Pergamon

Tetrahedron Letters, Vol. 35, No. 52, pp. 9697-9700, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)02127-9

Isoquinolines as Receptors for Resorcinol

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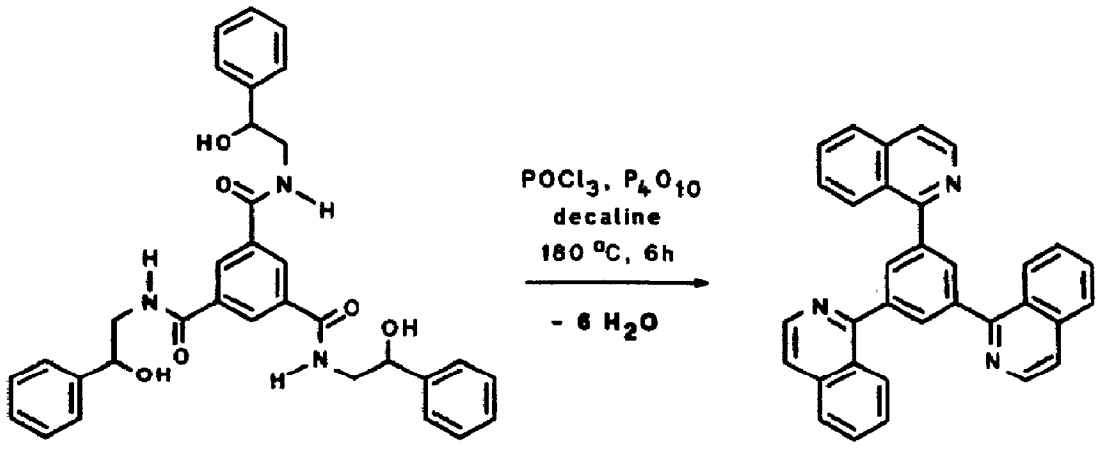
Abstract: Multiple condensation reactions based on the Pictet-Gams isoquinoline synthesis lead to receptors for resorcinol. The host-guest interaction is confirmed by anisotropic highfield shifts and by NOE enhancement between aryl protons.

Artificial receptors with functional groups capable of forming hydrogen bonds are of special interest as model compounds for studying association phenomena.[1] We have synthesized several benzene derivatives with two and three isoquinoline substituents in order to evaluate their complexation ability for phenolic guest molecules.

The Pictet-Gams synthesis opens up a short and efficient pathway to 1-substituted isoquinolines.[2] This annulation reaction affords a double condensation and proceeds at elevated temperatures in the presence of excess phosphorus pentoxide and phosphorus oxychloride. A threefold Pictet-Gams reaction with trisamide 1[3] leads to the trisisoquinoline 2 in a single preparative step.[4] Starting from the corresponding isophthalic acid and terephthalic acid bisamides up to 75 % yield of the biisoquinolines 3 and 4 is obtained.[5] In the case of the phthalic acid bisamide the annulation reaction fails, presumably due to the close proximity



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2 (14 %)

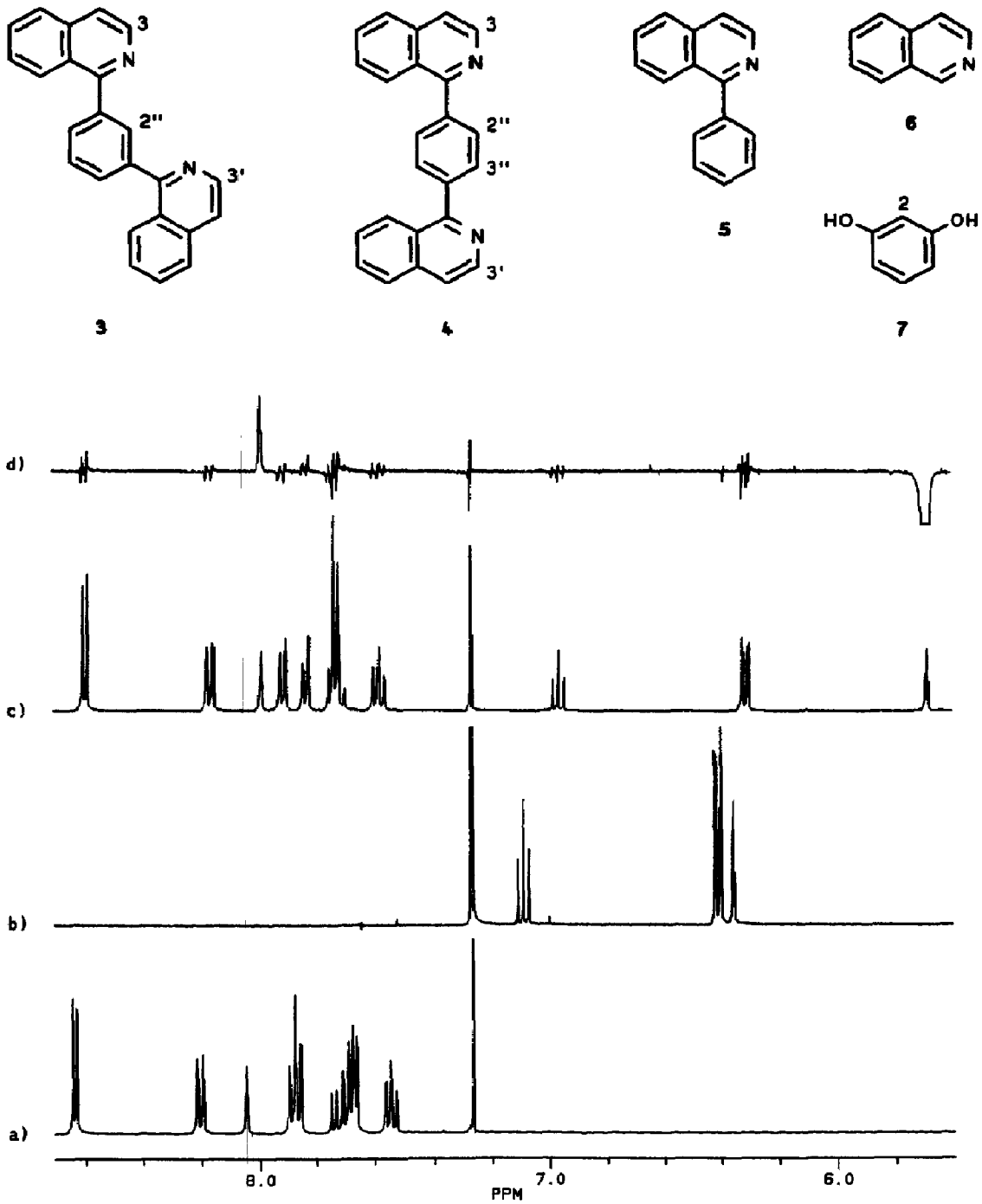

Figure 1. ^1H NMR spectra (400.1 MHz, $CDCl_3$, TMS): a) spectrum of **3**; b) spectrum of **7**; c) spectrum of a mixture of **3** and **7**; d) NOE difference experiment with a mixture of **3** and **7**: spin saturation at 5.7 ppm.

of the side chains.

The isoquinoline derivatives **2**, **3** and **4** were tested as bidentate host molecules for resorcinol (**7**)[5] in deuterochloroform solution monitored by ^{1}H NMR spectroscopy. In addition to a significant change in the NMR pattern of the host molecules a dramatic upfield shift of the resorcinol proton in position 2 is observed in each case ($\Delta\delta_{max}$: 0.72 ppm for **2**, 0.81 ppm for **3**, 0.71 ppm for **4**).[6] In comparison, an excess of 1-phenylisoquinoline **5** leads to a smaller upfield shift ($\Delta\delta_{max} < 0.3$ ppm) whereas the unsubstituted isoquinoline **6** causes a small downfield shift for H-2 of resorcinol (**7**). These observations can be explained by the formation of bidentate complexes through hydrogen bonds in the cases of receptors **2**, **3** and **4**: H-2 of resorcinol (**7**) is placed above the central benzene ring of the host molecules causing an anisotropic upfield shift for this proton.

This result is confirmed by a NOE enhancement experiment with a mixture of **3** and **7** (figure 1). Spin saturation at the resonance of H-2 of guest molecule **7** causes a positive NOE effect (+5 %) for H-2'' at the central benzene ring of host molecule **3** demonstrating the close proximity of these two protons (on a temporary average, as the complexation is a highly dynamic process).

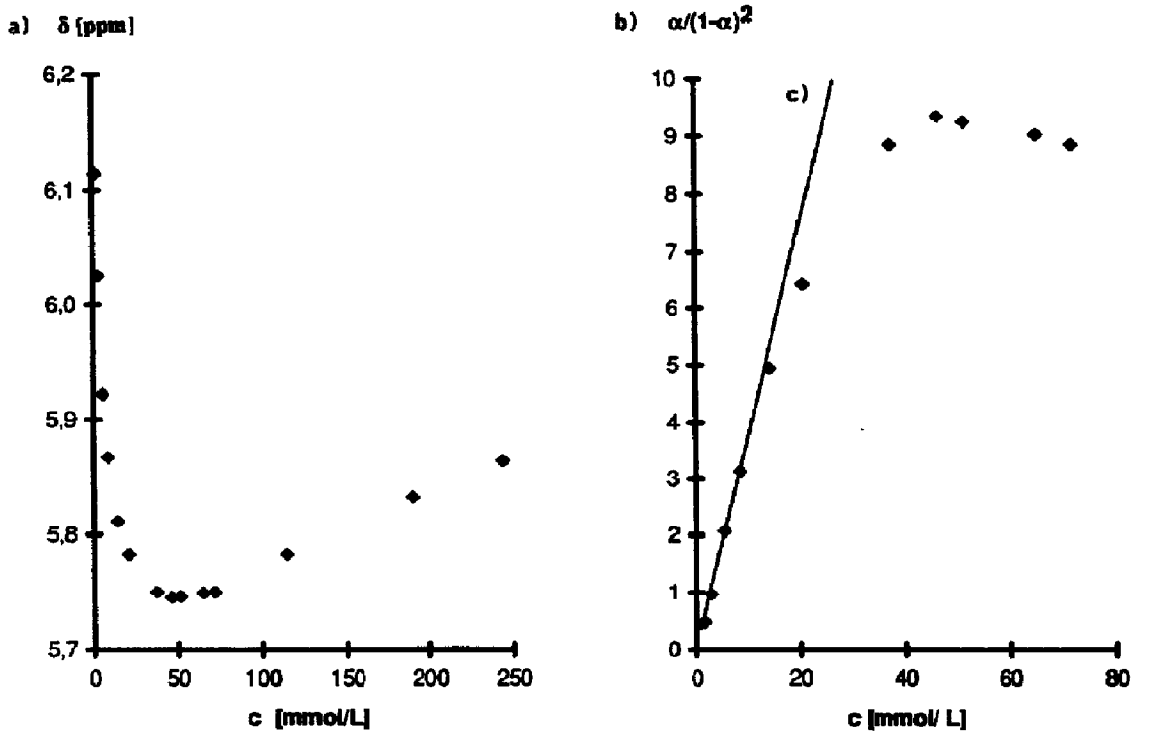

Figure 2. Dilution experiment with an equimolar mixture of **3** and **7** at 20 °C: a) chemical shift δ of resorcinol proton H-2 versus concentration; b) $\alpha/(1-\alpha)^2$ versus concentration with $\alpha = (\delta-\delta_0)/(\delta-\delta_{max})$;[7] δ_0 = 6.33 ppm; δ_{max} = 5.52 ppm (estimated by extrapolation); c) the initial gradient represents an estimation for the association constant: $K_a \sim 360$ L/mol.

In order to determine the association constants the dilution method[7] was applied as illustrated in figure 2. As an example ^{1}H NMR spectra of an equimolar mixture of **3** and **7** were recorded covering concentrations from 250 to 2 mmol/L. Surprisingly, at concentrations above 50 mmol/L the chemical shift of resorcinol proton H-2 is increasing presumably due to the formation of higher order aggregates.[1a] Therefore the complexation constant K_a was only roughly estimated using a "$\alpha/(1-\alpha)^2$ versus concentration"-plot (figure 2 for further information): K_a = 200-400 L/mol for the complex formation of **7** with **3** and **4**; K_a > 1000 L/mol in the case of **2** as a consequence of multiple binding sites.

In summary, we have synthesized several receptors for resorcinol through multiple Pictet-Gams reaction and confirmed the formation of bidentate complexes by ^{1}H NMR spectroscopy including NOE experiments.

Acknowledgement: This work was supported by the "Fonds der Chemischen Industrie".

References and Notes:

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3. Trisamide **1** is obtained in 94 % yield by the reaction of 1,3,5-benzenetricarboxylic acid trichloride with racemic 2-amino-1-phenylethanol (triethylamine added as base in dichloromethane, 16 h, room temperature).
4. All new compounds have been fully characterized by spectroscopic means (^{1}H NMR, ^{13}C NMR, IR, UV, MS and elemental analysis); selected data (^{1}H NMR at 400.1 MHz): **1**: mixture of diastereoisomers; mp 193 °C (decomp.); ^{1}H NMR (DMSO-d_6): δ = 3.35-3.44 (m, 3H), 3.53-3.61 (m, 3H), 4.83 (m, 3H), 5.61 (d, J = 4.3 Hz, 3H, OH), 7.27-7.44 (m, 15H, phenyl-H), 8.47 (s, 3H, aryl-H), 8.73 (t, J = 5.6 Hz, 3H, NH); calcd for $C_{33}H_{33}N_3O_6$: C 69.83, H 5.86, N 7.40; found: C 69.70, H 5.89, N 7.21.
2: mp 228 °C; ^{1}H NMR ($CDCl_3$, TMS): δ = 7.55 (m, 3H), 7.66-7.72 (m, 6H), 7.89 (d, J = 8.3 Hz, 3H), 8.24 (s, 3H), 8.31 (d, J = 8.6 Hz, 3H), 8.64 (d, J = 5.6 Hz, 3H); calcd for $C_{33}H_{21}N_3$: C 86.25, H 4.61, N 9.14; found: C 85.88, H 4.72, N 9.12.
3: mp 163-164 °C; ^{1}H NMR ($CDCl_3$, TMS): δ = 7.54 (m, 2H), 7.65-7.75 (m, 5H), 7.85-7.90 (m, 4H), 8.04 (t, J = 1.7 Hz, 1H, H-2''), 8.20 (d, J = 8.6 Hz, 2H), 8.63 (d, J = 5.6 Hz, 2H); calcd for $C_{24}H_{16}N_2$: C 86.72, H 4.85, N 8.43; found: C 86.68, H 4.81, N 8.38.
4: mp 243 °C; ^{1}H NMR ($CDCl_3$, TMS, signals assigned on the basis of 2D NMR spectra): δ = 7.57 (m, 2H, H-7/7'), 7.69 (d, J = 5.6 Hz, 2H, H-4/4'), 7.72 (m, 2H, H-6/6'), 7.89 (s, 4H, phenylene-H), 7.91 (d, J = 9 Hz, 2H, H-5/5'), 8.21 (d, J = 8.5 Hz, 2H, H-8/8'), 8.66 (d, J = 5.6 Hz, 2H, H-3/3'); calcd for $C_{24}H_{16}N_2$: C 86.72, H 4.85, N 8.43; found: C 86.68, H 4.65, N 8.31.
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6. Similar NMR effects could not be detected with 2-methylresorcinol, hydroquinone, 1,3-diaminobenzene, 1,2-dihydroxybenzene and 2,7-dihydroxynaphthalene. Neither the bidentate ligand **3** nor the tridentate ligand **2** could increase the solubility of 1,3,5-trihydroxybenzene.
7. Kelly, T. R.; Kim, M. H. *J. Am. Chem. Soc.* **1994**, *116*, 7072-7080.

(*Received in Germany* 5 *October* 1994; *accepted* 26 *October* 1994)