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# Covalent Hydration: A Side Reaction for Dihydropyridine-Derived Chemical Delivery Systems. An Example with GABAergic compounds.

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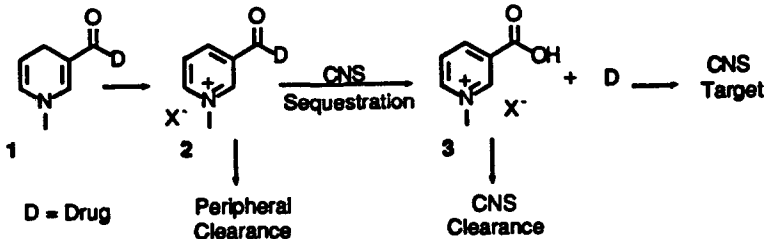
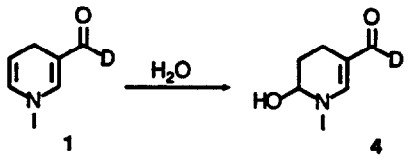
**Abstract:** Covalent hydration of dihydropyridine is a possible side reaction which could disturb the operation of the corresponding Chemical Delivery Systems (CDS). The hydration rate depends as well on the substituent in position 5, which is able to stabilize the double bond, as on the nature of the carried drug. The less stable CDS are those derived from dihydrotrigonelline and the most stable are those where the double bond is either engaged in an aromatic ring or conjugated with an ester or an amide function.

The Chemical Delivery Systems (CDS) introduced by Bodor enables to target drugs to the central nervous system (CNS).[1,2] These systems appeared particularly interesting to carry drugs which alone can not cross the blood brain barrier (BBB).[3,4] The targetor initially used by Bodor was dihydrotrigonelline. The drug (D) coupled with the targetor as an ester or an amide **1** is lipophilic enough to diffuse through out the body including the brain. The carrier is then oxidized giving a pyridinium salt **2**. This salt is locked in the brain whereas it is cleared from the blood. The active drug is finally liberated by hydrolysis and the free oxidized carrier **3** cleared from the CNS by an active transport system[5,6] (Scheme 1).



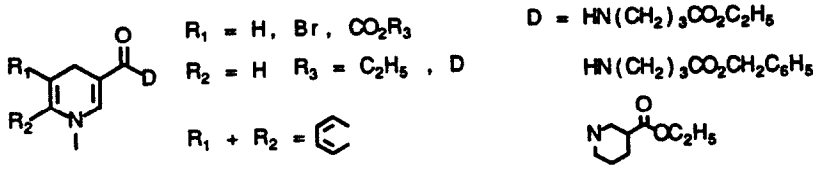

*Scheme 1: Principle of the Chemical Delivery Systems.*

As many nitrogen heterocycles,[7-9] dihydropyridines are known to be unstable in aqueous medium yielding 6-hydroxy derivatives.[10,11] Such a side reaction could disturb the operation of the CDS. Thus, the irreversible hydration of the dihydrotrigonelline carrier[10,12] (Scheme 2) leads to a more hydrophilic derivative **4** which could be eliminated from the blood stream before reaching the brain.




*Scheme 2: Hydration of dihydrotrigonelline CDS*

We report here the substituent effects in position 5 of the heterocycle on the hydration properties of the dihydropyridine carriers. The synthesis of the CDS used for this study were reported previously[13], the structure of the final products is given in scheme 3.




*Scheme 3: Structure of the CDS studied*

The hydration half times were determined at 30°C at pH 7.4 in a buffered solution (phosphate, 0.15M) and also at pH 2.0 to appreciate the stability of the CDS in a gastric medium. In all cases the solutions were degassed to minimize the oxidation of the dihydropyridines into pyridinium salts. The hydration rate was followed by the decrease of the dihydropyridine UV absorbance peak at 360 nm and the concomitant increase of the hydrated form which absorbs at 290 nm. In the case of dihydrotrigonelline derivatives ($R_1$ = H) the diminution of absorbance at 360 nm was not due to the reoxidation of the dihydropyridine as the absorption at 260 nm, characteristic of the pyridinium form, did not increase.

**Results and discussion.**

The hydration half time for the CDS are given in table 1. At the physiological pH the hydration half time stay between a few minutes to more than 20 hours. The classical

dihydrotrigonelline targetor carrying the GABA ester **5** had a $t_{1/2}$ of 9 min, the 5-bromo analogue had a $t_{1/2}$ of 246 min whereas the corresponding derivatives of 3,5-pyridine dicarboxylic acid **7, 8** appeared to be stable under the same conditions. Thus, the order of stability towards covalent hydration parallels this previously observed for redox potential[13]: dihydrotrigonelline derivatives < 5-bromo analogues < 5-carbethoxy analogues or quinoline derivatives. (Compare **9** < **10** < **12** ≤ **13** ≤ **11**; or **5** < **6** < **8** < **7**). For the 3,5-dicarboxylic acid derivatives **7**, **8**, **11**, **12** and for the quinolinic acid derivative **13** the double bond in position 5,6 is stabilized either by conjugation with the ester or the amide function in position 5 or by aromatisation compared to the unsubstituted dihydrotrigonelline 5,6 double bond. The type of junction between the carrier and the carried drug appeared also of some importance as shown by the higher stability of secondary amides compared to tertiary amides (compare **5** and **9**; or **6** and **10**) but this incidence is not as crucial as for the redox potential[13].

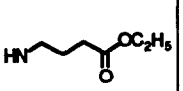
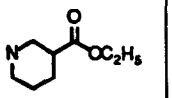
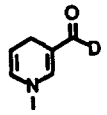
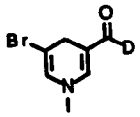
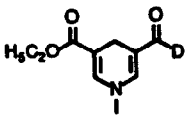
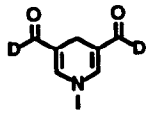
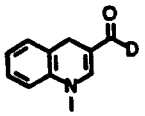
| | Half time (min) and Redox potential (mv) | Nr | D =  | Nr | D =  |
|---|---|---|---|---|---|
|  | $t_{1/2}$ pH = 7.4 | | 9.2 | | 5.0 |
| | $t_{1/2}$ pH = 2.0 | 5[a] | - | 9 | - |
| | Redox Potential | | - 419 | | - 365 |
|  | $t_{1/2}$ pH = 7.4 | | 246 | | 40 |
| | $t_{1/2}$ pH = 2.0 | 6 | - | 10 | 0.33 |
| | Redox Potential | | - 354 | | - 306 |
|  | $t_{1/2}$ pH = 7.4 | | > 300 | | > 300 |
| | $t_{1/2}$ pH = 2.0 | 7 | > 300 | 11 | 60 |
| | Redox Potential | | - 300 | | - 356 |
|  | $t_{1/2}$ pH = 7.4 | | > 300 | | > 300 |
| | $t_{1/2}$ pH = 2.0 | 8 | 75 | 12 | - |
| | Redox Potential | | - 328 | | - 424 |
|  | $t_{1/2}$ pH = 7.4 | | - | | > 300 |
| | $t_{1/2}$ pH = 2.0 | | | 13 | 50 |
| | Redox Potential | | | | - 311 |

*Table 1: Hydration half-time and redox potential for the CDS: (a: $CH_2C_6H_5$ instead of $C_2H_5$)*

The most stable CDS at the physiological pH were also tested at pH 2.0. In this more acidic medium, the hydration half times were shorter than those at the physiological pH. For instance the half life of compound **10** is diminished from 40 minutes at pH 7.4 to 20 seconds at pH 2.0. The most stable CDS at pH 7.4 (**11, 8, 7**) were also more rapidly hydrated at pH 2.0 but they appeared stable enough to be used *per os*. These compounds also possess the most stable redox potentials.[13] As already found for the redox potentials, the dihydrotrigonelline derivatives (**5, 9**) appeared the less stable derivatives toward covalent hydration.

The present results demonstrate that CDS derived from dihydrotrigonelline undergo covalent hydration in a relatively short time span even at the physiological pH. The 6-hydroxy tetrahydropyridines produced in this way may possess a lower central bioavailability, and one has to take this phenomenon into account in the design of chemical delivery systems. A possible modulation of the covalent hydration ability resides in the introduction of adequate substituents on the dihydropyridine ring.

Further work is in progress on these CDS, particularly in order to evaluate the ability of the substituted dihydropyridine to be oxidized, *in vivo*, in pyridinium species. The potentialities of these CDS are also investigated by behavioural experiments. These results will be published latter.

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