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Synthesis, spectroscopic characterization and chemical reactions of stable *o*-QM on solid phase

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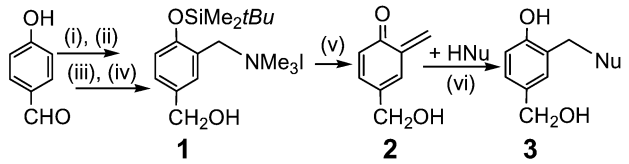
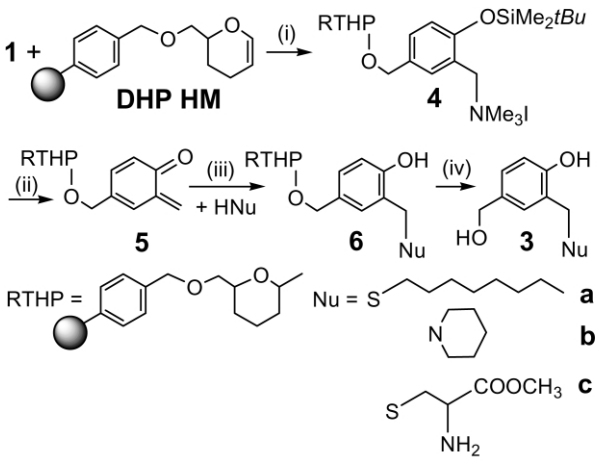
A novel approach towards quinone methides stabilization has been achieved by anchoring the reactive *o*-QM intermediate on solid phase (RTHP). The reactivity and selectivity of supported *o*-QM towards N and S centered nucleophiles have been explored.

Quinone methides (QMs) are highly reactive intermediates, which may act either as electrophiles[1] or electron poor heterodienes.[2] In fact, QMs have been widely used in organic synthesis, in particular for carrying out 'reverse electron demand' Diels–Alder cycloadditions to give chroman derivatives.[3] It has been suggested that QM-like structures play a key role as intermediates in several biological processes, including enzyme inhibition[4] and DNA cross-linking.[5] Recently, a transient QM-like structure has been proposed as covalent trapping device applied to the development of combinatorial antibody library,[6] and supported *p*-QM have been generated from pH cleavable linkers.[7] Despite this wide interest, examples of stable simple QMs, *i.e.* those bearing no substituents on the exocyclic double bond or at the *ortho* positions to the oxygen atom, are scarce. In fact, the parent compound, *o*-QM has been detected only as intermediate in solution[8,9] or stabilized in the form of a metal π-complex.[10] Recently it has been reported that *o*-QMs are effective alkylating agents for amino acids, peptides[9] and nucleobases in water.[11] This is a highly appealing application, but of limited scope, since with less reactive substrates, such as poor nucleophiles and non-electron rich alkenes, hydration[9] and polymerization processes[12] are competitive. Therefore, we explored a new approach to the stabilization of *unsubstituted o-QM, viz. supporting o-QM on solid phase* (SP) in order to inhibit bimolecular self-addition. For the same reason, the structurally related *o*-quinodimethane[13] has been supported on SP.[14] In the event, a general and unprecedented synthetic approach to prepare and spectroscopically characterize *stable o-QM supported on SP* was developed. The results of the reactions of resin-bonded *o*-QM towards nucleophiles, through the characterization of the resulting alkylation adducts (both grafted on the resin and after cleavage), offered alternative support for its formation and reactivity. Trapping reactions through Michael addition were performed with both N and S centered nucleophiles. The suitability of the ammonium salt **1** as *o*-QM precursor was positively tested in CH_2Cl_2 solution, where a completely selective formation of 5-hydroxymethyl-*o*-QM (**2**, Scheme 1) is triggered by fluoride anion. The protocol followed in order to anchor precursor **1** onto SP is straightforward (Scheme 2). Ammonium salt **1** was linked to **DHP HM** resin (loading 0.7–1.2 mmol g^{-1})[15] according to the standard PTSA coupling procedure[16] to afford the resin-bound ammonium salt **4** (Scheme 2). Gel-phase ^{13}C-NMR and FT-IR (Diffuse Reflectance, DR) spectroscopies monitored the successful SP step. In fact, comparison of the ^{13}C-NMR spectra of naked **DHP HM** resin and unsupported *o*-QM precursor (**1**) with that of supported ammonium salt (**4**), clearly showed for the modified resin **4** the presence of signals due to TBDMS methyl groups (δ = −3.88, 18.30 ppm) and of ammonium functional group ($CH_2NMe_3^+$; δ = 25.99, 52.93 ppm).† The modified resin **4** was then exposed to fluorine anion (*n*-Bu_4NF in CH_2Cl_2 at rt) to afford covalently linked *o*-QM to resin (**5**), within few minutes. The presence of supported *o*-QM was inferred after its generation in the absence of water or any trapping agent by monitoring the appearance of a strong carbonyl band at 1718–1707 cm^{-1} by FT-IR (Fig. 1a). To support the assignment, the experimental IR spectra were compared to the computed ones,[17] calculated for the 4-methyl-*o*-QM, at B3LYP/6-311G+(d,p) level of theory, both in gas phase (Fig. 1b) and in benzene solution [at C-PCM-B3LYP/6-311+G(d,p) level of theory]. Computational frequency calculation allowed the evaluation of the effect caused by polystyrene resin bulk on the IR spectra. Actually, the computed vibrational frequencies in gas phase and benzene solution for the carbonyl-stretching mode are 1722 and 1716 cm^{-1}, respectively. They are almost identical to the IR experimental maximum absorption registered for **5** (1718–1707 cm^{-1}). The broadening of the IR absorption band in the experimental spectra (Fig. 1a) is due to the effect of the resin bulk (computationally modeled by benzene as solvent), which slightly lowers the C=O stretching frequency, by increasing the zwitterionic character of *o*-QM. An aliquot of *o*-QM supported on resin (**5**) was kept in a dry box at rt and periodically checked for stability *via* FT-IR. The characteristic strong band did not change significantly upon standing for 24 hours.‡ Despite its stability, *o*-QM on SP (**5**) displays a remarkable reactivity toward N and S centered nucleophiles. In fact, samples of resin **5** suspended in CH_2Cl_2 solutions



Scheme 1 (i) CH_2=$N(Me)_2I$, K_2CO_3 in CH_2Cl_2, 75% yield. (ii) *t*$BuMe_2SiCl$, imidazole in CH_2Cl_2, 0 °C, 82% yield. (iii) $NaBH_4$, MeOH, 0 °C, 85% yield. (iv) MeI in CH_2Cl_2, 0 °C, 85% yield. (v) *n*-Bu_4NF, in CH_2Cl_2, rt. (vi) HNu 50 mM, in CH_2Cl_2, rt.



Scheme 2 (i) PTSA, $ClCH_2CH_2Cl$, rt. (ii) *n*-Bu_4NF, in CH_2Cl_2, rt. (iii) HNu 50 mM, in CH_2Cl_2, rt. (iv) $CF_3COOH:H_2O$ = 95:5.

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containing octane-1-thiol, piperidine and L-cysteine methyl ester, were converted at room temperature, within few minutes, into alkylated adducts grafted to resin (**6a–6c**, respectively). Spectroscopic analysis, after filtration and drying of the resulting resin under vacuum, disclosed the complete depletion of the absorption band centered at 1718–1707 cm^{-1} (see Fig. 1c), as well as the disappearance of the ^{13}C-NMR signals due to the TBDMS and the alkyl ammonium group (typical of resin **4**). New signals pertaining to the nucleophile moiety (alkylated by supported *o*-QM), appeared in parallel.† Assignments were unequivocally determined by comparisons with the ^{13}C-NMR signals of supported ammonium salt (**4**) and *o*-QM-alkylation adducts (**3a–3c**), obtained from nucleophile alkylation processes involving **2** in solution.† The above evidence shows clearly the efficiency of nucleophiles in trapping *o*-QM supported on resin. Standard cleavage[15] of resins **6a–6c**, afforded **3a–3c** alkylation adducts with yields from 66% to 54%. The increased stability of *o*-QM on resin is truly remarkable, since *o*-QM can only survive for a very short period in solution; *i.e.* < 10 ms in water[9] and < 1 s in organic non nucleophilic solvents (in the latter case due to dimerization–polymerization at rt),[12] while supported *o*-QM can be safely stored in a dry and cool place. On the other hand, SP does not preclude the typical reactivity/selectivity of *o*-QM in solution towards nitrogen and sulfur centered nucleophiles. In fact, similarly to free *o*-QM in solution, which is highly selective toward thiols, alkylation of cysteine methyl ester, *o*-QM on SP (**5**) attacks selectively only the SH moiety, since no *N*-alkylation adduct was detected. Our results, although preliminary, represent the first report of *persistent o-QM on solid phase*. THP-HM resin succeeds in stabilizing the most reactive *o*-QM among all known QMs and preserving it from dimerization–polymerization and hydration processes. It is quite evident that undesired intra-site reactions do not plague our solid phase synthesis. Although site–site isolation does not *per se* guarantee stabilization, since cross reactivity of highly reactive species on SP has been reported,[18] lack of proximity should play an important role. The effective stabilization of *o*-QM on SP is also the result of the protection from hydration, plausibly through π-stacking interactions, in the hydrophobic environment of the resin bulk. Due to the *o*-QM reactivity and selectivity towards amino acids and peptides, and to the photoreversibility of the alkylation process,[9] supported *o*-QM could work as a photo-removable linker of peptides, which can be mildly generated and stored. Therefore our approach appears promising and general for the preparation of further unsubstituted stable QMs on solid phase, with applications both to organic synthesis, and as anchored trapping agents of biological nucleophiles.

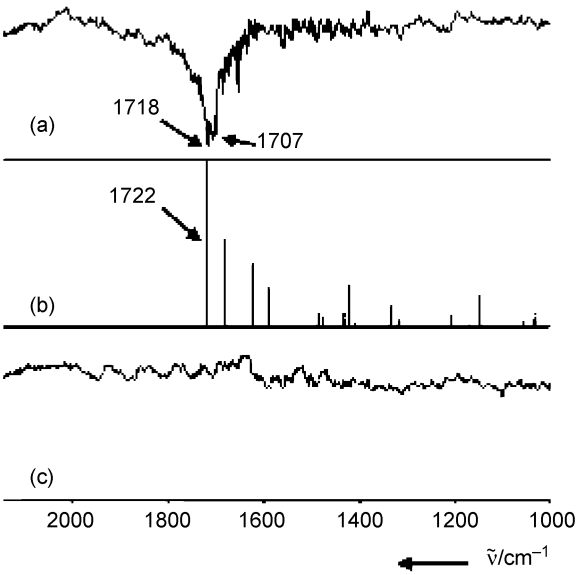

Fig. 1 IR detection of the *o*-QM supported on solid phase (SP). a) Difference IR spectrum of functionalized resins **5** and **4**. b) Calculated B3LYP/6-311+G(d,p) unscaled frequencies of 4-methyl-*o*-QM in gas phase. c) Difference IR spectrum of functionalized resin **6b** and **4**, showing the bleaching of IR absorption at 1722–1700 cm^{-1}, assigned to *o*-QM supported on SP.

Notes and references

† *Selected analytical data*: **1**: NMR ($CDCl_3$) δ_H 0.23 (s, 6H), 1.00 (s, 9H), 3.31 (s, 9H), 4.70 (s, 2H), 4.74 (s, 2H), 6.91 (d, 1H, J = 9.5 Hz), 7.37 (dd, 1H, J = 1.5, 9.5 Hz), 7.80 (d, 1H, J = 1.5 Hz). δ_C −3.98, 18.25, 25.91, 53.26, 63.13, 64.56, 117.35, 119.03, 134.62, 135.58, 154.39, 153.67. Anal. Calc. for $C_{17}H_{32}INO_2Si$: C, 46.68, H, 7.37, I, 29.01, N, 3.20, O, 7.32, Si, 6.42. Found: C, 46.70, H, 7.39, I, 29.06, N, 3.18, Si, 6.47%. **4**: δ_C −3.88, 18.30, 25.99, 52.93, 64.46, 65.77. Only δ_C of **1** aliphatic moiety on SP are reported. **3a**: NMR ($CDCl_3$) δ_H 0.90 (t, 3H, J = 7.0 Hz), 1.20–1.38 (m, 10H), 1.56 (m, 2H), 2.43 (t, 2H, J = 7.0 Hz), 3.80 (s, 2H), 4.60 (s, 2H), 6.90 (d, 1H, J = 9.0 Hz), 7.09 (s, broad, 1H), 7.21 (d, 1H, J = 9.0 Hz), 7.29 (s, 1H). δ_C 14.00, 22.54, 28.63, 28.89, 29.01, 29.04, 30.87, 31.69, 32.78, 64.87, 117.17, 122.55, 128.05, 129.47, 132.83, 155.07. Anal. Calc. for $C_{16}H_{26}O_2S$: C, 64.04, H, 9.28, O, 11.33 S, 11.35. Found: C, 68.07, H, 9.35, S, 11.31%. **6a**: δ_C 14.11, 22.60, 28.75, 29.10, 29.32, 29.85, 31.08, 31.74, 32.73, 65.77. Only δ_C of **3a** aliphatic moiety on SP are reported. **3b**: NMR ($CDCl_3$) δ_H 1.51 (bm, 2H), 1.64 (m, 4H), 2.52 (bm, 4H), 3.68 (s, 2H), 4.55 (s, 2H), 5.15 (bm, 1H), 6.80 (d, 1H, J = 9.0 Hz), 7.00 (s, 1H), 7.16 (d, 1H, J = 9.0 Hz). δ_C 23.76, 25.60, 53.70, 61.89, 65.00, 115.82, 121.46, 127.38, 127.52, 131.19, 157.63. Anal. Calc. for $C_{13}H_{19}NO_2$: C, 70.56, H, 8.65, N, 6.33, O, 14.46, S. Found: C, 70.58, H, 8.62, N, 6.39%. **6b**: δ_C 23.68, 25.52., 53.57, 61.79, 65.50. Only δ_C of **3b** aliphatic moiety on SP are reported. **3c**: NMR ($CDCl_3$) δ_H 2.90 (m, 2H), 3.78 (s, 3H), 3.83 (m, 1H), 4.50 (s, 2H), 6.80 (d, 1H, J = 9.0 Hz), 7.09 (d, 1H, J = 9.0 Hz), 7.21 (s, 1H). δ_C 32.35, 34.15, 52.65, 64.75, 65.99, 117.33, 125.47, 128.14, 130.65, 135.01, 156.00, 171.50. Anal. Calc. for $C_{12}H_{17}NO_4S$: C, 53.12, H, 6.32, N, 5.16, O, 23.59, S, 11.82. Found: C, 53.22, H, 6.21, N, 5.19, S, 11.81%. **6c**: 27.55, 29.57, 51.97, 62.30, 68.06. Only δ_C of **3c** aliphatic moiety on SP are reported.

‡ The relative intensity of the carbonyl band displayed a detectable decrease after 2 days. *o*-QM on SP kept under moisturised air displayed a detectable weakening of the characteristic band (−10%) after 10 h.

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