

Photochemical stability of the inclusion complexes formed by modified 1,4-dihydropyridine derivatives with β -cyclodextrin¹

Jadwiga Mielcarek

*Department of Inorganic and Analytical Chemistry, K. Marcinkowski University of Medical Sciences, Grunwaldzka 6,
60-780 Poznań, Poland*

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Abstract

The results of studies of photochemical stability of the derivatives of 1,4-dihydropyridine (NR) are reported. The NR with various substituents (-NO₂, -Cl, -F, CF₃) at different positions in the phenyl ring were identified by UV spectrophotometry. Photodegradation of NR in the inclusion complexes with β -cyclodextrin (β -CD) was studied in the liquid phase. The rate of photodegradation of NR derivatives was dependent on the position of -NO₂ group in the phenyl ring; for the ortho isomer it is ten times higher than for the meta one. The rate of photodegradation of 2-NO₂-NR (ortho isomer) in inclusion complex with β -CD was 200 times slower than that for this compound in the crystal phase. In the case of halogeno- and cyanoderivatives, the presence of β -CD caused a 4-fold increase in the photodegradation rate. © 1997 Published by Elsevier Science B.V.

Keywords: 1,4-Dihydropyridine derivatives; β -Cyclodextrin; Inclusion complexes; Photostability

1. Introduction

The 1,4-dihydropyridines (DHP) are of particular importance for the analysis of Ca²⁺ channel structure and function because of the availability of many analogues of nifedipine and the existence of both activator and antagonist ligands. According to the literature, the structure-activity relationship indicates that the nature and position of a substituent in the aryl ring of the DHP antagonists are very important determinants of the antagonist activity.

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Because of the suggestions that the ester substituents at C₃ and C₅ of the DHP ring influence tissue selectivity, a series of phenyl-substituted derivatives bearing different ester groups was synthesized [1–7].

From the point of view of the use in treatment, DHP derivatives reveal some undesirable characteristics such as poor solubility in water and high photochemical sensitivity, which lead to chemical changes responsible for weakening the therapeutic effect [8–10]. To overcome these problems, many authors have been working on modifications of these compounds consisting in the replacement of the groups responsible for photodegradation by other substituents [11].

Another approach to the upgrading of physical and chemical properties of DHP derivatives is based on preparation of inclusion complexes of these drugs with β -cyclodextrin (β -CD) [12–15].

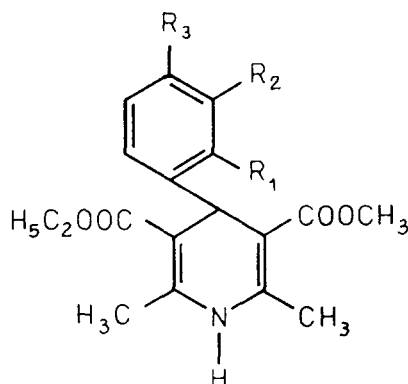
The aim of this work was to check the effect of the β -CD presence on the photochemical stability of the modified 1,4-dihydropyridine derivatives.

2. Experimental

2.1. Materials

The 1,4-dihydropyridine derivatives (NR) with various substituents at different positions in the phenyl ring were received from Professor D. Langa (Buffalo, USA)—Table 1. β -cyclodextrin (β -CD) was purchased from Merck, FRG; $M_r = 1134.98 \text{ g mol}^{-1}$.

Table 1
1,4-dihydropyridine derivatives (NR)



NR derivatives	R_1	R_2	R_3	M_r (g mol $^{-1}$)
2 NO $_2$ -NR	NO $_2$	H	H	125.89
3 NO $_2$ -NR	H	NO $_2$	H	160.99
2 CF $_3$ -NR	CF $_3$	H	H	136.22
4 Cl-NR	H	H	Cl	154.26
4 F-NR	H	H	F	148.66
3 CN-NR	H	CN	H	148.05

Table 2
Analytical wavelengths and molar absorption coefficients of 1,4-dihydropyridine derivatives (NR)

NR derivatives	Analytical wavelength (nm)	Molar absorption coefficient (dm 3 mol $^{-1}$ cm $^{-1}$ $\times 10^3$)
2 NO $_2$ -NR	235.0	29.26
	327.6	6.64
3 NO $_2$ -NR	235.0	38.95
	350.0	8.21
2 CF $_3$ -NR	236.6	32.66
	358.2	5.97
4 Cl-NR	235.0	37.25
	350.0	10.08
4 F-NR	235.0	15.04
	357.0	6.03
3 CN-NR	228.0	72.07
	358.0	6.15

2.2. UV absorption measurements

For the spectrophotometric studies, solutions of NR listed in Table 1 were prepared and the UV spectra were recorded using a UV-160 Shimadzu spectrophotometer.

The obtained values of molar absorption coefficients and analytical wavelength for the compounds studied are presented in Table 2.

2.3. Photochemical stability

2.3.1. Qualitative studies

Solutions of NR and their inclusion complexes with β -CD were placed in quartz cells which were covered to prevent solvent evaporation. The samples were exposed to UV radiation ('Fluotest' lamp, model NN 15/30; $\lambda = 254 \text{ nm}$) from a 30 cm distance. The exposure time of 2NO $_2$ -NR and 3NO $_3$ -NR samples was 1000 min. As the photodegradation of the other compounds was slower, the time of their exposure to UV radiation was increased to 2900 min.

To check the irradiation effect, UV spectra of the samples were recorded in the range from 200 to 400 nm. Differences in the spectra before and after the irradiation were observed only for the

samples of 2NO₂-NR and 3NO₂-NR, and the detected changes are presented for compound 2NO₂-NR (Fig. 1).

2.4. Determination of kinetic parameters

Measurements of absorbance at λ_{\max} were performed for the samples prepared for photochemical stability and subjected to UV exposure for a certain time.

The concentration changes of the NR during irradiation are described by the equation

$$\ln A = \ln A_0 - k_0 \cdot t$$

On the basis of the above equation the following kinetic parameters were estimated: the rate constants of the first order reaction (k), $t_{0.5}$ — the half life time, $t_{0.1}$ —the time of the decomposition of 10% of a parent compound.

The photodegradation of 2NO₂-NR was considered to be a two-stage process characterized by two rate constants: the k_2 constant was calculated from the linear portion of the diagram $\ln A = f(t)$, corresponding to the irradiation time $t_{\max} < t < t_{\infty}$, while the k_1 constant was calculated by subtraction.

The differentiation diagram $\ln (A_{\infty} - A) = f(t)$ was linear for the times $t_0 < t < t_{\max}$. Changes in the concentration of NR during the time of photochemical degradation are presented in Fig. 2 as a diagram of $\ln c = f(t)$, whereas the kinetic parameters are given in Table 3.

3. Results and discussion

Many of the hitherto performed studies have shown that the photochemical sensitivity of DHP derivatives can be reduced by molecule modification, in particular by replacing the photochemically sensitive -NO₂ group in a phenyl ring with other substituents.

In the first part of the paper the studied compounds were analyzed using UV spectrophotometry. As can be seen in Table 2, all UV spectra

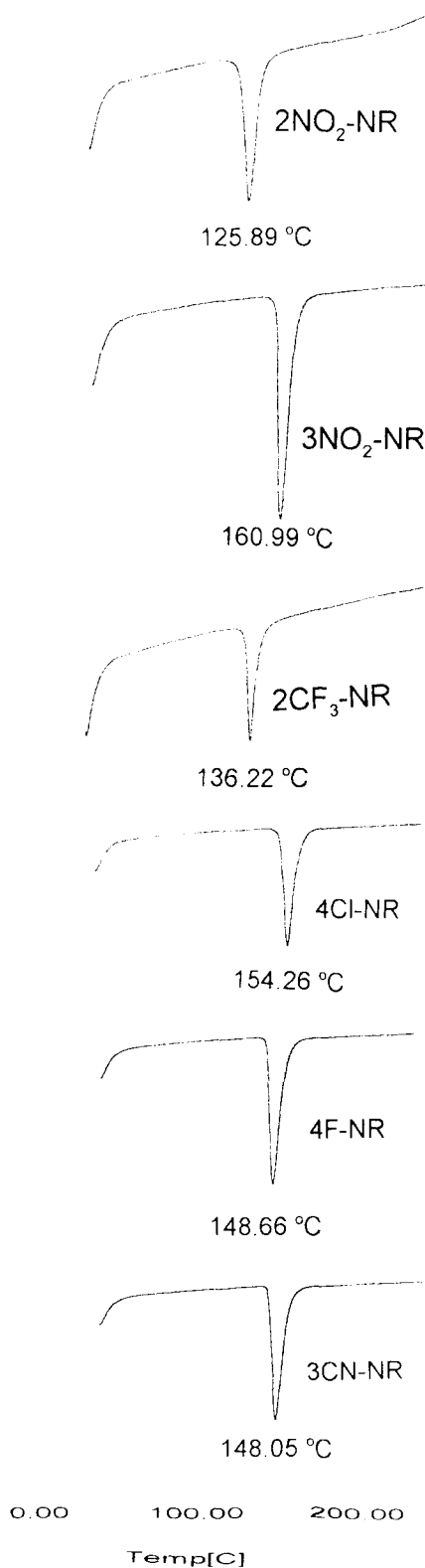


Fig. 1. DSC curves of 1,4-dihydropyridine derivatives.

Fig. 1.

revealed two absorption bands with a maximum in the range of the wavelengths 228.0–236.6 nm and 350.0–361.0 nm. The absorption band attributed to the presence of aromatic ring, which occurs at the shorter wavelength, was more intensive than the band at about 350 nm. The values of absorption molar coefficients for higher frequencies were in the range 1.5×10^4 – 7.2×10^4 , while for the longer waves they ranged from 5.9×10^3 – 7.3×10^4 [$\text{dm}^3 \text{mol}^{-1} \text{cm}^{-1}$].

DHP derivatives are characterized by high photosensitivity and they easily undergo conversion, most frequently to nitro- and nitrosoderivatives of pyridine which do not show therapeutic effect.

The photodegradation process of the NR was evaluated by analyzing the changes in the UV spectra. For this purpose, samples of the analyzed NR were exposed to irradiation under the same conditions, both in the presence and in the absence of β -CD.

In order to determine the influence of the position of $-\text{NO}_2$ group in a phenyl ring on the degradation rate, photodegradation of 2NO_2 -NR and 3NO_2 -NR was compared. Changes observed in the UV spectra of the irradiated isomers indicated that photodegradation of 2NO_2 -NR was much faster in comparison with that of the meta-isomer. Already after 15 min. of the irradiation, the intensity of absorption bands at 235 and 327 nm, in the spectrum of ortho-isomer, was observed to decrease, and new bands at about 281 and 313 nm appeared.

The results of our previous studies and literature data suggest that the observed changes in the

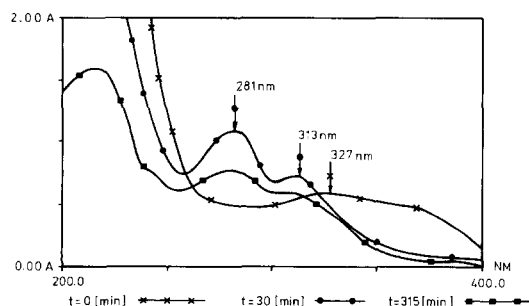


Fig. 2. Curves of photodegradation of 2-NO_2 -NR.

Table 3

Kinetic parameters of photochemical decomposition (UV light) of 1,4-dihydropyridine derivatives (NR)

NR derivatives	Kinetic parameters of photochemical decomposition		
	Rate constant k (s^{-1})	$t_{0.5}$ (h)	$t_{0.1}$ (h)
3 NO_2 -NR			
C	$k = 1.6 \times 10^{-5}$	12.1	1.8
I	$k = 2.9 \times 10^{-6}$	67.3	10.2
2 CF_3 -NR			
C	$k = 4.3 \times 10^{-7}$	450.8	68.6
I	$k = 9.3 \times 10^{-7}$	207.4	31.5
4 Cl-NR			
C	$k = 2.7 \times 10^{-7}$	713.0	108.4
I	$k = 4.8 \times 10^{-6}$	39.8	6.1
4 F-NR			
C	$k = 2.1 \times 10^{-7}$	913.6	138.8
I	$k = 9.3 \times 10^{-7}$	207.6	31.6
3 CN-NR			
C	$k = 4.3 \times 10^{-7}$	447.7	68.1
I	$k = 8.4 \times 10^{-6}$	22.9	3.5
2NO_2 -NR			
C	$k_1 = 2.2 \times 10^{-4}$ $k_2 = 6.3 \times 10^{-5}$	0.9 3.0	0.1 0.5
I	$k_1 = 3.4 \times 10^{-5}$ $k_2 = 1.6 \times 10^{-7}$	5.7 1210.7	0.9 184.1

C, crystalline compound; I, inclusion complex with β -cyclodextrin.

spectra of the irradiated compound are due to formation of pyridine nitrosoderivative in the degradation products [16].

Under the same irradiation conditions, the meta-isomer appeared to be more stable. In this case the appearance of new absorption maximum was observed only after 120 min of the exposition to light. Moreover, among the degradation products no compound revealing the absorption maximum at 313 nm was reported to occur.

Under similar conditions halogenoderivatives were subjected to the process of photochemical degradation. It was found that irradiation of these compounds did not result in any qualitative changes in the profile of the spectrum. Only a slight decrease in the intensity of absorption band at ~ 260 nm was observed.

Summing up the studies of photochemical stability of the analyzed compounds, evaluated by using the spectrophotometric method, it can be concluded that the rate of their degradation is diversified, it depends on the kind and position of a substituent in phenyl ring. The obtained results suggest that particularly photoliable are DHP derivatives containing a nitrogroup in the ortho- position of the phenyl ring. The isomer with a nitrogroup at the meta position was significantly more photostable.

Photodegradation of NR obeyed the first order kinetic equation. Except for the 2NO₂-NR, all other analyzed products revealed a linear dependence of concentration on the degradation time. It was found that photodegradation of 2NO₂-NR is a two stage process. The first stage, covering the irradiation time up to 160 min. involves reduction of the -NO₂ group to -N=O group and formation of pyridine nitrosylderivative in the photodegradation products. Such a mechanism of photodegradation was also anticipated on the basis of the changes observed during the irradiation of 2NO₂-NR, which is illustrated in Fig. 1. The second stage of the reaction, for which the value of $k_2 = 6.33 \times 10^{-5}$ (s⁻¹), entails a further conversion of the formed nitrosylderivative into other products of photodegradation. It is very likely that as a result of the irradiation, a further reduction of the -N=O group into hydroxylamine group may take place. The above conclusions agree with the results of studies carried out by Nunez-Vergara et al. who investigated the products of photochemical degradation of furnidipine using polarographic method [4].

It follows from the comparison of the values of constants of the photodegradation rates for 2NO₂-NR and 3NO₂-NR (Table 3), that the rate of meta-isomer degradation was 10 times lower than that of ortho-isomer.

The lowest rate of photodegradation was observed for halogenoderivatives, and the obtained low values of constants of the photodegradation rates confirm a low sensitivity of these compounds to light; e.g. the photodegradation of

halogenoanalogues was 50 times slower in comparison with 3NO₂-NR.

The photochemical studies also indicated that the presence of β -CD affects the rate of photodegradation of DHP derivatives. To confirm this effect, the rate of photochemical degradation of NR bonded in inclusion complexes was measured and then compared with the degradation rate of crystalline compounds. The obtained results showed that complexation of NR with β -CD changes the photochemical sensitivity of these compounds. The largest slow-down of the photodegradation process was observed for NR nitroderivatives which were the most photochemically sensitive. The greatest improvement was observed for inclusion complexes of 2NO₂-NR; in this case a 200-fold increase in the photochemical stability was recorded.

Unlike in the case nitroderivatives, the effect of β -CD on photodegradation of halogenoanalogues of NR was unfavorable; the rate of the photodecomposition of the compounds studied: 4Cl-NR, 4F-NR, 3CN-NR, 2CF₃-NR, was 4 times faster in the presence of β -CD. This might provide evidence for catalytic properties of β -CD in the degradation process of these compounds.

4. Conclusions

Photochemical stability of NR depends on the kind of substituent and its position in the phenyl ring. Replacement of -NO₂ group in an NR molecule by -Cl, -F, -CF₃ and -CN significantly improves photochemical stability of the compounds. The rate of photodegradation of NR is determined by the position of -NO₂ group in the phenyl ring; for the ortho isomer it is ten times higher than for the meta isomer. The rate of photodegradation of 2NO₂-NR in inclusion complex with β -CD is 200 times lower than for this compound in the crystal phase. However, in the case of halogeno- and cyanoderivatives, the presence of β -CD causes a 4-fold increase in the photodegradation rate.

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