[5] M. Menzel, C. Wieczorek, S. Mehle, J. Allwohn, H.-J. Winkler, M. Unverzagt, M. Hofmann, P. von R. Schleyer, S. Berger, W. Massa, A. Berndt, *Angew. Chem.* **1995**, *107*, 728; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 657.

[6] M. Menzel, H.-J. Winkler, W. Massa, K. Harms, A. Berndt, *Acta Crystallogr. Sect. C* **1999**, submitted.

[7] Crystal structure determinations: **8a** · Li_3 · $2Et_2O$: measurements were made with a red block-shaped crystal ($0.7 \times 0.6 \times 0.4$ mm^3) on a Stoe IPDS diffractometer at $-80\,^\circ$C using $Mo_{K\alpha}$ radiation. $C_{40}H_{71}B_2Li_3O_2Si_2$, orthorhombic, space group $P2_12_12_1$, $Z = 4$, $a = 1485.8(1)$, $b = 1620.0(1)$, $c = 1819.2(1)$ pm, $V = 4378.8(5) \times 10^{-30}$ m^3, $\rho_{calcd} = 1.035$ g cm^{-3}; a total of 21 536 reflections were recorded in the range $1.45^\circ < \theta < 24.2^\circ$, resulting in 6846 independent reflections from which 3646 with $F_o > 4\sigma(F_o)$ were observed. All 6846 independent reflections were used for the subsequent calculations; no absorption correction was applied ($\mu = 1.1$ cm^{-1}). The structure was solved by direct methods and refined against F_o^2 with full matrix. Disorder appearing in difference Fourier syntheses were taken into account by refining split positions for the following atoms: 1) the two trimethylsilyl groups (C9, C10, C11 and C12, C13, C14) as well as C7 with site occupations of 50%; 2) the Et_2O molecule coordinated to Li1 (C42, C43) with occupations of 63(2) and 37(2)%. Non-hydrogen atoms were refined using anisotropic displacement factors. Hydrogen atoms were kept on calculated positions, and 1.2 or 1.5 times (CH_3) the equivalent isotropic U values of the corresponding C atom were used as displacement factors. An indicated inversion twinning could not be verified significantly. The refinement converged at $wR_2 = 0.1060$ for all reflections, corresponding to a conventional $R = 0.0435$ for the observed reflections. **8a** · Li_3 · Et_2O: measurements were made with a red block-shaped crystal ($0.7 \times 0.4 \times 0.3$ mm^3) on a Stoe IPDS diffractometer at $-80\,^\circ$C using $Mo_{K\alpha}$ radiation. $C_{36}H_{61}B_2Li_3OSi_2$, orthorhombic, space group $Pnma$, $Z = 4$, $a = 1390.3(1)$, $b = 1590.6(1)$, $c = 1766.9(1)$ pm, $V = 3907.2(5) \times 10^{-30}$ m^3, $\rho_{calcd} = 1.033$ g cm^{-3}; a total of 24 794 reflections were recorded in the range $2.26^\circ < \theta < 25.94^\circ$, resulting in 3909 independent reflections from which 2194 with $F_o < 4\sigma(F_o)$ were observed. All 3909 independent reflections were used for the subsequent calculations; no absorption correction was applied ($\mu = 1.15$ cm^{-1}). The solution and refinement procedure was the same as above, but the hydrogen atoms at C7 – C9 were refined. The Et_2O molecule proved to be disordered over at least four positions. A residual $wR_2 = 0.1390$ was obtained for all reflections, corresponding to a conventional $R = 0.0517$ for the observed reflections. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publication no. CCDC-119471 (**8a** · Li_3 · $2Et_2O$) and CCDC-119470 (**8a** · Li_3 · Et_2O). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

[8] Gaussian 94, Revision D.3, M. J. Frisch, G. W. Trucks, H. B. Schlegel, P. M. W. Gill, B. G. Johnson, M. A. Robb, J. R. Cheeseman, T. Keith, G. A. Petersson, J. A. Montgomery, K. Raghavachari, M. A. Al-Laham, V. G. Zakrzewski, J. V. Ortiz, J. B. Foresman, J. Cioslowski, B. B. Stefanov, A. Nanayakkara, M. Challacombe, C. Y. Peng, P. Y. Ayala, W. Chen, M. W. Wong, J. L. Andres, E. S. Replogle, R. Gomperts, R. L. Martin, D. J. Fox, J. S. Binkley, D. J. Defrees, J. Baker, J. P. Stewart, M. Head-Gordon, C. Gonzalez, J. A. Pople, Gaussian, Inc., Pittsburgh, PA, **1995**.

[9] Owing to disorder, the hydrogen positions in **8a** · Li_3 · $2Et_2O$ are not refined.

[10] W. Hiller, M. Layh, W. Uhl, *Angew. Chem.* **1991**, *103*, 339; *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 324; U. Siemeling, T. Redecker, B. Neumann, H.-G. Stammler, *J. Am. Chem. Soc.* **1994**, *116*, 5507; R. J. Wehmschulte, P. P. Power, *J. Am. Chem. Soc.* **1997**, *119*, 2847, and references therein.

[11] Further examples for η^2-σ coordination of lithium ions to (partial) B=B double bonds: A. A. Korkin, P. von R. Schleyer, M. L. McKee, *Inorg. Chem.* **1995**, *34*, 961, and references therein; ref. [4].

[12] a) C. Dohmeyer, E. Baum, A. Ecker, R. Köppe, H. Schnöckel, *Organometallics* **1996**, *15*, 4702, b) D. Stalke, *Angew. Chem.* **1994**, *106*, 2256; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 2168.

[13] G. E. Herberich, M. Hostalek, R. Laven, R. Boese, *Angew. Chem.* **1990**, *102*, 330; *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 317.

[14] For terminology and methods in computational chemistry, see for example: J. B. Foresman, A. Frisch, *Exploring Chemistry with Electronic Structure Methods*, 2nd ed., Gaussian, Inc., Pittsburgh, PA, **1996**; *Encyclopedia of Computational Chemistry* (Eds.: P. von R. Schleyer, N. L. Allinger, T. Clark, J. Gasteiger, P. A. Kollman, H. F. Schaefer, P. R. Schreiner), Wiley, Chichester, **1998**.

[15] See footnote 19 in ref. [12a].

[16] The appearance of different signals in the NMR spectra at 25 °C for the boron atoms and their substituents, as well as for the boron-bound C atoms of the five-membered ring and the methyl groups attached to them, can be explained by hindered rotation of the bis(trimethylsilyl)methyl group. The rotational barrier was determined to be $\Delta G^{\ddagger} = 18.5$ kcal mol^{-1}. A rotational barrier of similar magnitude (18.8 kcal mol^{-1}) was deduced for 1,1,2,2 tetrakis(trimethylsilyl)-ethane: S. Brownstein, J. Dunogues, D. Lindsay, K. U. Ingold, *J. Am. Chem. Soc.* **1977**, *99*, 2073.

[17] a) H. Jiao, P. von R. Schleyer, *Angew. Chem.* **1993**, *105*, 1830; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1760; b) M. Bühl, W. Thiel, H. Jiao, P. von R. Schleyer, M. Saunders, A. A. L. Anet, *J. Am. Chem. Soc.* **1994**, *116*, 6005. An IGLO analysis of the individual contributions to the shielding in **8u** · Li_3 shows the influence of the ring current on the chemical shifts of the η^5-bound lithium ions.

[18] We have no explanation at present for the discrepancy between the experimental (−0.1 ppm) and the computed NMR chemical shift (3.2 ppm) of the third lithium ion in the ring plane.

Ramberg – Bäcklund Approaches to the Synthesis of C-Linked Disaccharides**

Frank K. Griffin, Duncan E. Paterson, and Richard J. K. Taylor*

C-Disaccharides have attracted considerable interest,[1] particularly in view of their hydrolytic stability and potential enzyme inhibitory properties. Since the first synthesis of a carba-disaccharide by Sinaÿ and Rouzaud in 1983,[2] a number of synthetic methodologies have been developed for the preparation of this class of compounds.[1–3] Recent work in our laboratory has focussed on the use of the Ramberg – Bäcklund rearrangement[4] of *S*-glycoside dioxides as the key step in the formation of di-, tri-, and tetra-substituted *exo*-glycals,[5a] which are useful intermediates for the preparation of more elaborate C-glycosides.[5b,c] Scheme 1a illustrates this approach with a glucose-derived sulfone: The Meyers variant[6] of the Ramberg – Bäcklund rearrangement is used to convert the sulfone directly into the corresponding *exo*-glycal without competing 1,2-glycal formation. We have now applied this methodology to the construction of C-linked disaccharides from readily prepared S-linked precursors. The general

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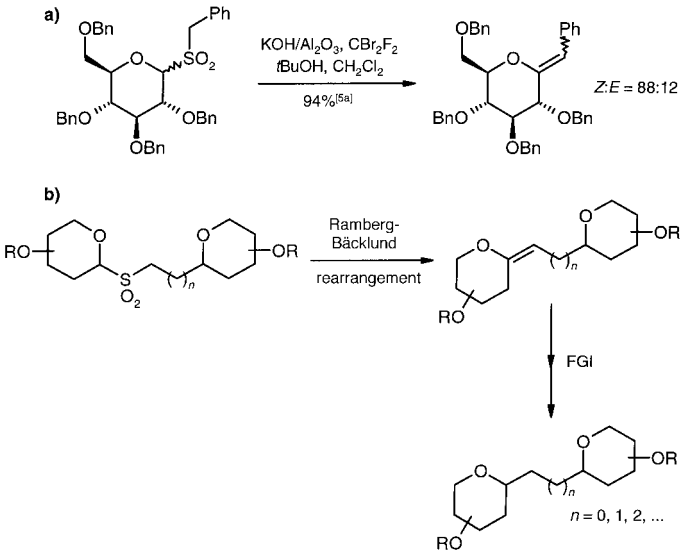
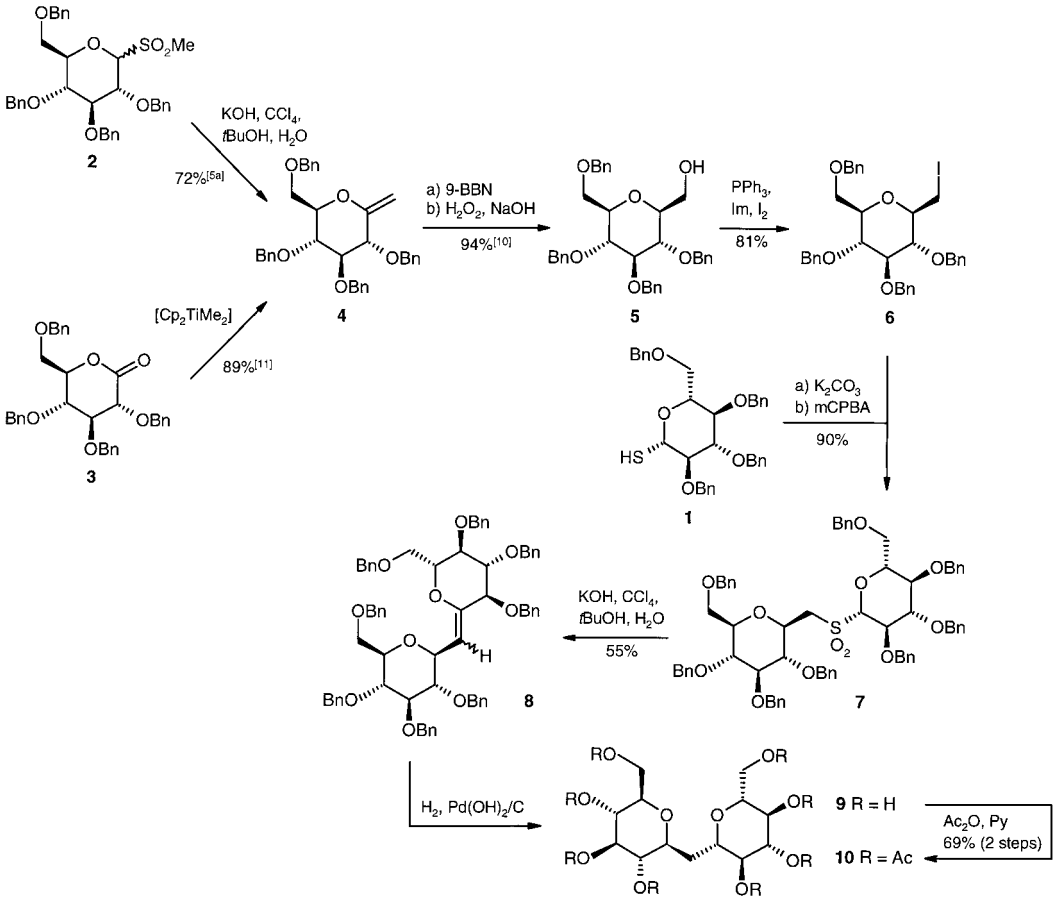


Scheme 1. The use of the Ramberg–Bäcklund rearrangement for the synthesis of an *exo*-glycal and its possible extension to C-disaccharide synthesis. Bn = benzyl, FGI = functional group interconversion.

approach is outlined in Scheme 1b: Our initial objective was to employ this methodology to prepare C-disaccharides ($n = 0$) and higher homologues. We then envisaged the extension of this chemistry to provide a more general route to a range of C-linked disaccharides. Herein we report the successful utilization of this approach for the synthesis of *C*-trehalose, a higher homologue of *C*-trehalose, and methyl *C*-gentiobioside.

Our first target was a carba-analogue of trehalose, a member of a family of disaccharides in which carbohydrate residues are linked together through their anomeric centers. *C*-Trehaloses have been prepared by the groups of Martin[3d] and Kishi,[7] and recently Schmidt and Patro have reported the synthesis of novel trehalose analogues with a functionalized linking carbon atom.[8] Our strategy (Scheme 2) required the initial preparation of sulfone **7**. This was readily obtained from the protected thioglucose **1**[9] and iodomethyl *C*-glucoside **6**. Iodide **6** was prepared from the corresponding alcohol **5**, which was obtained by the stereoselective hydroboration (9-BBN) and oxidation of *exo*-glycal **4**.[10] The *exo*-methylenic compound **4** was prepared from sulfone **2** using our Ramberg–Bäcklund procedure[5a] or by the methylenation of tetra-*O*-benzyl-D-gluconolactone (**3**) using $[Cp_2TiMe_2]$.[11] The two monosaccharides **1** and **6** were coupled in an efficient thioetherification process, and the resulting S-linked disaccharide was oxidized to the requisite sulfone **7** in 90% yield over the two steps.

We were delighted to find that the Ramberg–Bäcklund rearrangement of sulfone **7** proceeded under standard[6a] Meyers conditions and that no products arising from β-elimination were observed. Enol ether **8** was obtained in a moderate, but unoptimized, 48% yield, predominantly as the



Scheme 2. Synthesis of *C*-trehalose. 9-BBN = 9-borabicyclo[3.3.1]nonane, Im = imidazole, mCPBA = *meta*-chloroperoxybenzoic acid, Py = pyridine.

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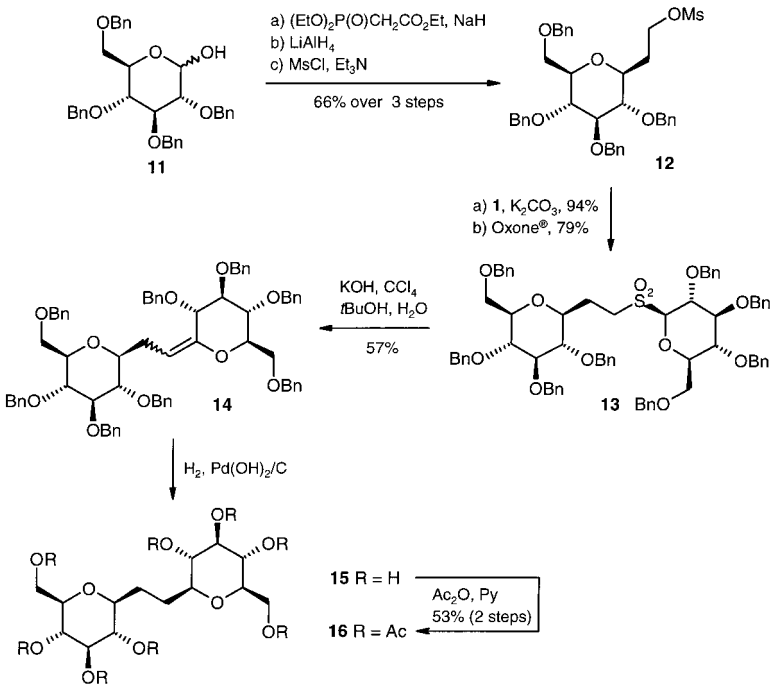
Z isomer (*Z*:*E* = 91:9). Catalytic hydrogenation of **8** achieved O-debenzylation and alkene reduction, and the product **9** was converted into octaacetate **10** to facilitate characterization. All spectroscopic data were consistent with the production of the symmetrical β,β-linked disaccharide **10**, and also agreed with published data[3d] (e.g. ^{13}C NMR (67.9 MHz, $CDCl_3$): $\delta_C = 62.4$, 68.9, 71.8, 73.1, 74.3, 75.9; literature values[3d] (90 MHz, $CDCl_3$): $\delta = 62.5$, 68.9, 72.0, 73.2, 74.3, 76.0).

We believe that this methodology offers a rapid, convergent, and practically simple route to β,β-(1,1′)-carba-disaccharides. In addition, the intermediate enol ether **8** could be elaborated further (e.g. by hydroboration, epoxidation, or dihydroxylation)[5b] prior to deprotection to introduce functionality to the carbon bridge.

This approach is ideally suited to analogue synthesis simply by variation of the alkylating agent. Thus, the homologated (1,1′)-carba-disaccharide **15** containing a two-carbon bridge was readily prepared (Scheme 3). Lactol **11** was converted into mesylate **12** by a straightforward three-step sequence,[12] and **12** was then employed with thiol **1** in the alkylation/oxidation sequence used earlier. This produced sulfone **13**, which underwent Ramberg–Bäcklund rearrangement to give *exo*-glycal **14** as a *Z*/*E* mixture (88:12) in 57% yield (unoptimized). Subsequent reduction/debenzylation produced the novel, ethylene-bridged disaccharide **15**, which was converted into octaacetate **16** ($[\alpha]_D = -10.9$ ($c = 0.53$, $CHCl_3$)) for characterization purposes. Again, the ^1H and ^{13}C NMR data were consistent with the production of the symmetrical β,β-linked disaccharide, with coincidental absorptions being observed for each sugar residue.

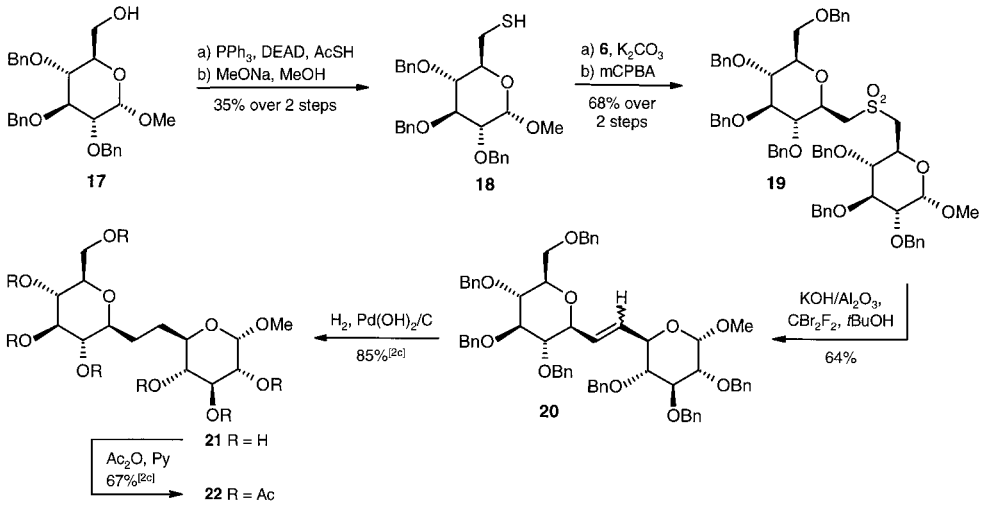


Scheme 3. Synthesis of a higher homologue of *C*-trehalose. Ms = mesyl = methanesulfonyl.

We next investigated the preparation of the (1,6′)-carba-disaccharide, methyl *C*-gentiobioside (**21**).[13] In view of the accessibility of the precursors, we explored the Ramberg–Bäcklund approach shown in Scheme 4. Whereas in previous examples the key Ramberg–Bäcklund rearrangement utilized an S-glycoside-derived sulfone, this alternative approach offered the opportunity to widen the scope of this synthetic route to C-linked sugars.

With iodide **6** (Scheme 2) in hand, we required only the complementary thiol **18**. This was obtained from alcohol **17**[14] by Mitsunobu reaction with thiolacetic acid followed by deacetylation. Subsequent coupling of **18** with **6** followed by oxidation of the resulting sulfide gave sulfone **19** in high yield. To our delight, treatment of sulfone **19** with KOH/Al_2O_3 and CBr_2F_2[6b] gave the desired unsaturated C-disaccharide **20** in 64% yield (*Z*:*E* = 70:30). This alkene has been prepared previously by Dondoni et al.[3c] and hydrogenated to furnish methyl *C*-gentiobioside (**21**). We repeated the hydrogenation step and then prepared heptaacetate **22**, which gave consistent NMR and optical rotation data ($[\alpha]_D = +65$ ($c = 0.45$, $CHCl_3$); literature value:[3c] $[\alpha]_D = +63$ ($c = 0.7$, $CHCl_3$)).

In summary, the Ramberg–Bäcklund rearrangement has been utilized to convert readily available sulfone-linked saccharides into C-linked disaccharides. This methodology has been employed to prepare *C*-trehalose, a higher homologue of *C*-trehalose, and methyl *C*-gentiobioside. Thus, (1,1′)- and (1,6′)-linked C-disaccharides have been prepared in this study: We are currently extending this methodology to prepare (1,4′)-linked systems and other C-glycosides of biological interest.



Scheme 4. Synthesis of methyl *C*-gentiobioside. DEAD = diethylazodicarboxylate.

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Experimental Section

All new compounds were fully characterized by high-field ^{1}H and ^{13}C NMR spectroscopy and by elemental analysis or high-resolution mass spectrometry.

8: To a stirred mixture of *t*BuOH (6 mL) and water (1.5 mL) at 60 °C was added powdered KOH (3 g, 53.5 mmol). After the base had dissolved, a solution of **7** (0.367 g, 0.326 mmol) in CCl_4 (6 mL) was added, and the biphasic mixture was stirred at 60 °C for 1 h. After cooling to room temperature, the pale yellow mixture was transferred to a separating funnel and the lower aqueous layer removed. The organic phase was washed with brine and dried (Na_2SO_4), and the solvent removed in vacuo. Purification by column chromatography on silica gel (light petroleum ether/EtOAc/Et_3N 74/25/1) gave alkene **8** (0.167 g, 48 %) as a pale yellow oil. TLC: R_f = 0.36 (light petroleum ether/EtOAc 3/1); IR: $\tilde{\nu}_{max}$ (liquid film) = 1687 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$): δ = 5.11 (1H, d, ^3J = 8.7 Hz, vinyl H); ^{13}C NMR (67.9 MHz, $CDCl_3$): δ = 68.7, 69.0, 72.1, 73.3, 73.5, 73.8, 74.2, 74.6, 74.9, 75.6, 77.9, 78.0, 78.2, 78.7, 83.1, 84.6, 86.7, 108.5 (*C*=C–O), 126.9 – 128.3 (aryl C), 137.8, 138.2, 138.3 (×2), 138.6, 138.7, 152.6 (C=*C*–O); FAB-MS: *m*/*z*: 1081 [*M*+Na$^+$].

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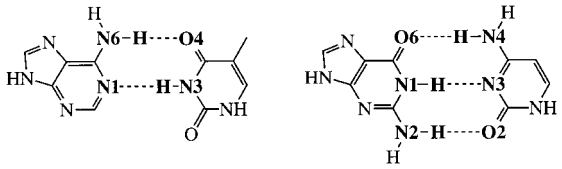
[1] Reviews: D. E. Levy, C. Tang, *The Chemistry of C-Glycosides*, Pergamon, Oxford, **1995**; M. H. D. Postema, *C-Glycoside Synthesis*, CRC Press, Boca Raton, FL, **1995**; Y. Du, R. J. Linhardt, I. R. Vlahov, *Tetrahedron* **1998**, *54*, 9913 – 9959.
[2] D. Rouzaud, P. Sinaÿ, *J. Chem. Soc. Chem. Commun.* **1983**, 1353 – 1354.
[3] a) A. Mallet, J.-M. Mallet, P. Sinaÿ, *Tetrahedron: Asymmetry* **1994**, *12*, 2593 – 2608; b) T. Skrydstrup, D. Mazéas, M. Elmouchir, G. Doisneau, C. Riche, A. Chiaroni, J.-M. Beau, *Chem. Eur. J.* **1997**, *3*, 1342 – 1356; c) A Dondoni, H. M. Zuurmond, A. Boscarato, *J. Org. Chem*. **1997**, *62*, 8114 – 8124; d) O. R. Martin, W. Lai, *J. Org. Chem*. **1993**, *58*, 176 – 185; e) H. Dietrich, R. R. Schmidt, *Liebigs Ann. Chem*. **1994**, 975 – 981; f) M. A. Leeuwenburgh, C. M. Timmers, G. A. van der Marel, J. H. van Boom, J.-M. Mallet, P. Sinaÿ, *Tetrahedron Lett*. **1997**, *38*, 6251 – 6254.
[4] L. Ramberg, B. Bäcklund, *Ark. Kemi. Mineral. Geol*. **1940**, 27, 1 – 50 [*Chem. Abstr*. **1940**, *34*, 4725]; for a recent review containing other key references, see R. J. K. Taylor, *Chem. Commun.* **1999**, 217 – 227.
[5] a) F. K. Griffin, P. V. Murphy, D. E. Paterson, R. J. K. Taylor, *Tetrahedron Lett*. **1998**, *39*, 8179 – 8182; b) M.-L. Alcaraz, F. K. Griffin, D. E. Paterson, R. J. K. Taylor, *Tetrahedron Lett*. **1998**, *39*, 8183 – 8186; c) P. S. Belica, R. W. Franck, *Tetrahedron Lett.* **1998**, 39, 8225 – 8228.
[6] a) C. Y. Meyers, A. M. Malte, W. S. Matthews, *J. Am. Chem. Soc*. **1969**, *91*, 7510 – 7512; b) T.-L. Chan, S. Fong, Y. Li, T.-O. Man, C. D. Poon, *J. Chem. Soc. Chem. Commun.* **1994**, 1771 – 1772.
[7] A. Wei, Y. Kishi, *J. Org. Chem*. **1994**, *59*, 88 – 96.
[8] B. Patro, R. R. Schmidt, *Synthesis* **1998**, 1731 – 1734.
[9] S. A. Holick, S.-H. Chiu, L. Anderson, *Carbohydr. Res.* **1976**, *50*, 215 – 225.
[10] T. RajanBabu, G. S. Reddy, *J. Org. Chem*. **1986**, *51*, 5458 – 5461.
[11] R. Csuk, B. I. Glänzer, *Tetrahedron* **1991**, *47*, 1655 – 1664.
[12] P. Allevi, P. Ciuffreda, D. Colombo, D. Monti, G. Speranza, P. Manitto, *J. Chem. Soc. Perkin Trans. 1* **1989**, 1281 – 1283; P. Allevi, M. Anastasia, P. Ciuffreda, A. Fiecchi, A. Scala, *J. Chem. Soc. Perkin Trans. 1* **1989**, 1275 – 1280.
[13] P. G. Goekjian, T.-C. Wu, H.-Y. Kang, Y. Kishi, *J. Org. Chem.* **1987**, *52*, 4823 – 4825; P. G. Goekjian, T.-C. Wu, H.-Y. Kang, Y. Kishi, *J. Org. Chem.* **1991**, *56*, 6422 – 6434.
[14] B. Bernet, A. Vasella, *Helv. Chim. Acta* **1979**, *62*, 1990 – 2016.

Charge Transfer and Environment Effects Responsible for Characteristics of DNA Base Pairing**

Célia Fonseca Guerra and F. Matthias Bickelhaupt*

Although it is one of the weakest chemical interactions the hydrogen bond plays a key role in the chemistry of life, being involved, for example, in various types of self-organization and molecular recognition. A case in point is the hydrogen bonds in Watson – Crick base pairs, that is, adenine – thymine (AT) and guanine – cytosine (GC), that hold together the two helical chains of nucleotides in DNA and form the basis of the genetic code. These hydrogen bonds are commonly believed



AT GC

to be predominantly electrostatic phenomena that, as suggested by Gilli et al., are substantially reinforced by resonance in the π-electron system, which makes the proton-acceptor atom more negative and the proton-donor atom more positive the so-called resonance-assisted hydrogen bonding (RAHB).[1]

Herein we provide evidence from quantum chemical analyses that challenges this picture and emphasizes the importance of the charge-transfer nature of and environment effects on the hydrogen bonds in DNA base pairs. This has led us to the solution of a hitherto unresolved and significant discrepancy between experimental[2] and theoretical[3] values for distances between the proton-donor and proton-acceptor atoms in AT and GC base pairs. Our evidence is based on a thorough nonlocal density functional theoretical (DFT) investigation with the ADF program (at BP86/TZ2P) of various AT and GC model systems.[4, 5]

Whereas our base-pairing enthalpies (298 K, BSSE corrected) of −11.8 and −23.8 kcal mol^{-1} for AT and GC, respectively, are in excellent agreement with gas-phase experimental values (−12.1 and −21.0 kcal mol^{-1}),[6] we still arrive at the same striking discrepancies with experimental (X-ray crystal) structures[2] that were encountered before in conventional ab initio (HF) and hybrid DFT (B3LYP) studies.[3] As shown in Figure 1 we find N6–O4 and N1–N3

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