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PAPER

Cucurbituril-resisted acylation of the anti-tuberculosis drug isoniazid *via* a supramolecular strategy†

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A chemical investigation reveals that the resistance to acylation of an anti-tuberculosis drug, isoniazid is a consequent result of the inclusion or exclusion of cucurbit[*n*]urils (*n* = 6 or 7). The ^{1}H NMR spectra analysis shows that the different interaction models of the isoniazid with the two cucurbiturils are dependent on the cavity size of the hosts. Quantum chemistry calculations with density functional theory method indicate that the interaction of the isoniazid with both cucurbiturils is through thermodynamic stabilization in both the gas phase and aqueous solution through hydrogen bonding on the portal carbonyls of the cucurbiturils. Electronic absorption titration spectra suggest the hosts and guest interact in a ratio of 1 : 1 with moderate binding constants. Acylation kinetics of isoniazid with various acylating agents in the presence of the cucurbiturils revealed that resistance is only dependent on the host–isoniazid ratio, and independent on the size of the cucurbiturils and the species of acylating agents.

Introduction

Cucurbit[*n*]urils (Q[*n*], *n* = 5–8 or 10) are a set of macrocyclic compounds synthesized with glycoluril and formaldehyde (Scheme 1).[1] The cavity of Q[*n*] can encapsulate and recognize the amines and azaheterocyclic compounds *via* hydrophobic effects, size effects, as well as ion–dipole interactions at the portals of Q[*n*].[2] The supramolecular characterization of the Q[*n*] hosts provided platforms for the design and functionalization of host–guest complexes involving Q[*n*] components.[3] With a potential application in drug-delivery, the special inclusion complexes of drug molecules have been extended with Q[*n*] as the host to increase chemical stability.[4] Herein, the powerful bactericidal agent against tuberculosis (**TB**), isonicotinic acid hydrazide, commonly known as isoniazid (**INH**, Scheme 1), has been stabilized by supramolecular interactions with Q[6] and Q[7].

INH was first introduced for the effective treatment of **TB** in 1952.[5] It is estimated that about one-third of the world's population is currently infected with **TB** and 2–3 million deaths are caused by this disease every year.[6] **INH** is a front-line antibiotic that has become one of the principal agents used in both therapeutic and prophylactic treatments. The metabolic pathway of this drug involves acetylation of **INH** by arylamine *N*-acetyltransferase (**NAT**), which is a drug-metabolizing enzyme that is able to transfer an acetyl group from acetyl coenzyme A (Scheme 1) onto the terminal nitrogen of the drug.[7] The N-acetylation reaction can directly inactivate **INH** during therapy, and the metabolite is believed to be responsible for the hepatotoxic effects observed.[8] In general, two phenotypes can occur depending on the N-acetylation rate of **INH** in the body, these are referred to as slow and fast acetylators. Fast acetylators have been significantly associated with **INH** resistance.[8,9] It is therefore of great importance to effectively control the N-acetylation of **INH**. In this study, we used a supramolecular strategy to chemically investigate the resistance to acetylation of **INH** encapsulated by Q[6] and Q[7], with the aim of developing these as a potential drug-carrier of **INH**, ensuring its resistance to acetylation.

Experimental section

Materials and instruments

Cucurbit[*n*]urils (*n* = 6 or 7) were prepared and purified according to the methods developed in our laboratory.[10] The chemical agents isoniazid, acetic anhydride (**1**), benzoyl chloride (**2**), benzenesulfonyl chloride (**3**) and *p*-toluenesulfonyl chloride (**4**) were purchased from Alfa Aesar (Tianjing) Chemical Co., Ltd. and used without further purification. The acylating agents *S*,*N*-diacetylcysteine (**5**) and *S*-acetylcysteine (**6**) were synthesised referring to literature.[11]

^{1}H NMR spectra were recorded at 20 °C on a VARIAN INOVA-400 spectrometer in D_2O. UV-vis absorption spectra of the guest

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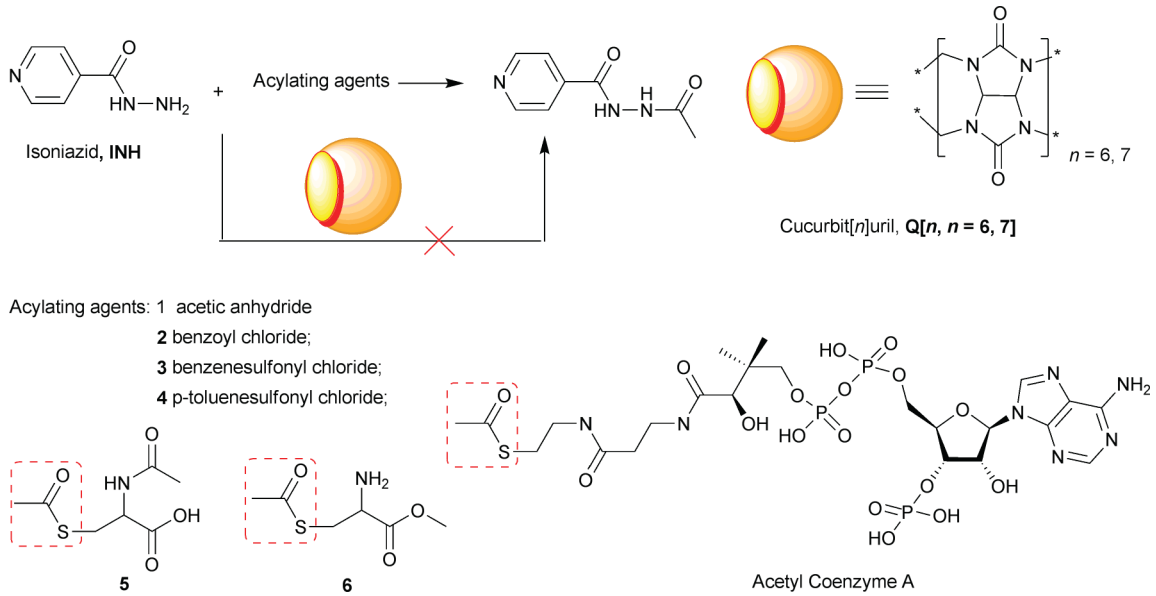


Scheme 1 The acylation reaction pathway of isoniazid (**INH**) and the chemical structures of **INH**, cucurbiturils Q[6] and Q[7], acetyl coenzyme A and acylating agents. The dashed box indicates active thioester groups that are used to convey the acetyl group to **INH**.

and the host–guest complexes were recorded on an Unico UV-2102 instrument at 25 °C at pH = 6.0.

Theoretical calculations

All calculations have been processed with Gaussian 03 W (Revision C.02) software package.[12] The initial geometries of all structures were constructed with the aid of Hyperchem Release 7.52 package.[13] Q[6] and Q[7], and their complexes were constructed based on their ^{1}H NMR and electronic spectra titration analysis. Becke's three-parameter hybrid functional with the correlation functional of Lee, Yang and Parr (B3LYP)[14] was used for full geometry optimization, solvent effect, and BSSE-corrected[15] (Basis Set Superposition Error corrected) binding energy with STO-3G basis set.[16] The Onsager model[17] was used to calculate the solvent effect, as part of this computing package.

Results and discussion

^{1}H NMR analysis of the interaction between Q[6, 7] and INH guest

Comparison of the ^{1}H NMR spectra between free and bound **INH** suggested that the host–guest interaction models of Q[6, 7] and **INH** were largely dependent on the cavity size of the macrocyclic hosts. Based on the pioneering work of Mock and Shih,[18] the upshield shifts of the resonances from guest protons represent insertion of cucurbituril into the cavity, while the downshield shifts of the resonances from guest protons represent the proximity of cucurbituril to the outside of the portal. The ^{1}H NMR titration spectra of **INH** guest recorded in the absence, and in the presence of various equivalents of the hosts Q[6] and Q[7] in aqueous solution are collected in Fig. 1, respectively. As shown in Fig. 1a, the proton resonances of the bound **INH** are observed to undergo downshield shifts in the presence of Q[6]. The resonance of the proton H1 experiences a downfield shift of 0.27 ppm, while the resonance of the proton H2 experiences a downfield shift of 0.20 ppm when the ratio of $C_{Q[6]}/C_{INH}$ reaches 1 : 1. The above changes in chemical shift correspond to the interaction model that the **INH** molecule is prevented from entering into the cavity and remains at the portal of Q[6]. With the addition of Q[7], however, the aromatic resonances are now shifted between 0.38 and 0.45 ppm upfield when the **INH** : Q[7] ratio is 1 : 2. The observed upfield shift resonances for protons H1 and H2 correspond to a different host–guest interaction model with Q[7]–binding **INH**, and the pyridyl moiety of the guest is located in the cavity of Q[7]. On the other hand, the interactions between **INH** and Q[6, 7] lead to broadened resonance signals of the guest to different degrees, which are related to the formation of loose encapsulations. The broadness of the resonances indicates a relatively fast exchange on the NMR time scale.

Absorption spectrophotometric analysis of the interaction between Q[6, 7] and INH guest

UV-visible spectroscopy was employed to monitor the interaction between **INH** and Q[6, 7]. With the electronic absorption spectra of **INH** exhibiting a slight blue-shift in the presence of Q[6], the increase in the peak at 262 nm and the increase in the concentration of Q[6] fits to a 1 : 1 binding model with a moderate binding constant of $(2.3 \pm 0.4) \times 10^5$ L mol^{-1} (Fig. 2a). The stoichiometry of this host–guest interaction is affirmed by Job plots (Fig. S2, ESI†). The UV-visible spectra changes of **INH** with increasing amounts of Q[7] are similar to the Q[6]–**INH** supramolecular system, and the 1 : 1 inclusion complex of **INH** and Q[7] is formed with an binding constant of $(1.7 \pm 0.6) \times 10^5$ L mol^{-1}, as shown by the molar ratio plots (Fig. 2b) and Job plots. The binding constants of Q[6, 7] with **INH** indicate that there is no obvious difference in the interaction stability of the two host–guest species despite their different interaction models, related to the size of the macrocyclic host, as indicated by ^{1}H NMR.

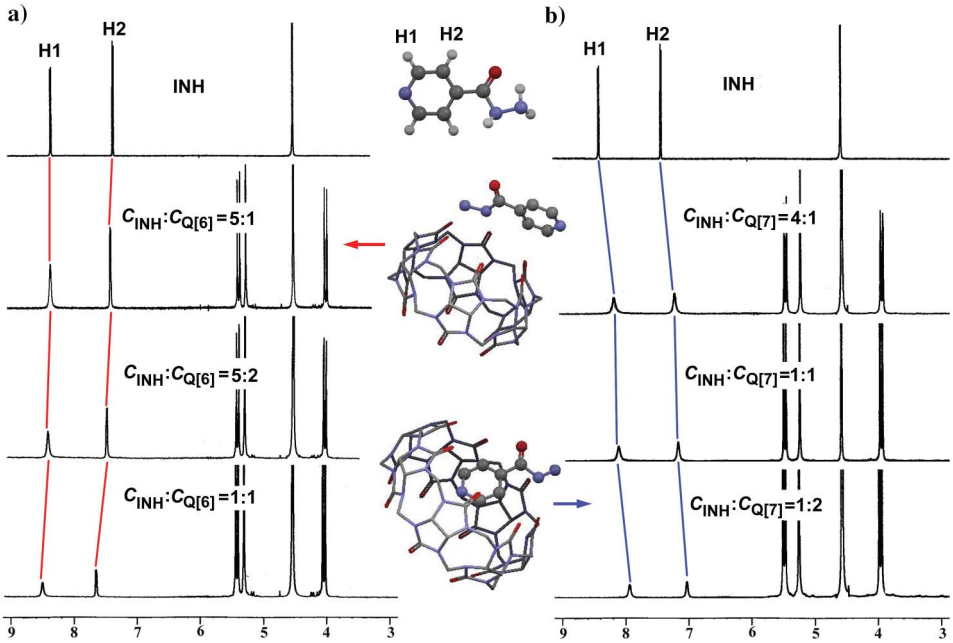
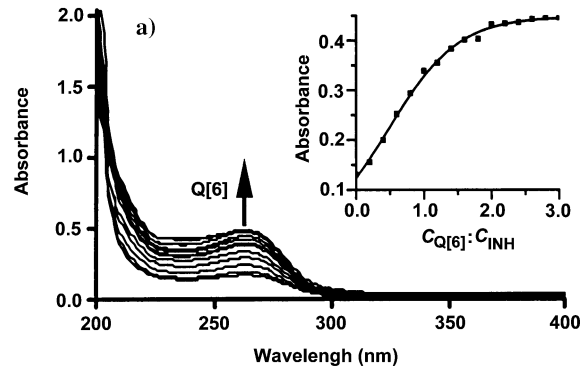


Fig. 1 Variation in the ^{1}H NMR spectra of (a) Q[6]–**INH** system and (b) Q[7]–**INH** system with increasing concentration of hosts.



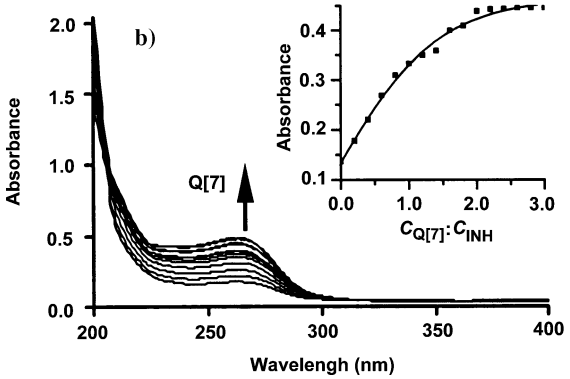


Fig. 2 UV-visible spectra with a fixed concentration (2.5×10^{-5} mol L^{-1}) of **INH** and a variable concentration (from 0 to 7.5×10^{-5} mol L^{-1} along the arrow direction) of (a) Q[6] and (b) Q[7].

Acidity effect on interaction of Q[6, 7] with INH guest

Generally, **INH** as a sort of weak basic drug can be absorbed in the intestine where the pH value is kept in neutrality (pH = 6–8), and the pH of a solution can influence on the interaction in a host–guest system.[16] In Fig. 3, the curves **A**, **B** and **C** show the absorbance *vs.* pH for **INH** and its host–guest complexes with Q[6] and Q[7] at a ratio of 1 : 1, respectively. The plots exhibit a significant absorbance difference between the guest and its interaction complex with Q[7] in both acidic ($2 < pH < 3$) and neutral aqueous solution ($5 < pH < 9$), but the different absorption between **INH** and Q[6]–**INH** arises only at neutrality. The curves become slightly different in the pH range from 4 to 5, while the curves **B** and **C** incline to be above curve **A** (pH > 9), which indicates that we can not use UV-visible spectroscopy to study the interaction of Q[6, 7]–**INH** systems at these pH ranges.

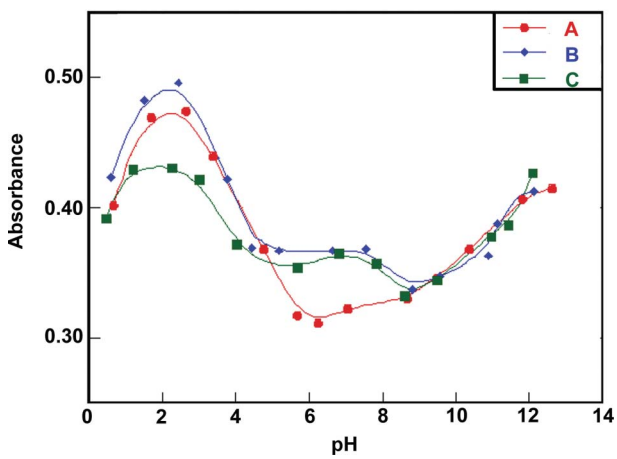


Fig. 3 Maximum absorbance (λ_{max} = 262 nm) change at different pH of **INH** (curve **A**) and its interaction complexes with Q[6] (curve **B**) and Q[7] (curve **C**).

To take into account protonation of the guest and evaluation of the binding constant (and binding geometry) changes, the same ^{1}H NMR titrations and UV-vis titration of Q[6]–**INH** and Q[7]–**INH**

systems at pH = 2 have also been performed (Fig. S2–S4 in ESI†). The titration experiments of the Q[7]–**INH** system shows that the interaction model of Q[7] with **INH** is still an encapsulation model, and a higher binding constant of 1.0×10^6 L mol^{-1} is obtained with the competition of **INH** with glutamic acid (Glu), which can be encapsulated in the cavity of Q[7] with a binding constant of 10^2 L mol^{-1}.[19] However, the titration experiments of the Q[6]–**INH** system show that almost no chemical shift and absorption band changes of **INH** are observed, and it suggests that no obvious interaction occurs between Q[6] and the guest **INH** under more acidic conditions. Moreover, the absorption band of the guest **INH** exhibits a progressively lower absorbance as the ratio of Q[7] : **INH** is increased at pH = 2.0, consistent with the results shown in the Fig. 3.

The host–guest interaction could lead to a change of pK_a value of guest,[20] and the drug guest has three sites which can be protonated, the nitrogen on the pyridine moiety, the hydrazine –NH group and the hydrazine –NH_2 group[21] One can see from the Fig. 3 that ΔpK_a values of about –0.3 units for hydrazine –NH group, and 0.6 units for hydrazine –NH_2 group are found in the presence of Q[6, 7], respectively. At pH ≈ 6.0, **INH** is considered protonated at the hydrazine –NH_2 group.

Molecular geometry simulation of Q[6, 7] and their interaction complexes

Generally, cucurbit[*n*]urils form stable inclusion complexes with guests through a combination of dipole–ion, hydrogen bonding, hydrophobic interactions, and size effect of cavity. To understand what the static structures of the interaction of ionogenic **INH** with Q[6, 7] look like and their thermodynamic stability, quantum chemistry calculations were performed and the simulated supramolecular structures (Fig. 4) are consistent with the above experimental results of ^{1}H NMR analysis, spectrometric titrations and deterministic searching (potential energy curves shown in Fig S5, ESI†). It is seen that the interaction models of **INH** with Q[6, 7] depend on the size of host's cavity strongly as the experimental and calculated results unambiguously demonstrate different binding for Q[6] and Q[7]. Thus the pyridyl moiety of the **INH** guest lies outside Q[6] when they interact with each other but it is included inside the bigger cavity of Q[7]. Therefore, a portal interaction involving hydrogen bonding could be the reason leading to stable formation of the two host–guest inclusion complexes. Principally, the protons of the hydrazide on the guest offer an opportunity to form hydrogen bonds with the carbonyl oxygen on one portal of the hosts. The optimized structure of the complex of Q[6]–**INH** has four hydrogen bonds, N1–H···$O_{carbonyl}$ (1.41 and 1.42 Å), N2–H…$O_{carbonyl}$ (1.47 Å) and $C_{Pyridyl}$–H…$O_{carbonyl}$ (1.79 Å), respectively, while only two hydrogen bonds of 1.41 Å (N1–H…$O_{carbonyl}$) and 1.32 Å (N2–H…$O_{carbonyl}$), respectively, are found for the complex of Q[7]–**INH**. Consequently, the multi-site interactions account for the extra stability in the 'excluded' supramolecule of the Q[6]–**INH** system.

On the other hand, the negative differences of the energy minima between the free host, free guest, and the host–guest inclusion complex (stabilization energy, $\Delta E < 0$) reveal that the hosts Q[6, 7] favor inclusion of the guest *via* supramolecular interactions in either gas phase or aqueous solution. The BSSE-corrected binding energies are –277.1 kJ mol^{-1} for the encapsulation of **INH** with Q[6] host and –236.4 kJ mol^{-1} for the encapsulation of **INH** with Q[7] host in gas phase, and in liquid phase they are –362.6 and –316.9 kJ mol^{-1}, respectively. Accordingly, the approximate stabilization energies indicate that the different interaction models of exclusion for the Q[6]–**INH** system and inclusion for the Q[7]–**INH** are thermodynamically stable in either the gas and liquid phrase.

Acylation kinetics of INH and its interaction with Q[6, 7]

Based on the investigation of host–guest interactions described above, the acylation kinetics of **INH** with some classic acylating agents **1–4** (Scheme 1) in the presence and absence of macrocyclic compounds were used to estimate the acylation resistance of **INH** with supramolecular formation at a ratio Q[6, 7] : **INH** of 0.8 : 1 and 1 : 1. A fixed concentration of **INH** and acylation agents (2.5×10^{-5} mol L^{-1}, respectively) and a reaction temperature of 40 °C were adopted from the kinetic data (Table S1, ESI†). As expected, the host–guest interaction hindered the acylation of **INH**. The stoichiometric addition of Q[6] or Q[7] made **INH** almost unavailable for acylation, whereas the presence of host in a 0.8 : 1 ratio to **INH** caused the initial rate of the acylation reaction to be decreased about 10–100 times and the **INH** resistance was found to be independent of the nature of the acylating agents. The cavity size of the cucurbiturils and the relevant observed initial rates (denoted by pk_{obs}, see ESI†) are collected in Fig. 5.

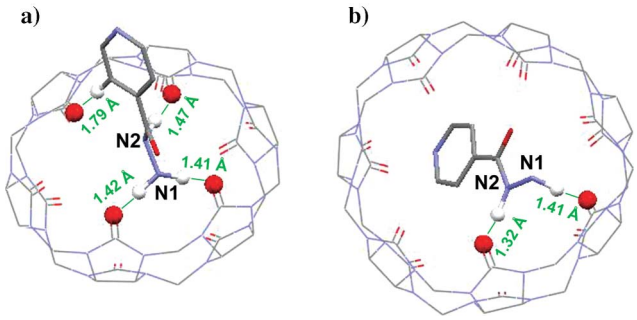


Fig. 4 Energy minimized structures of **INH** and host–guest complexes of **INH** with Q[6, 7] optimized at the B3LYP/STO-3G level,[10] Color codes: carbon, gray; nitrogen, blue; oxygen, red; white: hydrogen.

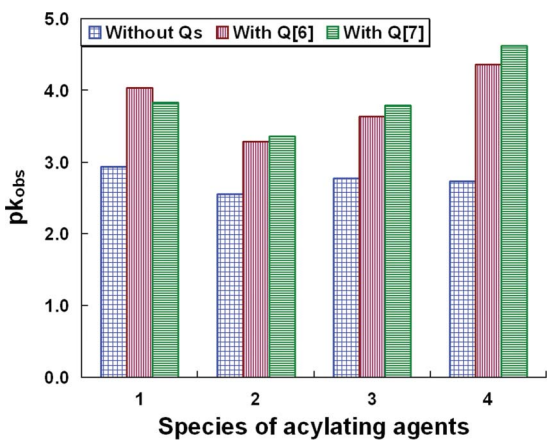
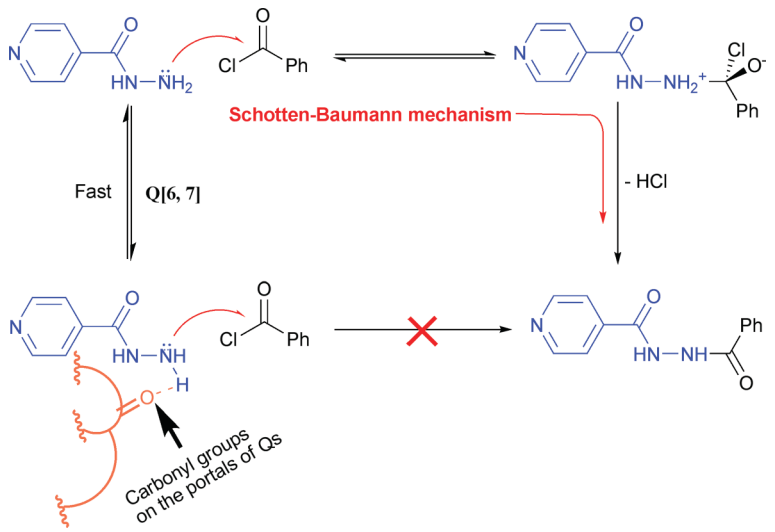


Fig. 5 Initial rates of **INH** with acylating agents **1–4** in the absence and presence of Q[6, 7].



Scheme 2 Possible mechanism of supramolecular prevention of **INH** from acylation reaction with cucurbiturils (taking benzyl chloride as an example).

In the biochemical reaction, **INH** is generally acetylated by acetyl coenzyme A (Scheme 1). Acetyl coenzyme A is a thioester that comprises a cysteine residue as a thiol and an acetyl moiety that is the main active group in acetylation of **INH** and can be transferred to **INH**. Analogues of the active moiety in Acetyl Coenzyme A, compounds **5** and **6** (Scheme 1), which comprise cysteine and acetyl chlorine, were used to investigate the influence of the amount and cavity size of cucurbiturils on the rate of transfer of the acetyl moieties from the thioesters to **INH**. Fig. 6 shows the obvious dependence of **INH** resistance of acetylation on the amount of cucurbiturils at 40 °C, as observed with a fixed concentration of **INH** and thioesters (2.5×10^{-5} mol L^{-1}, respectively). The initial reaction rates are sharply decreased by increasing the amount of Q[6] or Q[7], and are decreased by a factor of 10^{-2} in the presence of 0.8 equivalent of supramolecular hosts. The controllable acetylation resistance of **INH** is unrelated to the models of host–guest interactions, the cavity size of macrocyclic compounds and the thioester species. The addition of Q[6] or Q[7] in 1 : stoichiometry causes the **INH** acetylation to be so slowed that no obvious kinetic behavior can be observed in the experimental time of about 300 min. The kinetic evidence suggests that only free **INH** can be attacked by acetylating agents and the formation of loose encapsulation of **INH** with Q[6] or Q[7] is unfavorable for the acetylation reaction, and the so the effectiveness of resistance depends on the ratio of Q[6, 7] to **INH**.

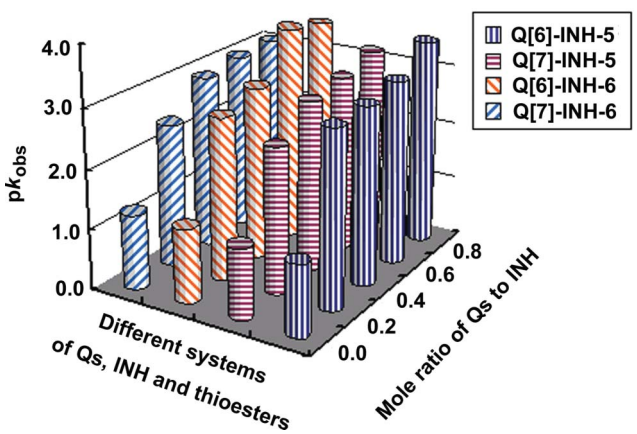


Fig. 6 Relationship between the acetylation rates of **INH**, the amount of Q[6, 7] and thioester species at 40 °C.

Supramolecular protection mechanism of INH with Q[6, 7]

According to the above experimental evidences and results of calculation chemistry, a possible mechanism of supramolecular resistance of **INH** to acylation reaction in the presence of Q[6, 7] has been established. In general the acylation reaction of the amino group shows the Schotten–Baumann mechanism,[22] which involves a two-step pathway of nucleophilic addition, then elimination (Scheme 2). In the first step, the lone-pair electron of the hydrazide group attacks the carbonyl group of acylating agents, and then, in the second step, the activity of the hydrazine group is crucial in the elimination reaction. The increased pK_a values of the Q[6, 7]-bound **INH** predicate the protons on the hydrazine can be stabilized and the reactivity of hydrazine is decreased, that is, the binding **INH** by cucurbiturils and the formation of hydrogen bonding between the amino protons and portal carbonyls of the Q[6, 7] could protect the amino proton from the elimination reaction.

Conclusion

In summary, we propose that the resistance of **INH** to acylation is due to the host–guest interaction with cucurbit[6, 7]urils. The amount of host available is crucial to the prevention of **INH** acylation, whereas the site of guest **INH** moieties relative to the cucurbit[6, 7]urils, and the size of the host, had little effect. The chemical results provide evidence that cucurbiturils can be used as potential drug-carriers of **INH**, and that by altering the amount of cucurbiturils added, the acylation rate of **INH** can be modified. This will potentially enable the acylation rate to be slowed down in fast acetylators. These findings may have important implications for a patient's response to anti-TB therapy.

Acknowledgements

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