Tetrahedron 71 (2015) 6148–6154

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Resonance driven regioselective demethylation of berberine. Microwave assisted synthesis of berberrubine and its assessment as fluorescent chemosensor for alkanes

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ARTICLE INFO

Article history:
Received 25 February 2015
Received in revised form 26 June 2015
Accepted 27 June 2015
Available online 3 July 2015

Keywords:
Berberrubine
Fluorescence
Petrochemistry
Chemosensor
Alkanes

ABSTRACT

Berberrubine has been synthesized by microwave assisted selective demethylation of berberine. The high selectivity observed in this reaction has been explained and justified by means of computational calculations using Density Functional Theory (DFT) and Natural Resonance Theory (NRT). The existence of two resonant structures of berberrubine is the driving force of regioselective demethylation. Berberrubine is a chemosensor of alkanes, and may have practical applications in petrochemical analysis as a 'mass' detector because fluorescent response of saturated hydrocarbons does not depend on hydrocarbon chain length. Berberrubine operates via dipole-induced dipole interactions. Likewise, it has two fluorescent forms in acidic and basic media, which correspond to a keto-enol tautomerism. The fluorescent signal for berberrubine and the amplification of berberrubine-alkane signals by heating can be rationalized from the predominance of enol form when berberrubine is adsorbed onto silica gel.

1. Introduction

In the field of hydrocarbon conversion, it is necessary to combine the use of progressively heavier hydrocarbon-containing feedstocks with the development of sustainable processes that meet environmental standards more and more stringent and restrictive.

Development of economical and environmental friendly techniques for characterizing heavy hydrocarbon-containing feedstocks is crucial for anticipating their behaviour in refining optimization, both in terms of the quality of the obtained final product as with regard to the fine-tuning of the process variables that contribute to its environmental impact. For this, it is necessary to have a detailed knowledge of the composition of chemical families, which constitute these heavy products. Hydrocarbon-containing products consist of an important proportion of saturated hydrocarbons, which have structures of increasing chain length and boiling point. A rapid and accurate determination of these compounds as a group, i.e. Saturates, and other hydrocarbon types in heavy petroleum products has not been fully solved yet.[1]

Despite the interest of this problem and the emergence in the development of systems in the field of fluorescent sensing,[2] little research has been conducted for detecting and quantitatively determining these compounds in such matrices.

In a previous work, berberine cation was proposed as a chemosensor for alkanes, based on non-specific interactions.[3,4] When berberine is in presence of an alkane, and the system is irradiated with appropriate UV light, a fluorescent signal is produced, which depends on the alkane concentration and on the alkane length. Computational results suggested that enhancements in fluorescent signal are consequence of the interaction between the cationic fluorophore and the alkanes (or the hydrocarbon chain in other

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http://dx.doi.org/10.1016/j.tet.2015.06.098
0040-4020/

low-polarity analytes), which isolates the fluorophore in an apolar microenvironment. This protects it from polar nonradiative decays.

A model was proposed[3,5] for this ion-induced dipole interaction, which accounted for experimental results. As the intensity enhancement will also be proportional to the interaction energy, we have, for an ionic probe P and analyte *i* (alkane)

$$U_{P,i} = -1/\left(4\pi\varepsilon_0^2\right)\left(Z_P^2 e^2 \alpha_i\right)/\left(2r^4\right) \quad (1)$$

where r is the average probe-analyte intermolecular distance, Z_P is the charge of the fluorescent probe, ε_0 is the dielectric permittivity of the medium, and α_i is the polarizability of *i*.

At a given temperature and concentration, the enhancement of intensity is linearly dependent of α_i of the neutral molecule surrounding the fluorophore, since the remaining magnitudes must be practically constant on passing from one alkane to another.

The possibility of using dipolar probes (*DP*) for sensing alkanes was also suggested in another work,[4] using the Debye equation for modelling the corresponding dipole-induced dipole interactions.[6] In the case of polarizable analytes with no permanent dipole moments, i.e., alkanes, the equation for the interaction energy becomes:

$$U_{DP,i} = -1/\left(4\pi\varepsilon_0^2\right)\left(\mu_{DP}{}^2 \alpha_i\right)/\left(r^6\right) \quad (2)$$

where α_i is the polarizability of *i* and μ_{DP} is the corresponding permanent dipole moment.

We report in this paper that dipolar probe berberrubine, a berberine-derivative, provides increases in its fluorescence emission in the presence of alkanes, behaving as a quantitative chemosensor for them. In this way, non-absorbing alkanes can be quantitatively detected.

Berberrubine shows different properties than berberine. They are described here, and applied to determine saturated hydrocarbons in petroleum products in a rapid way with low solvent consumption.

Berberrubine has been obtained from berberine by solvent-free, microwave-based synthesis. The origin on the selectivity of this demethylation process has also been analysed by means of computational calculations.

2. Results and discussion

2.1. Berberrubine synthesis

Berberrubine was reported to be obtained by direct microwave irradiation (5 min) in a simple, straightforward way under solvent and catalyst-free conditions, according to Das and Srinivas[7] although working power was not specified in that work. Under the described conditions, we were unable to reproduce their results probably by using a different power. Berberrubine was finally synthesized by direct microwave irradiation under different conditions of temperature, time, and power, which are detailed in Table 1.

Table 1
Catalyst and solvent-free, microwave-assisted synthesis of berberrubine from berberine

Entry	Temperature (°C)	Time (min.)	Power (W)	Conversion (%)	Yield (%)
1	180	20	300	…[a]	…[a]
2	200	15	300	…[a]	…[a]
3	130	5/10/5[b]	300	47	n.m.
4	130/180	5/10[c]	300	100	85.3

n.m.: not measured.
[a] Berberrubine was not obtained.
[b] Reaction carried out in three steps.
[c] Reaction carried out in two steps.

Berberine chloride (100 mg, 0.287 mmol) was introduced in a vial, and vacuum was made. After selecting conditions of maximum temperature, time, and power, reaction was carried out in one step (entry 1 and 2, Table 1), two steps (entry 4, Table 1) or three steps (entry 3, Table 1).

Selected conditions were those of entry 4 (two steps, 100% conversion): i) sample was irradiated 5 min at 300 W up to 130 °C, then allowed to cool to room temperature; and ii) 10 min-irradiation at 300 W to 180 °C. The ketonic form of berberrubine was obtained as a reddish solid (yield: 85.3%).

Characterization of reaction products and monitoring of conversion of berberine into berberrubine were done by ^{1}H NMR spectroscopy (Fig. 1). Furthermore, assignment of the signals were verified by comparison with the NMR spectra simulated at GIAO-B3LYP/6-31+G* level of theory (See Supplementary data for further details).

2.2. DFT study

In order to shed some light on the high selectivity observed in the demethylation of berberine to form berberrubine, we have performed a computational study of this process. Formally, this transformation consists of a S_N2 reaction on a methyl group, in which the nucleophile is the chloride counterion and the leaving group can be berberrubine **2** or, alternatively, thalifendine **3**. Since there are two possible methyl groups capable of reacting with chloride, formation of both demethylated compounds was considered (Fig. 2). Moreover, the non-standard reaction conditions (namely high temperature and low pressure) were also considered in the study.

Our results show that the activation barrier associated with the formation of berberrubine is lower than that of thalifendine (ca. 3 kcal/mol). In both cases, the high activation barriers computed agree well with the harsh experimental reaction conditions required. In addition, the polarity increases going from the reactant to the possible transition structures, thus explaining the suitability of microwave irradiation as heating source[8,9] Besides, berberrubine formation is more exergonic than the formation of thalifendine. Therefore, generation of berberrubine is both kinetically and thermodynamically favoured.

NRT analysis of the final products show that berberrubine has two possible resonance forms, being the neutral structure the most relevant one (>90% of the computed relative weight). On the other

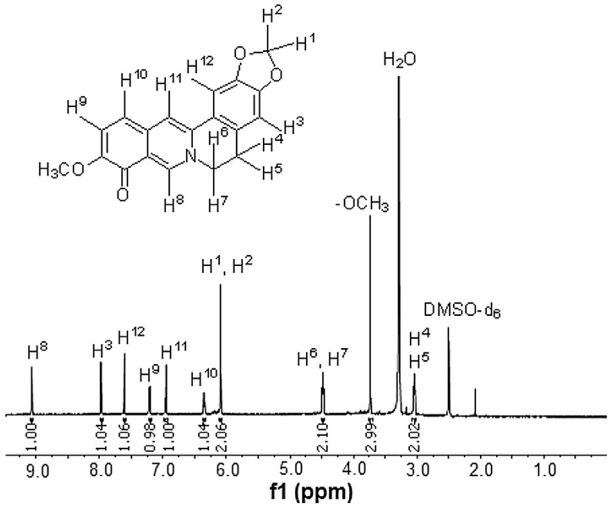

Fig. 1. The ketonic form of berberrubine obtained by microwave irradiation. Signal assigned ^{1}H NMR.