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ScienceDirect
Tetrahedron 63 (2007) 10260–10268
Tetrahedron

Mononuclear rearrangements of heterocycles in water/β-CD: information on the real site of reaction from structural modifications of substrates and from proton concentration dependence of the reactivity

Susanna Guernelli,[a] Paolo Lo Meo,[b] Stefano Morganti,[a] Renato Noto[b,*] and Domenico Spinelli[a,*]

[a]*Dipartimento di Chimica Organica 'A. Mangini', Università di Bologna, Via San Giacomo 11, 40126 Bologna, Italy*
[b]*Dipartimento di Chimica Organica 'E. Paternò', Università di Palermo, Viale delle Scienze, Parco d'Orleans II, pad. 17, 90128 Palermo, Italy*

Received 8 May 2007; revised 10 July 2007; accepted 20 July 2007
Available online 31 July 2007

Abstract—The effect of β-cyclodextrin (β-CD) on the reactivity in the base-catalyzed pathway for the rearrangement in water of some (*Z*)-hydrazones of 3-benzoyl-1,2,4-oxadiazoles (**1b–f**) into the relevant triazoles (**2b–f**) was investigated, finding different behavior as a function of the proton concentration. ESIMS and ^{1}H NMR data evidence the formation of *host–guest* complexes. The whole of the experimental and calculated (MM2) data enabled us to draw some intriguing conclusions concerning the influence of the structures of the substrates and the nature of the formed *host–guest* complexes on the real site of the reaction.

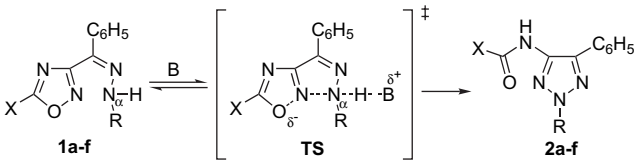
1. Introduction

Cyclodextrins (CDs) represent interesting materials for the study of organic reactions:[1] their ability to form inclusion complexes with several hydrophobic guest molecules[2] makes it possible to use them as artificial enzyme systems.[3]

The effect of CDs on organic reactions can be of two types. CDs and reagents can at first form an intermediate involving a covalent bond, which then leads to the product; or the employed CD can act like a *host* able to solvate the reagents, thus also making possible the occurrence of the reaction in water.[1b,4]

As a matter of fact, the cavity of CDs represents a new reaction environment, which is hydrophobic and significantly different from the hydrophilic bulk solvent (water), hence the reactivity of the substrates examined may change.[3,5] In this case, the role of CD can be defined as a catalyst, because it can 'organize' reagents thus affecting also the entropic contribution to activation energy of the organic reactions.[1,2]

In the framework of a supramolecular study of the behavior of some (*Z*)-hydrazones in the presence of β-CD we investigated the rearrangement of the (*Z*)-phenylhydrazone of 3-benzoyl-5-phenyl-1,2,4-oxadiazole (**1a**)[4] into the relevant triazole **2a** (Scheme 1), examining, for the first time, the course of the mononuclear rearrangement of heterocycles (MRH) in a 'confined environment' and thus observing the formation of *host–guest* inclusion complexes.



Scheme 1.

The use of the β-CD causes the solubilization in water of **1a**: thus the kinetic process can be carried out in aqueous solution, avoiding the use of the operational pS$^+$ scale,[6] necessary in the dioxane/water (D/W) mixture (see Section 4.5).

A further contribution to the understanding of the complexation process is derived from MM2 calculations: reactive or

Keywords: Host–guest interactions; Reaction in β-CD; Azole rearrangement; ESIMS.
* Corresponding authors. Tel.: +39 091 596919; fax: +39 091 596825 (R.N.); tel.: +39 051 2095689; fax: +39 051 2095688 (D.S.); e-mail addresses: rnoto@unipa.it; domenico.spinelli@unibo.it

0040–4020/$ - see front matter © 2007 Published by Elsevier Ltd.
doi:10.1016/j.tet.2007.07.084

non-reactive complexes, which are unable to rearrange into **2a**, are possible; they show different stabilities and can be in equilibrium between one another.

For understanding the course of the reaction, it is essential to estimate the effect of the structure of the *guest* molecules in the formation of the inclusion complexes. In this paper, we present the results of a kinetic study of the MRH, in the presence of β-CD using substrates (**1b–f**) with chosen different structures: as a matter of fact they are variously substituted at both the C(5) of the 1,2,4-oxadiazole ring and/or at the N_α of the hydrazono group (Scheme 1). Such structural changes could influence the stability and the actual number of the possible complexes between (*Z*)-hydrazones **1b–f** and β-CD. The binding properties of the guest molecules (**1b–f**) in the presence of β-CD were also ascertained in gas phase and in solution by ESIMS and ^{1}H NMR spectrometry, respectively.

The overall results obtained support the previous hypothesis about the nature of the β-CD/**1a** interactions[4] and provide new and interesting information about the MRH in confined environment.

2. Results and discussion

Firstly the obtained results (kinetic, UV–vis, MM2, ESIMS as well as ^{1}H NMR data) will be separately examined. Finally the results will be globally discussed.

The kinetic behavior of some (*Z*)-phenylhydrazones (**1b**,**c**) and (*Z*)-hydrazones (**1d–f**) of 3-benzoyl-1,2,4-oxadiazoles, containing at the C(5) of the 1,2,4-oxadiazole ring one hydrogen atom (**1c**), alkyl chains (**1b**,**e**: X=C_6H_{13}; **1d**: X=C_2H_5) or a phenyl ring (**1f**), that is, substituents with different electronic and steric requirements, has been investigated at various pH values and at different temperatures. All the kinetic measurements were performed at [β-CD]=1.0×10^{-4} M and [**1b–f**]=5.0×10^{-5} M in aqueous borate buffer solution ([borate]=1.25×10^{-2}; pseudo-first-order conditions with respect to the base). Under these experimental conditions, β-CD was effectively able to dissolve **1b–f**, otherwise almost insoluble in water.

The data collected for the MRH of the above substrates can be compared with those obtained by the rearrangement of the (*Z*)-phenylhydrazone **1a** in the presence of β-CD[4] or in the dioxane/water mixture (D/W; 1:1, v/v).[6a]

2.1. The rearrangement of the (*Z*)-phenylhydrazone of 3-benzoyl-5-hexyl-1,2,4-oxadiazole (1b)

The conversion of **1b** into **2b** was studied in aqueous solution (borate buffer, at pH 7.76, 8.96, and 9.60) at different temperatures (293–313 K) in the presence of β-CD. A typical set of UV–vis absorption spectra, recorded at different times during the conversion, is shown in Figure 1.

As observed for the MRH of **1a**,[5] two distinct periods can be identified during the course of the reaction. Initially, spectra show a significant bathochromic shift of the absorption maximum (from 368 nm to 405±3 nm at pHs 7.76, 8.96, and 9.60) as well as a fair isosbestic point. The time length of this period progressively decreases on increasing the pH value (at 313 K, from ca. 170 min at pH 7.76 down to ca. 30 min at pH 9.60). During the second phase ('regular period'),[4] λ_{max} remains nearly constant and the absorption decays exponentially as expected for a simple pseudo-first-order process, in line with the triazole optical densities being much lower than those of the starting (*Z*)-hydrazones.

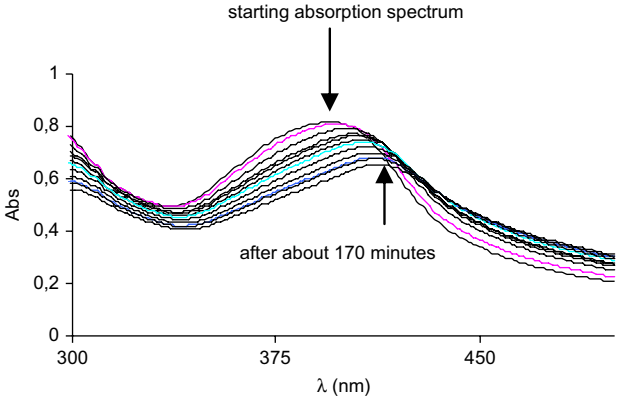


Figure 1. Absorption spectra of **1b** recorded in the first period of the process (at pH 7.76, about 170 min).

Using a suitable non-linear-regression-analysis, we observed that the trend of the absorption versus time plots at given wavelengths (curves registered at 285, 290, and 295 nm, in the region of appearance of the final product **2b**, and at 360, 370, 380, 390, 400, and 410 nm, in the region of disappearance of the starting **1b**) are conveniently fitted by a sum of three exponential functions, and therefore may be rationalized assuming the existence of at least three distinct consecutive processes. The values of the apparent constants k_1 and k_2 for the first two processes (Table 1), which could be calculated only at the lowest pH values, showed only minor variations with pH and at times large uncertainties; in contrast, the apparent rate constants k_3 for the last process reveal a large dependence on pH.

Within the range of the pHs examined, it is known that the reaction is generally base-catalyzed,[6] thus the increase of k_3 values with pH suggests that the calculated k_3 is the one ($k_{A,R}$) that actually measures the rate of the rearrangement. By analogy with the behavior of **1a**,[4] we suppose that k_1 and k_2 are related to some quite rapid complexation equilibria between **1b** and β-CD, which result in the formation of different *host–guest* complexes, some of which are 'non-reactive'. It was not possible to calculate the k_1 and k_2 for the reactions at pH 9.60, probably because the rearrangement becomes so fast as to conceal the occurrence of the complex formation processes.

It is possible to compare these $k_{A,R}$ values with some kinetic data concerning the rearrangement of **1b** in D/W (1:1, v/v). For the reaction in the mixed solvent and at the values of pS^+ 11.35 and 11.80 (corresponding about to pH 8.96 and 9.60 in aqueous solution) apparent rate constants of 9.36×10^{-4} s^{-1} and 2.30×10^{-3} s^{-1}, respectively, were determined. The lower value of $k_{A,R}$, measured in the presence of β-CD (e.g., at pH 9.60 and at 313 K, rate ratio=ca. 31), suggests

Table 1. Calculated rate constants[a] in the 293–313 K temperature range and activation parameters for the rearrangement of **1b** into **2b** in β-CD at different pH

T (K)	pH	10^3 k_1 (s^{-1})	10^4 k_2 (s^{-1})	10^5 k_3[b] (s^{-1})	$\Delta H^{\neq}$[c,d] (kJ mol^{-1})	$\Delta S^{\neq}$[c,e] (J K mol^{-1})
293	9.60	1.10 (±0.50)	2.00 (±0.30)	0.65 (±0.10)	90.9	−33.8
303	9.60	2.10 (±0.12)	2.16 (±0.06)	2.46 (±0.19)		
313	9.60			7.50 (±0.30)		
313	8.96	2.00 (±0.14)	1.69 (±0.11)	3.82 (±0.27)		
313	7.76	1.50 (±0.10)	1.62 (±0.07)	1.97 (±0.20)		

[a] Data are mean values on at least two independent runs. Uncertainty in parenthesis represents the standard deviation of least square treatment.
[b] k_3 represents the apparent rate constants ($k_{A,R}$) for the rearrangement (see text).
[c] Thermodynamic data refer to k_3, measured at pH 9.60.
[d] The maximum error is 4 kJ mol^{-1}.
[e] The maximum error is 8 J K mol^{-1}.

that the reaction always occurs with the base-catalyzed mechanism but now the substrate experiences a more hydrophobic environment, i.e., the cavity of *host* (β-CD). As a consequence, because the reaction goes through a transition state more polar (**TS**, Scheme 1) than the reagents, it is disfavored by a non-polar reaction medium such as the cavity of the β-CD.[4,6]

This finding is consistent with the behavior observed previously for **1a**:[4] in that case, the MRH process in β-CD occurs more slowly than in D/W (rate ratio=ca. 300) and at reaction rates intermediate between those observed in benzene and in D/W. The results agree with the hydrophobic character of the cavity of β-CD that appears intermediate between those of the two solvents and with the stabilization of the substrate by means of its inclusion, due to hydrogen bonding, hydrophobic interactions, and so on. Moreover, in D/W for all of the (*Z*)-hydrazones of 3-benzoyl-1,2,4-oxadiazoles studied we observed a linear increase of the log $k_{A,R}$ versus pS^+ with slopes near to unity (s 0.89–0.93)[6,7] as expected for a base-catalyzed reaction occurring in a water-like medium;[8] on the contrary, in the presence of β-CD the plot of log $k_{A,R}$ versus pH for **1b** shows a slope of 0.31 clearly demonstrating that the rearrangement does not occur in the aqueous medium.

With regard to the red shifts of λ_{max}, the presence of β-CD causes both a chromophore displacement because of a more hydrophobic environment upon host binding[9,10] and the occurrence of specific constraints/interaction effects. Considering that in D/W the absorption maximum of **1b** was at 361 nm, the large shift toward longer wavelengths (from the initial value, 368 nm, to 408 nm) observed during the reaction in the presence of β-CD was likely related to specific interactions of **1b** with the hydrophobic cavity of the *host*, rather than to a simple 'solvent effect'. As a matter of fact, the absorption maximum of **1b** in different mixtures of D/W (from 20:80 to 100:0) remains almost unchanged (361±2 nm) and shifts 'only' to 367 nm in benzene,[11] however, to 408 nm in β-CD.[4,9,10]

A computational (MM2/QD)[12] approach can provide useful insights. Simple models in the gas phase suggest that at least six different *host–guest* complexes might be formed between **1b** and β-CD (Fig. 2, models **A**–**F**), bearing *n*-hexyl (**A**, **B**), the phenylhydrazone moiety (**C**, **D**) or 3-benzoyl group (**E**, **F**) within the cavity. Moreover, the 1,2,4-oxadiazole ring could be either in the correct 'ready-to-close' conformation (**A**, **C**, **E**) with respect to the N_α of the hydrazono group or not (**B**, **D**, **F**). Steric energies for the models of the complexes in the gas phase are also reported in Figure. 2. In all cases, inclusion appears to occur through the side of the secondary rim.[13]

As discussed elsewhere for the corresponding complexes of **1a**,[4] we may reasonably presume that only **A** is the actual precursor of the rearranged **2b**, because in model **C** the N_α of the hydrazono group seems to be too deeply inserted into the host cavity and then it does not seem able to interact effectively with the base. Moreover, dynamic simulations show that **E** quickly collapses into **F**. However, **A** has the highest energy and is separated from **F** and **B** by nearly 16.8 and 12.7 kJ mol^{-1}. Models **C** and **D** are very close in energy, and the dynamic simulations show that they very rapidly interconvert into each other. In contrast, mutual conformational interconversions between **A** and **B** do not seem to occur rapidly. Therefore the overall computational data seem to suggest that **B** and **F** (which are not reactive as such) could be the first formed complexes in solution. They probably afford the truly 'reactive' complex **A** via **D** and **C** according to the scheme in Figure 2.[13]

To gain further information about the influence of the chemical structure of the substrates involved in the MRH, we investigated the behavior of **1c–f**, substrates less substituted in their skeleton: **1c** is the (*Z*)-phenylhydrazone of 3-benzoyl-1,2,4-oxadiazole (i.e., unsubstituted at C(5) of the 1,2,4-oxadiazole ring), while **1d–f** are (*Z*)-hydrazones of 3-benzoyl-5-X-1,2,4-oxadiazoles (X=C_2H_5, C_6H_{13}, C_6H_5; i.e., unsubstituted at the N_α of the hydrazono group: R=H), but with different substituents at C(5). Thus we have examined a set of substrates, which would presumably show different ability to complex with β-CD.

2.2. The rearrangement of the (*Z*)-phenylhydrazone of 3-benzoyl-1,2,4-oxadiazole (1c)

The conversion of **1c** into **2c** in the presence of β-CD was studied in aqueous solution (borate buffer, at pH 7.76, 8.53, 8.99, and 9.60) at 313 K. Interestingly, **1c** showed a kinetic behavior different from that observed for the (*Z*)-phenylhydrazones substituted at C(5) with a phenyl group (**1a**) or with a long alkyl chain (**1b**). Compound **1c** does not show an isosbestic point during the recording of the spectra. After a short initial period (about 100 s or less up to pH 8.99, but not observed at pH 9.60), the UV–vis absorption decays exponentially as expected for a simple pseudo-first-order process, with the absorption maximum wavelength nearly constant during the

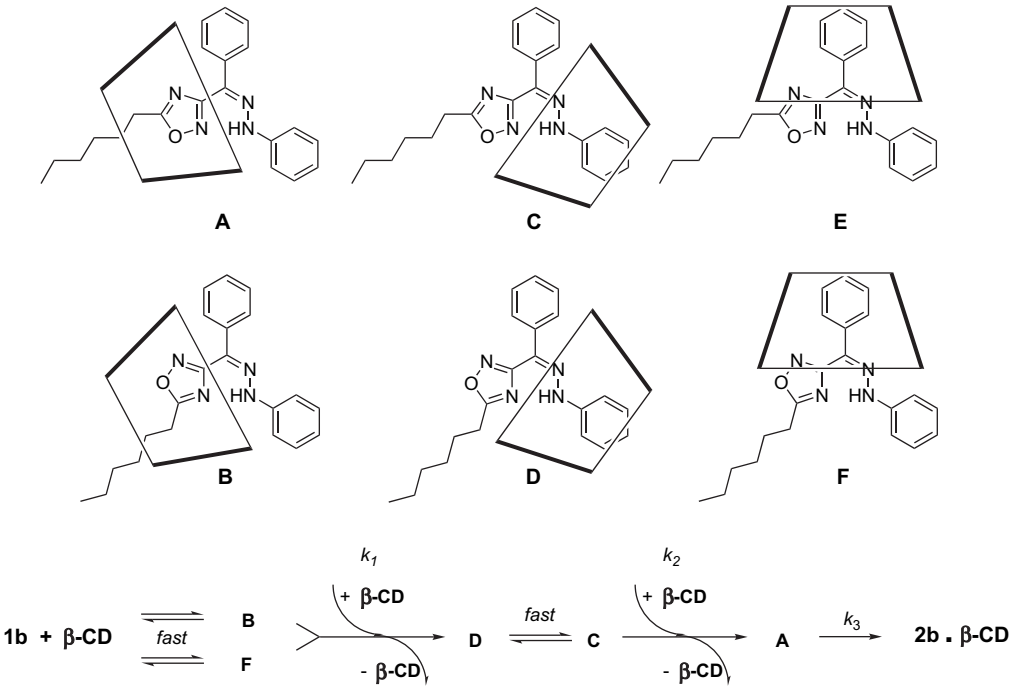


Figure 2. Different *host–guest* complexes between **1b** and β-CD. Steric energies for the complexes: **A**: 247.1 kJ mol^{-1}; **B**: 234.4 kJ mol^{-1}; **C**: 243.9 kJ mol^{-1}; **D**: 244.0 kJ mol^{-1}; **F**: 230.3 kJ mol^{-1}. Model **E** collapses to **F**. Structures are not intended to give a correct picture of the actual minimized structures (or of how deeply the guest moieties are included) and only indicate the host–guest interaction mode.

rearrangement. The $k_{A,R}$s at the four different pHs examined are reported in Table 2.

The plot of log $k_{A,R}$ for **1c** versus pH shows a linear trend (base-catalysis) with a slope much closer to unity (0.88)[7,8] than that for **1b** (0.31), evidencing the occurrence of different situations. Provided that some interaction between the substrate and β-CD cavity is required for the solubilization in water, the observation of a slope value much higher for **1c** than for **1b**, clearly indicates that the reaction site (i.e., the region of the CD where the **TS** is located) for **1c** is in a more 'water-like' environment.

Substrates with different structures may penetrate into the CD cavity to different extents, giving inclusion complexes that are able to affect the reaction pathways. Thus, at pH 9.6 and 313 K, **1c** rearranges much faster than **1a**[4] (reactivity ratio>1750) enforcing the hypothesis that for **1c** and **1a** the rearrangements occur in very different media (water-like and hydrophobic). In contrast, **1c** and **1a** in D/W show quite similar reactivity (reactivity ratio<9).[6b]

Table 2. Apparent rate constants[a] at 313 K for the rearrangement of **1c** into **2c** in β-CD

pH	10^3 $k_{A,R}$ (s^{-1})
7.76	0.603 (±0.012)
8.53	3.66 (±0.080)
8.99	7.50 (±0.50)
9.60	26.0 (±0.10)

[a] Data were obtained as mean values at least on two independent runs. Moreover, for each experiment the $k_{A,R}$ was calculated as mean values at different wavelengths (curves registered at 280, 290, and 300 nm, in the region of appearance of the rearrangement product **2c**, and at 345, 355, 365, and 375 nm, in the region of disappearance of the starting **1c**). Uncertainty in parenthesis represents the standard deviation of least square treatment.

Moreover a comparison between the $k_{A,R}$s in the presence of β-CD and that relative to the rearrangement of **1c** in D/W shows that the reactivity observed in aqueous solution of β-CD is not significantly different from that observed in the mixed solvent. In D/W at 313 K and at pS$^+$ 10.10 or pS$^+$ 11.25 (corresponding to about pH 7.76 or pH 8.99 in aqueous solution, respectively) the $k_{A,R}$s are 7.50×10^{-3} s^{-1} and 1.00×10^{-2} s^{-1}:[6b] the reactivity observed in D/W was only slightly higher (rate ratio=1.3) than that in the presence of β-CD, thus confirming that the rearrangement of **1c** into **2c** proceeds in a 'water-like' environment. Nonetheless, the importance of the medium effect on the MRH reactivity of **1c** can be confirmed by looking at the low kinetic constants, in contrast measured for the same rearrangement (**1c** into **2c**) in benzene.[6c]

MM2 calculations indicate that the lack of a substituent at C(5) of the 1,2,4-oxadiazole ring does not allow, in the case of **1c**, the formation of low-energy inclusion complexes similar to **A** and **B** of Figure 2. Among the remaining models, the complex with a structure similar to **C** is predicted to be the most stable; but it could hardly be the precursor of the rearranged product **2c**, as the reacting hydrazone group appears too deeply buried in the CD cavity. However, the most likely precursor of the product (**E**) is predicted to be only 10.5 kJ mol^{-1} higher in energy; therefore interconversion could now be a fast process.

2.3. The rearrangement of the (*Z*)-hydrazones of some 3-benzoyl-5-X-1,2,4-oxadiazoles (1d–f)

The MRHs of **1d–f** into **2d–f** were carried out in aqueous (borate buffer, at pH 10.20 or 10.60 and in the 313–333 K range) solution of β-CD (Table 3). The kinetic behavior resembles that observed for the **1c** into **2c** rearrangement:

Table 3. Apparent rate constants[a] in the 313–333 K temperature range and activation parameters for the rearrangement of **1d–f** into **2d–f** in β-CD at different pH

Substrates	T (K)	pH	$10^5\ k_{A,R}$ (s^{-1})	$\Delta H^{\neq}$ [b]	$\Delta S^{\neq}$ [b]	$10^6\ k_{A,R}$ [c] (s^{-1})
1d	313	10.20	1.45 (±0.08)	99.4	−20.5	1.00
	323	10.20	4.85 (±0.04)			
	333	10.20	15.20 (±0.50)			
	333	9.96	10.0 (±0.25)			
	333	9.64	5.93 (±0.12)			
	333	9.27	3.50 (±0.20)			
	333	8.92	2.30 (±0.10)			
1e	313	10.60	2.20 (±0.08)	99.3	−16.7	1.57
	323	10.60	8.00 (±0.08)			
	333	10.60	23.00 (±0.40)			
1f	313	10.60	5.22 (±0.02)	96.3	−19.7	3.88
	323	10.60	16.40 (±0.20)			
	333	10.60	51.00 (±0.20)			

[a] Data were obtained as mean values at least on two independent runs. Moreover, for each experiment the $k_{A,R}$ was calculated as mean value at different wavelengths (curves registered at 230, 240, 250, 255, 260, and 265 nm). Uncertainty in parenthesis represents the standard deviation of least square treatment.
[b] $\Delta H^{\neq}$: kJ mol^{-1}, the maximum error is 4 kJ mol^{-1}; $\Delta S^{\neq}$: J $K^{-1}mol^{-1}$, the maximum error is 8 J $K^{-1}mol^{-1}$.
[c] Apparent kinetic constants (at 293 K) calculated by activation parameters.

a 'regular period' attributable to a pseudo-first-order process was observed without shifts of the wavelength of maximum absorption or occurrence of isosbestic points.

A comparison of the $k_{A,R}$s calculated at 293 K from activation parameters for MRH of **1d–f** into **2d–f** with those for the rearrangement in D/W is of some interest. On going from an aqueous solution of β-CD to D/W only a small increase in the reactivity is observed [(for **1d** reactivity ratio is 1.6 at pH 10.20; $k_{A,R}=2.33\times10^{-5}\ s^{-1}$ at pS^+ 12.50 in D/W, data now collected, for **1e** reactivity ratio is again 1.6 at pH 10.60; $k_{A,R}=3.50\times10^{-5}\ s^{-1}$ at pS^+ 12.90, data now collected, for **1f** calculated reactivity ratio is 4.3 at pH 10.60; $k_{A,R}=1.67\times10^{-5}\ s^{-1}$ at pS^+ 12.85 in D/W)].[15] The small kinetic effect observed for the rearrangement of **1d–f** studied in confined environments supports the idea that the formation of the transition state for the rearrangement occurs in a water-like environment rather than in the hydrophobic cavity of the *host*. By contrast, for the rearrangement of **1a** and **1b** in β-CD the calculated rate ratios were ca. 300 and 31, respectively. Moreover, the plot of log $k_{A,R}$ versus pH for the MRH of **1d** into **2d** shows a linear increase versus the pH and the slope value (0.64) is intermediate between those of **1b** and **1c**.

The kinetic data collected at different temperatures show that the $k_{A,R}$s increase with temperature (as for **1b**): then, the analysis of the Arrhenius plot leads to 'normal' positive values for the activation enthalpy (Table 3). By contrast, in the instance of the MRH of **1a** in the presence of β-CD[4] an anomalous behavior was observed (negative value of activation enthalpy), which was explained considering that the calculated activation parameters were composite values, affected by the contribution of complexation, where $\Delta H^{\neq}$ values are usually large and negative.[14]

A comparison among activation parameters for the MRH of **1d–f** evidences that they show almost the same activation enthalpy and entropy in line with the comparable $k_{A,R}$s measured. Similar results were observed studying the behavior of the relevant (*Z*)-phenylhydrazones in D/W.[6]

It is interesting to compare the activation parameters for the MRH of **1f** in β-CD and in D/W[15] ($\Delta H^{\neq}=100$ kJ mol^{-1} and $\Delta S^{\neq}=-7.9$ J $mol^{-1}\ K^{-1}$ in D/W mixture at the comparable proton concentration). Indeed, the rearrangement in the presence of β-CD is accompanied by similar enthalpy factors, but by less favorable entropy factors. Such fact clearly indicates that the parameters for the reaction in β-CD are little affected by some contribution ascribable to a feeble complexation equilibrium. This result is also in line with the observation that in the instance of **1f** there is some difference between the reactivity in D/W and in the presence of β-CD (calculated reactivity ratio=4.3) and at the same time suggests a role to the presence or not of a phenyl linked to the hydrazono nitrogen.

Owing to the lack of a phenyl group on the hydrazono moiety, computations for **1d—f** predict the absence of stable complexes similar to **C** and **D** of Figure 2. This means that, upon complexation, the hydrazone group is never buried into the CD cavity and it can interact more or less freely with the aqueous buffer solvent pool, in agreement with the observed dependence of the $k_{A,R}$s on the pH value.

2.4. ESIMS and ^{1}H NMR evidences for the formation of *host–guest* complexes

In order to find stronger evidence of the formation of *host–guest* complexes between **1b–f** and β-CD, we examined their behavior by means of ESIMS analysis in gas phase and ^{1}H NMR measurements in solution (see Supplementary data). The ESIMS experiments were carried out in water/methanol solution (1:1, v/v), using for β-CD and **1b–f** the same concentrations of the kinetic investigations and recording the spectra in positive mode. They are characterized by intense peaks corresponding to the 1:1 *host–guest* complexes (Figs. 4–8, Supplementary data). Moreover, no signals for 2:1 complexes were observed, even in the presence of a large excess of β-CD.

^{1}H NMR measurements also give evidences for the *host–guest* complexes formation in solution.[9,16] The binding affinity was evaluated by monitoring the chemical shift changes of the protons of the *guest* in the presence of β-CD. The low solubility in water of **1b**,**c** and **1e**,**f** induced us to examine only the ^{1}H NMR behavior of **1d**. The ^{1}H NMR spectrum of a 5.5×10^{-2} M solution of **1d**, containing 12% CD_3OD to ensure the sample dissolution, showed at

298 K shifts of aliphatic protons toward lower frequencies after addition of the β-CD (1.1×10^{-2} M). The detected signals represent averaged peaks relative to the free molecule in rapid equilibrium (compared to the NMR timescale) with its *host–guest* complex. The higher shifts of aliphatic signals ($\Delta\delta$ 0.02–0.07 ppm) in comparison to those of the aromatic ones, suggest that the part of the molecule located inside the hydrophobic cavity is the small alkyl chain (C_2) linked to the C(5) of the heterocyclic ring.

From the collected data some interesting remarks can be drawn.

In the instance of (*Z*)-phenylhydrazone of 3-benzoyl-5-hexyl-1,2,4-oxadiazole **1b** the rearrangement, as for the 5-phenyl derivative **1a**,[4] is largely affected by the presence of β-CD, showing the occurrence of a large shift of λ_{max} and of isosbestic points. Moreover, the $k_{A,R}$s of **1b** in water in the presence of β-CD are lower than in D/W [$(k_{A,R})_{D/W}/(k_{A,R})_{\beta\text{-CD}}$=ca. 31] and the plot of log $k_{A,R}$ versus pH shows a slope much lower than unity (0.31; i.e., it does not occur in water or in a water-like medium).[8] Finally the activation parameters show the normal positive value for the activation enthalpy and the expected negative value for the activation entropy.[6]

By contrast, in the instance of (*Z*)-phenylhydrazone of 3-benzoyl-1,2,4-oxadiazole **1c** and (*Z*)-hydrazones of 3-benzoyl-1,2,4-oxadiazole 5-ethyl, -hexyl and -phenyl substituted **1d–f**, the $k_{A,R}$s are scarcely affected by the presence of β-CD, although the occurrence of inclusion complexes was ascertained both in gas phase and in solution by means ESIMS and ^{1}H NMR data. Thus, for the rearrangement of **1c–f** neither a significant shift of λ_{max} nor the occurrence of isobestic points were evidenced and their $k_{A,R}$s in water in the presence of β-CD are comparable to those in D/W [$(k_{A,R})_{D/W}/(k_{A,R})_{\beta\text{-CD}}$=1.3, 1.6, 1.6, and 4.3]. The slopes of the plots of log $k_{A,R}$ versus pH are linear and for **1c** and **1d** higher (0.88 and 0.64) than that for **1b** (0.31) (Fig. 2). In the case of **1c** the MRH 'occurs' in water or in a water-like medium, while in the case of **1d** a situation intermediate between that of **1b** and **1c** occurs. These results confirm the importance of the substituent at the C(5) of the 1,2,4-oxadiazole ring for the *host–guest* interaction and in determining the real site of the reaction. Accordingly, shortening the linear chain from C_6 (**1b**) to C_2 (**1d**) causes a weakening of these interactions and then an increase of the relevant slopes of the log $k_{A,R}$ versus pH from 0.31 to 0.64. Interestingly enough, in the case of **1c**, where no substituent is present at C(5), the slope of this plot rises up to 0.88 (Fig. 3).

The most striking evidence concerning the influence of the site of reaction on the reactivity comes from a comparison of the reactivity ratios concerning **1a** and **1c** in β-CD and in D/W. In β-CD and at comparable proton concentration **1c** rearranges much faster than **1a** (reactivity ratio>1750), in line with the hypothesis that **1c** and **1a** rearrange in a hydrophilic (water-like) and in a hydrophobic environment, respectively. This is confirmed by the observation that in contrast the same couple of (*Z*)-phenylhydrazones shows in D/W quite similar reactivity (reactivity ratio<9).

The substituent at N_α of the hydrazone moiety (Ph or H) plays a minor role, confirming that the most important

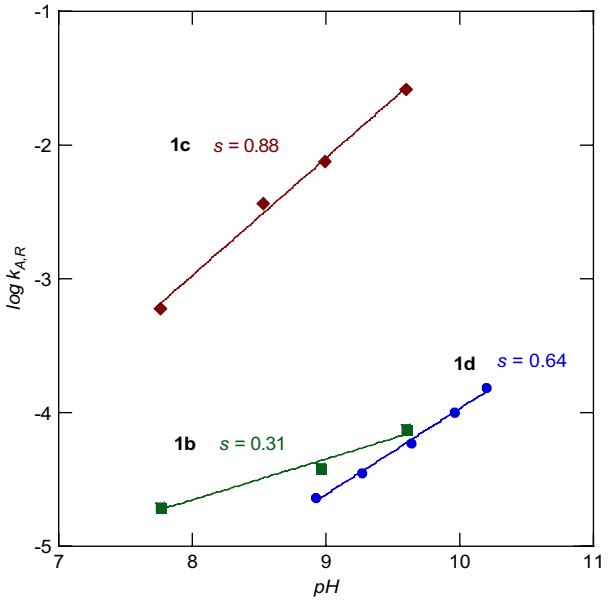


Figure 3. Plot of log $k_{A,R}$ in presence of β-CD for the rearrangement of **1b–d** into the relevant triazoles **2b–d** versus pH. Near each line the value of the slopes is reported.

substrate/β-CD interactions occur at the level of the substituent at C(5) of the 1,2,4-oxadiazole ring as we ascertained by studying the rearrangement of **1a**.[4] Perhaps R could play some role (by interacting with two units of β-CD or, more probably, by determining an increase of the lypophilic character of the substrate, which augments its ability to interact with β-CD), as evidenced by the different behavior of **1a** and **1f**. The above considerations gain support from the MM2 calculations.

As previously pointed out (see also under Section 2.1),[4] we observed an interesting dichotomy in the rearrangement of **1a** in D/W and in water in the presence of β-CD. Indeed **1a** is much more reactive in D/W [$(k_{A,R})_{D/W}/(k_{A,R})_{\beta\text{-CD}}$=300]; moreover, it shows in D/W a positive $\Delta H^{\neq}$, whereas large negative apparent $\Delta H^{\neq}$ is found in the presence of β-CD. In contrast, examining the reactivity of **1c–f** in the presence of β-CD we observed reactivity similar to those measured in D/W [$(k_{A,R})_{D/W}/(k_{A,R})_{\beta\text{-CD}}$: 1.3, 1.6, 1.6, and 4.3]; and the observed reactivity trend seems to be affected by small and unfavorable variations on $\Delta S^{\neq}$ values rather than on $\Delta H^{\neq}$. The decrease of $\Delta S^{\neq}$ accounts for the fact that also in these instances some weak complexation phenomena between β-CD and the substrates **1c–f** could occur.

3. Conclusions

Interestingly, the results indicate that quite different behaviors are at work in the rearrangement of (*Z*)-hydrazones **1a–f**. In the instance of **1a** and **1b** the rearrangement occurs more or less deeply in the β-CD cavity, whereas in the instances of **1c–f** the rearrangement occurs in the border region between β-CD and water pool. Thus, the kinetic and thermodynamic data, and the reactivity plots versus pH for the rearrangement of a set of (*Z*)-hydrazones with well-chosen structure differences indicated that the presence of β-CD always causes their solubilization in water. However, this

phenomenon depends on different kinds of (*Z*)-hydrazone/β-CD interactions that can occur at the external shell (still hydrophilic) of β-CD or, by contrast, at the internal core (quite hydrophobic) of β-CD, differently affecting the interaction of the substrate with the basic catalyst and the formation of the transition state.

4. Experimental

4.1. General synthesis procedure

Compounds (**1c**, **2c**)[6a] and (**1f**, **2f**)[15] were prepared following known procedures.

4.2. Synthesis and characterization of the (*E*)- and (*Z*)-isomer of the phenylhydrazone of 3-benzoyl-5-hexyl-1,2,4-oxadiazole (1b) and of the relevant triazole 1d

The (*E*-**1b**) and (*Z*-**1b**) were synthesized according to known methods.[6a,17] Together with the phenylhydrazones (or the hydrazones) also a certain amount of the rearranged relevant triazoles was obtained. In this paper we have examined only the kinetic behavior of the (*Z*)-isomers. Concerning the general reactivity of the (*E*)-isomers see Ref. 6c.

4.2.1. (*Z*)-Phenylhydrazones of 3-benzoyl-5-hexyl-1,2,4-oxadiazole (*Z*-1b). Yellow oil (yield 53%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.92 (br t, 3H), 1.32–1.54 (m, 6H), 1.90 (m, 2H), 3.02 (t, J=7.5 Hz, 2H), 6.94–7.02 (m, 1H), 7.26–7.35 (m, 4H), 7.35–7.48 (m, 3H), 7.86–7.92 (m, 2H), 11.37 (s, 1H). ^{13}C NMR (300 MHz, $CDCl_3$) δ 13.9, 22.3, 26.2, 26.3, 28.5, 31.1, 113.8, 121.5, 126.2, 127.8, 127.9, 128.2, 129.1, 136.6, 143.8, 163.2, 178.6. ESIMS m/z=347.2 $[M-H]^-$, 371.3 $[M+Na]^+$. Anal. Calcd for $C_{21}H_{24}N_4O$: C, 72.39; H, 6.94; N, 16.08. Found: C, 72.60; H, 7.03; N, 16.15. HRMS calcd for $C_{21}H_{24}N_4O$: 348.1950; found 348.1955.

4.2.2. (*E*)-Phenylhydrazone of 3-benzoyl-5-hexyl-1,2,4-oxadiazole (*E*-1b). Traces as yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.91 (br t, 3H), 1.28–1.50 (m, 6H), 1.87 (m, 2H), 2.96 (t, J=7.7 Hz, 2H), 6.90–6.98 (m, 1H), 7.12–7.64 (m, 9H), 8.10 (s, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.9, 22.3, 26.5, 26.6, 28.7, 31.2, 113.7, 121.5, 128.9, 129.1, 129.6, 129.9, 132.2, 143.0, 168.0, 179.9. ESIMS m/z=347.2 $[M-H]^-$, 371.3 $[M+Na]^+$.

4.2.3. 4-Heptanoylamino-2,5-diphenyl-1,2,3-triazole (2b). Thermal rearrangement of **1b** gave **2b** by heating the sample (0.2 g) in a preheated oil bath (150 °C) for few minutes. By purification on a silica gel column (petroleum ether/ethyl acetate 85:15) the triazole **2b** was obtained in practically quantitative yields. White solid mp 132.2–132.8 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (broad band, 3H), 1.20–1.44 (broad band, 6H), 1.73 (broad band, 2H), 2.45 (t, J=7.5 Hz, 2H), 7.30–7.56 (m, 7H), 7.80 (broad band, 2H), 8.04–8.13 (br d, 2H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.0, 22.4, 25.2, 28.8, 31.4, 36.4, 36.2, 118.4, 126.9, 127.4, 128.6, 129.1, 139.4, 140.1, 142.4, 172.8. ESIMS m/z=347.2 $[M-H]^-$, 371.3 $[M+Na]^+$. Anal. Calcd for $C_{21}H_{24}N_4O$: C, 72.39; H, 6.94; N, 16.08. Found: C, 72.30; H, 7.10; N, 16.16. HRMS calcd for $C_{21}H_{24}N_4O$: 348.1950; found 348.1950.

4.3. Synthesis and characterization of the (*E*)- and (*Z*)-isomer of the 5-ethyl and 5-hexyl-1,2,4-oxadiazol-3-yl-(phenyl)methanone *N*-hydrazones (1d–e) and of the relevant triazoles 2d–e

These compounds were prepared according to methods reported for other Z-hydrazones.[15]

4.3.1. (*Z*)-(5-Ethyl-1,2,4-oxadiazol-3-yl)-(phenyl)methanone *N*-hydrazone (*Z*-1d). White solid mp 64.2–65.4 °C (yield 19%). ^{1}H NMR (200 MHz, DMSO) δ 1.32 (t, J=7.6 Hz, 3H), 3.02 (q, J=7.6 Hz, 2H), 7.21–7.41 (m, 3H), 7.52–7.61 (m, 2H), 8.45 (br s, 2H). ^{13}C NMR (200 MHz, DMSO) δ 10.5, 19.7, 126.7, 126.9, 127.3, 128.0, 137.3, 162.4, 180.2. ESI–MS m/z=238.9 $[M+Na]^+$. Anal. Calcd for $C_{11}H_{12}N_4O$: C, 61.10; H, 5.59; N, 25.91. Found: C, 61.19; H, 5.64; N, 25.86. HRMS calcd for $C_{11}H_{12}N_4O$: 216.1011; found 216.1009.

4.3.2. (*E*)-(5-Ethyl-1,2,4-oxadiazol-3-yl)-(phenyl)methanone *N*-hydrazone (*E*-1d). White solid mp 88.9–90.0 °C (yield 20%). ^{1}H NMR (200 MHz, DMSO) δ 1.28 (t, J=7.5 Hz, 3H), 2.89 (q, J=7.6 Hz, 2H), 7.23–7.59 (m, 7H). ^{13}C NMR (200 MHz, $CDCl_3$) δ 10.6, 20.1, 128.6, 129.2, 129.4, 129.5, 135.3, 167.8, 180.3. ESIMS m/z=238.9 $[M+Na]^+$. Anal. Calcd for $C_{11}H_{12}N_4O$: C, 61.10; H, 5.59; N, 25.91. Found: C, 61.20; H, 5.68; N, 25.83. HRMS calcd for $C_{11}H_{12}N_4O$: 216.1011; found 216.1010.

4.3.3. (*Z*)-(5-Hexyl-1,2,4-oxadiazol-3-yl)-(phenyl)methanone *N*-hydrazone (*Z*-1e). White solid mp 57.0–58.5 °C (yield 39%). ^{1}H NMR (200 MHz, DMSO) δ 0.86 (br t, J=6.4 Hz, 3H), 1.20–1.48 (m, 6H), 1.76 (m, 2H), 3.00 (t, J=7.6 Hz, 2H), 7.22–7.44 (m, 3H), 7.52–7.64 (m, 2H), 8.46 (s, 2H). ^{13}C NMR (200 MHz, DMSO) δ 14.0, 22.0, 25.8, 26.0, 28.1, 30.8, 126.6, 127.0, 127.3, 128.0, 137.3, 162.4, 179.4. ESIMS m/z=295.0 $[M+Na]^+$. Anal. Calcd for $C_{15}H_{20}N_4O$: C, 66.15; H, 7.41; N, 20.57. Found: C, 66.23; H, 7.34; N, 20.46. HRMS calcd for $C_{15}H_{20}N_4O$: 272.1637; found 272.1642.

4.3.4. (*E*)-(5-Hexyl-1,2,4-oxadiazol-3-yl)-(phenyl)methanone *N*-hydrazone (*E*-1e). White solid mp 91.0–93.0 °C (yield 28%). ^{1}H NMR (200 MHz, DMSO) δ 0.86 (br t, J=6.6 Hz, 3H), 1.20–1.47 (m, 6H), 1.72 (m, 2H), 2.87 (t, J=7.5 Hz, 2H), 7.20–7.57 (m, 7H). ^{13}C NMR (200 MHz, DMSO) δ 14.0, 22.0, 25.8, 26.0, 28.1, 30.8, 129.0, 129.2, 130.9, 131.0, 168.3, 179.0. ESIMS m/z=295.0 $[M+Na]^+$. Anal. Calcd for $C_{15}H_{20}N_4O$: C, 66.15; H, 7.41; N, 20.57. Found: C, 66.21; H, 7.46; N, 20.59. HRMS calcd for $C_{15}H_{20}N_4O$: 272.1637; found 272.1639.

The relevant triazoles (**2d**–**e**) were isolated from the reaction mixture and purified by chromatography; the above compounds could also be obtained from **1d**–**e** by thermally induced rearrangement (see before).

4.3.5. 5-Phenyl-4-propanoylamino-2*H*-1,2,3-triazole (2d). Yellow solid mp 145.8–147.5 °C (yield 14%). ^{1}H NMR (200 MHz, DMSO) δ 1.19 (t, J=7.6 Hz, 3H), 2.38 (q, J=7.6 Hz, 2H), 7.35–7.46 (m, 3H), 7.77–7.86 (m, 2H), 9.68 (s, 1H), 12.17 (s, 1H). ^{13}C NMR (200 MHz, $CDCl_3$) δ 10.3, 26.4, 128.1, 128.6, 130.4, 132.2, 145.1, 146.4,

159.1. ESIMS m/z=238.9 $[M+Na]^+$. Anal. Calcd for $C_{11}H_{12}N_4O$: C, 61.10; H, 5.59; N, 25.91. Found: C, 61.15; H, 5.91; N, 25.95. HRMS calcd for $C_{11}H_{12}N_4O$: 216.1011; found 216.1010.

4.3.6. 4-Heptanoylamino-5-phenyl-2*H*-1,2,3-triazole (2e). Yellow solid mp 116.8–118.0 °C (yield 5%). ^{1}H NMR (200 MHz, DMSO) δ 0.87 (br t, J=6.6 Hz, 3H), 1.18–1.40 (m, 6H), 1.58 (m, 2H), 2.33 (t, J=7.1 Hz, 2H), 7.30–7.52 (m, 3H), 7.62–7.78 (m, 2H), 9.84 (br s, 2H). ^{13}C NMR (200 MHz, $CDCl_3$) δ 14.0, 22.4, 26.3, 28.7, 31.4, 33.1, 128.1, 128.6, 130.4, 132.3, 145.3, 146.3, 158.6. ESIMS m/z=294.9 $[M+Na]^+$. Anal. Calcd for $C_{15}H_{20}N_4O$: C, 66.15; H, 7.41; N, 20.57. Found: C, 66.30; H, 7.50; N, 20.61. HRMS calcd for $C_{15}H_{20}N_4O$: 272.1637; found 272.1640.

4.4. Kinetic measurements in water in the presence of β-CD

For the reaction of **1b–f** in the presence of β-CD the solution was prepared by introducing the suitable amount of a mother solution of the substrate in dioxane into a buffered and thermostated solution of β-CD (1.00×10^{-4} M); in the reaction mixture the dioxane concentration was about 1% (v/v) and the concentration of **1** was 5.00×10^{-5} M. Pseudo-first-order conditions were assured by the large excess of borate buffer (1.25×10^{-2} M). The kinetics were followed recording the spectra at due times in the 200–500 nm range and at 293–333 K. All the kinetic measurements were collected with a double-beam spectrophotometer (Varian Cary 1E). The absorbances at various wavelengths were plotted versus time, the curves were processed both by the Guggenheim method[18] and by fitting them directly into the equation $Abs=a+be^{-kt}$ keeping a, b, and t as fitting parameters. The values calculated for the kinetic constant with the two different methods and for the absorbance curves were all in excellent agreement. The KaleidaGraph™ 3.0.1 software delivered by Abelbeck Software was used to perform data processing.

4.5. pS$^+$ and kinetic measurements in water/dioxane

The kinetics in water/dioxane mixture (1:1, v/v) were followed spectrophotometrically as described[6,15,17] by measuring the disappearance of **1b**, **1d**, and **1e** at the wavelengths of their absorption maxima, where the absorption of the relevant triazoles **2** was minimal. An operational pH scale, pS$^+$,[17,19] was established in aqueous dioxane by employing the pK_a values of acids determined by interpolation from the data reported by Harned and Owen.[19b] For dioxane/water (1:1, v/v) the meter reading after calibration against buffers was not significantly different from pS$^+$, requiring a correction of only +0.16.

4.6. MM2 calculations

MM2 calculations were performed by means of the CS Chem3D Pro 5.0 software package (Cambridgesoft Corporation). Models of the guest–CD complexes in the gas phase were elaborated on the basis of the 'quenced dynamics' (QD) method:[12] for each complex, the MD algorithm within the Chem3D software was used to obtain a suitable simulation pool of structures (simulations performed at 300 K for 500 ps), from which starting point models were randomly sampled and allowed to undergo geometry optimization by simulated annealing. In this way only a limited amount of energy minima are found. An energy cutoff of 0.05 kcal mol^{-1} was used for calculations.

4.7. ESIMS measurements

ESIMS spectra were acquired with a ZMD Micromass single quadrupole mass spectrometer operating at m/z 4000. A Hamilton syringe driven by a Harvard pump was used for the injection of the sample into the instrument. To minimize the influence of variations in instrumental conditions on the reliability of spectra, the ESIMS parameters (pressure of gas, desolvation temperature, capillary cone voltages, etc.) were kept rigorously constant from run to run in each series of experiments. In particular a capillary voltage of 3.00 kV and a cone voltage of 30 V were applied; and a desolvation temperature of 423 K was used. The solutions of **1b–f** with β-CD in water/methanol (1:1, v/v) were introduced at a flow-rate of 15 μl min^{-1}. For all of the mass spectra the measurements were averaged over typically 50 scans.

4.8. ^{1}H NMR measurements

^{1}H NMR spectra were recorded on a Varian Inova spectrometer operating at 300 MHz. ^{1}H NMR experiments were performed in mixed solutions of D_2O/CD_3OD using residual HOD as an internal standard (4.76 ppm at 298 K). ^{1}H and ^{13}C NMR spectra of all the synthesized compounds were carried out on a Varian Inova spectrometer operating at 200 MHz (proton) and 50 MHz (carbon) using the solvent peak as internal reference. Chemical shifts are reported in parts per million (δ scale).

Acknowledgements

We thank M.I.U.R. (Rome) [PRIN 2005 (2005034305) and PRIN 2006 (20066034372)] for financial support. Investigations supported by the Universities of Bologna and Palermo (ex-60%, funds for selected research topics).

Supplementary data

ESIMS spectra of the *host–guest* complexes between **1b–f** and β-CD are provided. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2007.07.084.

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