ostapchuk^c, Svitlana P. Melnychuk^c, Silvio C. de Oliveira^b, Volodymyr V. Parchenko^d, Ilona I. Aksyonova^d, Vira M. Odyntsova^d, Petro I. Yagodynets^a, Zholt O. Kormosh^e, Olga V. Luganska^f, Lucinda Vaz dos Reis^g, Alina Yo. Zavolovych^c

^aChernivtsi National University, 58012, Kotsyubyns'ky Str., 2, Chernivtsi, Ukraine.

^bUniversidade Federal de Mato Grosso do Sul, Av. Sen. Felinto. Müller, 1555, C/P. 549, 79074-460, Campo Grande, MS, Brazil.

^cBukovinian State Medical University, 58001, Teatralna Sq., 9, Chernivtsi Ukraine.

^dZaporizhzhia State Medical University, 69600, Mayakovsky Ave, 24, Zaporizhzhia, Ukraine.

^eEast Ukrainian National University, 43000, Voli Ave., 13, Lutsk, Ukraine.

^fZaporizhzhia National University, 69600, Zhukovsky Str. 66, Zaporizhzhia, Ukraine.

^gUniversidade de Trás-os-Montes e Alto Douro, Quinta de Prados, 5001-801, Folhadela, Vila Real, Portugal.

Article history: Received: 22 August 2020; revised: 06 November 2020; accepted: 09 November 2020. Available online: 29 December 2020. DOI: <http://dx.doi.org/10.17807/orbital.v12i4.1537>

Abstract:

In this work, the electrochemical description for metformin electrochemical determination, assisted by Ag_2O_2 composite with squaraine dye, is evaluated from the theoretical point of view. Metformin oxidation is realized via assisted electrochemical 1,2,4-triazole formation, followed by its polymerization and N-oxidation. The correspondent mathematical model has been developed and analyzed by means of linear stability theory and bifurcation analysis. It has shown that the neutral and basic media are more efficient for metformin electrochemical determination than acidic media, due to the absence of the influences of non-protonated aminogroups and, furtherly, pyridinic nitrogen atoms to double electric layer (DEL) ionic force, conductivity and impedance. In these conditions, the electrochemical instabilities are less capable to realize and, therefore, the linear dependence between the analyte concentration and the current of the system will be easier to obtain and maintain, as no side reaction or additional process, capable to compromise the monomer and (or) modifier stability is realized.

Keywords: metformin; silver oxide; squaraine dye; electrochemical sensors; 1,2,4-triazole; stable steady-state

1. Introduction

Type 2 diabetes comprises about 70 – 90 % of all cases of diabetes, and approximately one half of them remain undetected [1]. It has already reached epidemic proportions, currently affecting more than 200 million people worldwide. A significant growth is predicted, generally in developing countries of Asia, Africa and Latin America. It is not a single disease, but a heterogeneous collection of phenotypically and

genotypically different hyperglycemic syndromes. Some 90% of cases have a multifactorial pathogenesis due to unhealthy life-style habits (overnutrition, lack of physical activities, overconsumption of alcohol, sedentary life-style etc) [2].

One of the the first-line medication for the treatment of type 2 diabetes is metformin (Fig. 1) [3-8]. It is also used in the treatment of polycystic ovary syndrome.[9] Limited evidence suggests metformin may prevent the

*Corresponding author. E-mail:  nightwatcher2401@gmail.com

cardiovascular disease and cancer complications of diabetes [10-11]. It is not chemically or pharmacologically related to any other classes of oral antihyperglycemic agents [12-13].

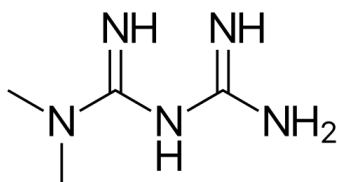


Figure 1. Metformin.

Although metformin is generally well tolerated [13], side effects are possible [14-17], including diarrhea, nausea and abdominal pain, muscle pain, decreased appetite and sleepiness. Lactic acidosis and the vitamin B12 deficit are a concern if the drug is prescribed inappropriately and in overly large doses [18-20]. It should not be used in those with significant liver disease or kidney problems [21-22]. Thus, the development of the efficient and rapid methods of its quantification is really actual [23-25].

Many electrochemical techniques, involving metformin electrochemical detection have been developed [26-29]. They involve different electrode modifiers for the electrochemical determination of metformin by different mechanism, dependent on the oxidation strength and solution composition. They use a wide variety of oxidants as electrode modifiers including conducting polymers, graphene and metal oxide networks. One of those modifiers may be silver (I, III) oxide. It is used as specific oxidant in organic synthesis, electrocatalysis and gas filtration [30], thus its use in electrochemistry could be interesting.

On the other hand, its electroanalytic properties' investigation has only begun, and an Ag_2O_2 -assisted electrochemical oxidation may confront the problems like:

- the indecision in the modifier mechanism of action;
- the compatibility of the modifier with the tissue or biological object (some modifiers, used *in vitro* may be non-compatible with *in vivo* sensing);
- the presence of electrochemical

instabilities, accompanying both electrochemical synthesis of cobalt (III) oxyhydroxide [31-32], and electrochemical oxidation and electrooxidative polymerization of organic molecules [33-34].

The mentioned problems may only be solved by means of an analysis of a mathematical model, capable to describe adequately the electroanalytical system. By modeling it is also capable compare the behavior of this system with that for the similar ones without any experimental essay.

So, the goal of this work is the mechanistic theoretic analysis of the possibility of metformin electrochemical quantification by Ag_2O_2 -Squaraine Dye modified electrode. In order to achieve it, we realize the specific goals:

- suggestion of the mechanism of the electroanalytical reaction sequence, including the participation of hydroxyl ions, leading to the appearance of analytical signal;
- development of the balance equation mathematical model, correspondent to the electroanalytical system;
- analysis and interpretation of the model in terms of the electroanalytical use of the system;
- the seek for the possibility of electrochemical instabilities and for the factor, causing them;
- the comparison of the mentioned system's behavior with the similar ones [35].

2. Materials and Methods

In this work, the dynamic electrochemical system is evaluated as a set of state functions, time change of which is described by balance equations, derived from the physical laws describing its behavior, taking into account the chemical behavior of the described substances.

These equations form a set:

$$\begin{cases} \frac{dA}{dt} = f_1(A, B, C) \\ \frac{dB}{dt} = f_2(A, B, C) \\ \frac{dC}{dt} = f_3(A, B, C) \end{cases} \quad (1)$$

permitting stable and unstable solutions. As even the most stable steady-states permit fluctuations, in the concrete point, the most stable state, in other words, most susceptible to the fluctuations is realized.

The steady-state stability is evaluated by linear stability theory, investigating the behavior of the system after the little perturbations of the steady-state. The unstable states are considered deviations, in relation on steady-states – the less is the deviation from a steady-state, more stable this state is. If we consider

$$A=A_{SS}+ a; B=B_{SS}+ b; C= C_{SS}+b \quad (2-4)$$

where a , b and c are deviations from the stable steady-state, the functions f_1 , f_2 and f_3 may be linearized, described as:

$$\begin{cases} \frac{dA}{dt} = a_{11}a + a_{12}b + a_{13}c \\ \frac{dB}{dt} = a_{21}a + a_{22}b + a_{23}c \\ \frac{dC}{dt} = a_{31}a + a_{32}b + a_{13}c \end{cases} \quad (5)$$

Herein the elements a_{xx} are the correspondent steady-state Jacobian matrix members, calculated as the derivatives of the functions f_1 , f_2 and f_3 on the variables A , B and C .

Due to the linearity, the equation-set (5) permits the solutions, exposed as normal modes:

$$A=A_0e^{wt}, B=B_0e^{wt}, C=C_0e^{wt} \quad (6-8)$$

Imputing of them into the equation (5), we obtain the linear equation system, related to the coefficients A_0 , B_0 and C_0 , solution of which gives the pass to characteristic equation, analysis of which derives the stability and instability requisites, as shown below. More developed description for this methodology is given in [36].

2.1. System and its Modeling

Silver (I, III) oxide oxidizes metformin by a

specific interesting mechanism. Firstly, two protons leave the electronically rich imine part of the guanidine group, being oxidized by the oxygen atom, attached to the trivalent silver. forcing its electrochemical heterocyclization. It yields 3-amino-5-methylamino-1,2,4-triazole (Fig. 2):

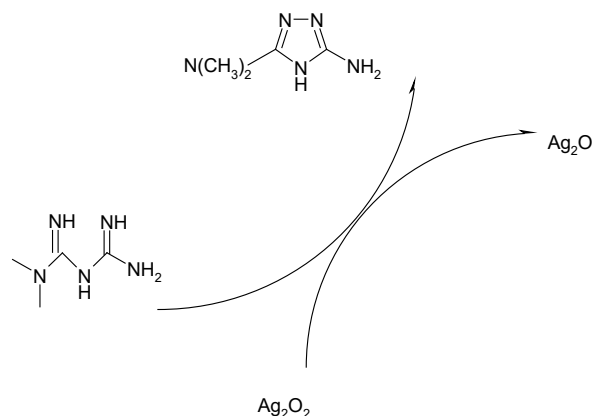


Figure 2. The first stage of metformin Ag_2O_2 -assisted oxidation.

The formation of a stabilized cyclic aromatic system from a less stable guanidic fragment is favored by both kinetic and thermodynamic properties of the system, yielding a triazole. The triazolic derivative, possessing both cyclic conjugated system and pyridinic nitrogen atoms may be oxidized by two manners (Fig. 3).

As the silver (I, III) oxide is a highly-energetic oxidized form, it easily oxidized the pyridinic nitrogen atoms to the correspondent N-oxide. Also, it is capable to oxidize the electrophilic centers of the triazole derivative (pyrrolic nitrogen and aminogroup, like in polyaniline), providing an efficient radical-cation formation with further chain propagation by the modified classical assisted electropolymerization mechanism.

The initial (non-oxidized) metformin participates in the polymerization reaction as a dopant. The resulting polymer is highly conducting and is also capable to be used for electroanalytical processes as electrode modifier.

The squaraine dye matrix in the electroanalytical process serves as both Ag_2O_2 stabilizer and redox transfer mediator. Its stabilization mechanism is based on its capability to coordinate with silver.

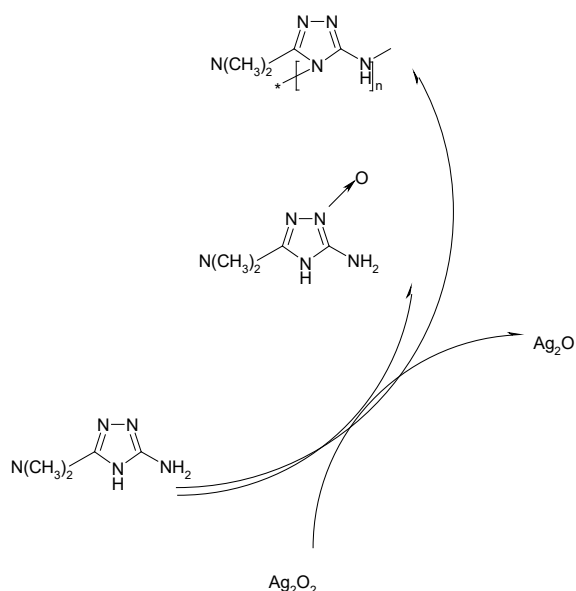


Figure 3. Triazolic product oxidation scheme.

So, this system will resemble that described for isotipuron electrochemical determination [35], and its behavior will be described by a trivariant equation-set of the variables:

m – metformin concentration in the pre-surface layer;

m^* - monomer concentration in the pre-surface layer;

s – silver (I) oxide matrix coverage degree.

To simplify the modeling, we suppose that the reactor is intensively stirred, so we can neglect the convection flow. Also we assume that the background electrolyte is in excess, so we can neglect the migration flow. The diffusion layer is supposed to be of a constant thickness, equal to δ , and the concentration profile in it is supposed to be linear.

It is possible to show that the behavior of the system will obey the model, described by a

Herein,

$$a_{11} = \frac{2}{\delta} \left(-\frac{\Delta}{\delta} - k_1(1-s) - yk_p m^* m^{y-1} (1-s)^z \right) \quad (15)$$

$$a_{12} = \frac{2}{\delta} \left(-xk_p m^* m^{x-1} (1-s)^z \right) \quad (16)$$

trivariant balance equation-set as:

$$\begin{cases} \frac{dm}{dt} = \frac{2}{\delta} \left(\frac{\Delta}{\delta} (m_0 - m) - r_1 - r_p \right) \\ \frac{dm^*}{dt} = \frac{2}{\delta} (r_1 - r_2 - r_p) \\ \frac{ds}{dt} = \frac{1}{s} (r_1 + r_2 + r_p - r_3) \end{cases} \quad (9)$$

Herein, Δ is the diffusion coefficient, m_0 is the metformin bulk concentration, S is the silver (I) oxide maximal matrix concentrations and the parameters r stand for the correspondent reaction rates, which may be calculated as:

$$r_1 = k_1 m (1-s) \quad (10)$$

$$r_2 = k_2 m^* (1-s) \quad (11)$$

$$r_p = k_p m^* m^y (1-s)^z \quad (12)$$

$$r_3 = k_3 s \exp\left(\frac{2F\varphi_0}{RT}\right) \quad (13)$$

Herein, the parameters k are the correspondent reaction rate constants, x , y and z are the reaction orders in the polymerization reactions, F is the Faraday number, φ_0 are the DEL potential slope, related to the zero-charge potential, R is the universal gas constant and T is the absolute temperature.

In this case, the system's behavior in neutral and basic media, in which neither guanidine moiety, nor triazolic derivative are ionized, is evaluated. Therefore, the system has to be relatively stable, as shown below.

3. Results and Discussion

In order to investigate the behavior of the system with metformin electrochemical determination on Ag_2O_2 , we analyze the equation-set (9), taking into account the algebraic relations (10 – 13), by means of linear stability theory. The steady-state Jacobian matrix members may be described as:

$$\begin{pmatrix} a_{11} & a_{12} & a_{13} \\ a_{21} & a_{22} & a_{23} \\ a_{31} & a_{32} & a_{33} \end{pmatrix} \quad (14)$$

$$a_{13} = \frac{2}{\delta} (k_1 m + z m *^x m^y (1-s)^{z-1}) \quad (17)$$

$$a_{21} = \frac{2}{\delta} (k_1 (1-s) - y k_p m *^x m^{y-1} (1-s)^z) \quad (18)$$

$$a_{22} = \frac{2}{\delta} (-k_2 (1-s) - x k_p m *^{x-1} m^y (1-s)^z) \quad (19)$$

$$a_{23} = \frac{2}{\delta} (k_2 m * + z m *^x m^y (1-s)^{z-1}) \quad (20)$$

$$a_{31} = \frac{1}{s} (k_1 (1-s) + y k_p m *^x m^{y-1} (1-s)^z) \quad (21)$$

$$a_{32} = \frac{1}{s} (k_2 (1-s) + x k_p m *^{x-1} m^y (1-s)^z) \quad (22)$$

$$a_{33} = \frac{1}{s} \left(-k_1 m - k_2 m * - z m *^x m^y (1-s)^{z-1} - k_3 \exp\left(\frac{2F\phi_0}{RT}\right) + j k_3 s \exp\left(\frac{2F\phi_0}{RT}\right) \right) \quad (23)$$

Contrarily to the similar system [35], involving the direct electrooxidation of isoproturon, the oscillatory behavior is less probable in this system, due to the indirect analyte and product electrooxidation. The electrochemical stage on double electric layer capacitance and conductivity. It is described by the positivity of the element $j k_3 s \exp\left(\frac{2F\phi_0}{RT}\right) > 0$ if $j > 0$. The oscillations are expected to be frequent and of small amplitude and are expected to be observed beyond the detection limit.

In order to investigate the steady-state stability, we apply the Routh-Hurwitz stability criterion to the equation-set (9). Avoiding the cumbersome expressions, we introduce new variables, rewriting the determinant as:

$$\frac{4}{\delta^2 s} \begin{vmatrix} -\kappa - \mathcal{E} - \Lambda & -\Sigma & P + \Gamma \\ \mathcal{E} - \Lambda & -\Sigma - T & K + \Gamma \\ \mathcal{E} + \Lambda & \Sigma + T & -K - P - \Gamma - \mathcal{E} \end{vmatrix} \quad (24)$$

Opening the brackets and applying the Det $J < 0$ requisite, salient from the criterion, we obtain the stability requisite exposed as:

$$-\kappa(\Sigma P + T\Pi + \Sigma\mathcal{E} + T\mathcal{E}) - \mathcal{E}(T\Pi + \Sigma\mathcal{E} + T\mathcal{E} + \Sigma K - 2TP - 2T\Gamma + \Sigma K + \Sigma\mathcal{E}) - \Lambda(\Sigma P + T\Pi + \Sigma\mathcal{E} + T\mathcal{E} + \Sigma P + \Sigma\mathcal{E}) < 0 \quad (25)$$

It is correspondent to either diffusion or kinetically controlled system, due to the high contribution of both diffusion κ and kinetical parameters (\mathcal{E} and Λ) with the presence of either fast and slow chemical and electrochemical stages. In the case of the positivity of the electrochemical parameter \mathcal{E} , correspondent to the fragility of DEL influences of the electrochemical stages, the left side of the inequation (25) is driven to more negative values, corresponding to low exponential deviations, related to the steady-states and, therefore, to its stability. The condition (25) is

realized in large topological parameter region.

From the electroanalytical point of view, it is correspondent to the linear relation between the metformin concentration and the current, providing a simple and exact analytical signal interpretation, like also its quick appearance.

As for the detection limit, it is described by *monotonic instability*, serving as margin between the stable steady-states and unstable states. Its condition is Det $J = 0$. Or, for this system,

$$-\kappa(\Sigma P + T\Pi + \Sigma\mathcal{E} + T\mathcal{E}) - \mathcal{E}(T\Pi + \Sigma\mathcal{E} + T\mathcal{E} + \Sigma K - 2TP - 2T\Gamma + \Sigma K + \Sigma\mathcal{E}) - \Lambda(\Sigma P + T\Pi + \Sigma\mathcal{E} + T\mathcal{E} + \Sigma P + \Sigma\mathcal{E}) = 0 \quad (26)$$

This model describes metformin electrochemical determination in neutral or basic media. In acidic media, all of the compounds appear in their ionized forms, contributing to DEL ionic forces. Those ionic forms will give high impact to DEL conductivity changes, which is also responsible for the instabilities. Therefore, the use of neutral and basic media in this metformin determination is recommended.

4. Conclusions

From the theoretical analysis of Ag₂O₂-squaraine dye-assisted metformin electrochemical determination, it was possible to conclude that it has to be an efficient diffusion- and kinetically controlled system. The dependence between the drug concentration and the electrochemical parameter obeys the linear relation in a vast region of parameter value. As for the oscillatory behavior, it is of less probability, due to the absence of the DEL-affecting influences of the chemical stages in neutral and basic media.

References and Notes

- [1] Azab, Sh.; Fekry, A. M. *RSC Adv.* **2017**, *7*, 1118. [\[Crossref\]](#)
- [2] Kopelman, P.; Caterson, I.D.; Dietz, W.H. *Clinical Obesity in Adults and Children*, Wiley, London, 2008.
- [3] Serrano Ríos, M.; Gutiérrez Fuentes, J. A. *Type II Diabetes Mellitus*, Elsevier España, Madrid, 2009.
- [4] Maruthur, N. M.; Tseng, E.; Hutflesset, S. *et al. Ann Int. Med.* **2016**, *164*, 740. [\[Crossref\]](#)
- [5] Dunn, C. J.; Peters, D. H. *Drugs* **1995**, *49*, 721. [\[Crossref\]](#)
- [6] Hundal, R. S.; Inzucchi, S. E. *Drugs* **2003**, *63*, 1879. [\[Crossref\]](#)
- [7] Laschen, H. *Ther. Adv. Endocrinol. Metabol.* **2010**, *1*, 117. [\[Crossref\]](#)
- [8] Malek, M.; Aghili, R.; Emami, Z.; Khamseh, M. E. *Int. Schol. Res. Not.* **2013**, *2013*, 636927. [\[Crossref\]](#)
- [9] <https://www.ncbi.nlm.nih.gov/pubmed/25954799>, accessed on the 23rd of August 2020.
- [10] <https://www.drugs.com/pro/metformin.html>, accessed on the 23rd of August 2020.
- [11] Triggler, C. R.; Ding, H. *Acta Phys.* **2017**, *219*, 138. [\[Crossref\]](#)
- [12] <https://www.drugs.com/sfx/metformin-side-effects.html>, accessed on the 3rd of March 2017.
- [13] Aguayo Rojas, L. B.; Gomes, M. B. *Diabetol. Metabol. Syndr.* **2013**, *5*, 6. [\[Crossref\]](#)
- [14] Bouchoucha, M.; Uzzan, B.; Cohen, R. *Diabet. Metabol.* **2010**, *37*, 90. [\[Crossref\]](#)
- [15] Bonnet, F.; Scheen, A. *Diab. Obes. Metabol.* **2017**, *19*, 473. [\[Crossref\]](#)
- [16] Sharma, S.; Ray, A.; Sadasivam, B. *Diabetes. Res. Clin. Pract.* **2020**, *164*, 108183. [\[Crossref\]](#)
- [17] Liu, K. W.; Dai D. L. K. *et al. As. J. Gerontol. Geriatr.* **2011**, *6*, 82. [\[Link\]](#)
- [18] Lalau, J. D. *Drug Safety* **2010**, *33*, 727. [\[Crossref\]](#)
- [19] Crowley, M. J.; Diamantidis, C. J.; McDuffie, J. R. *et al. Ann. Int. Med.* **2017**, 191. [\[Crossref\]](#)
- [20] Nye, H. J.; Herrington, W. G. *Nephrol. Clin. Pract.* **2011**, *118*, 380. [\[Crossref\]](#)
- [21] Ujwala, Ch.; Krishna, N. V.; Karthik, Y. *et al. J. Chem. Pharm. Res.* **2017**, 9260. [\[Link\]](#)
- [22] El-Shal, M.; Azab, M.; Hendawy, A. *Bull. Nat. Res. Centre* **2019**, *43*, 95. [\[Crossref\]](#)
- [23] Kumar, Y.; Vashistha, V. K.; Das, D. K. *Lett. Appl. Nanobiosci.* **2020**, *9*, 866. [\[Crossref\]](#)
- [24] Rajaram, R.; Kiruba, M.; Suresh, C. *et al. Microchimica Acta* **2020**, *187*, 334. [\[Crossref\]](#)
- [25] Maeda, T.; Liess, A.; Kudzus, A. *et al. Chem. Comm.* **2020**, *56*, 9890. [\[Crossref\]](#)
- [26] Chen, Y.; Wang, S.; Li, Z. *RSC Advances* **2020**, *10*, 29119. [\[Crossref\]](#)
- [27] Aguilera, L.; Aguiar, P. C. M.; Ruiz, Y. L. *et al. J. Mat. Sci.* **2020**, *31*, 3084. [\[Crossref\]](#)
- [28] Shamraiz, U.; Badshah, A.; Raza, B. *Langmuir* **2020**, *36*, 2223. [\[Crossref\]](#)
- [29] Bagheri, A.; Hassani Marand, M. *Russ. J. Electrochem.* **2020**, *56*, 453. [\[Crossref\]](#)
- [30] Jiang, W.-X.; Liu, W.-X.; Wang, C.-L. *et al. New J. Chem.* **2020**, *44*, 2721. [\[Crossref\]](#)
- [31] Stadnik, A.; Caldas, E. M.; Galli, A.; Anaissi, F. J. *Orbital: Electron. J. Chem.* **2015**, *7*, 122. [\[Crossref\]](#)
- [32] Bonini, J. S.; Mariani, F. Q.; Guimarães Castro, E. *et al. Orbital: Electron. J. Chem.* **2015**, *7*, 318. [\[Crossref\]](#)
- [33] Tkach, V.; Kushnir, M.; Ivanushko, Y. *et al. Appl. J. Env. Eng. Sci.* **2020**, *6*, 51. [\[Crossref\]](#)
- [34] Tkach, V. V.; Storoshchuk, N. M.; Romaniv, L. V. *et al. Vietnam Journal of Chemistry* **2018**, *56*, 440. [\[Crossref\]](#)
- [35] Tkach, V.; Kushnir, M. *et al., Appl. J. Env. Eng. Sci.* **2020**, *6*, 143. [\[Crossref\]](#)
- [36] Koper, M. T. M. *Far-from-equilibrium Phenomena in Electrochemical Systems. Instabilities. Oscillations and Chaos*. Universiteit Utrecht, The Netherlands, 1994.