Pergamon

Tetrahedron Letters 39 (1998) 591–594

TETRAHEDRON LETTERS

New Aspect of Thermodynamic Stability of 3-*C*-Nitro-D-glycal Derivatives

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Received 25 August 1997; accepted 14 November 1997

Abstract: *Thermodynamic stability of 3-C-nitro-D-glucal and -D-allal derivatives as well as the corresponding 5a-carba sugars was reproduced by ab initio (6-31G*) calculations. The calculations also predicted that 3-C-nitro- D-gulal should be more stable than its 3-epimer, in spite of strong bias for a nitro group at C-3 to occupy the equatorial position. This prediction was experimentally proved.*

Under thermodynamically controlled conditions a nitro group of 3-*C*-nitropyranoside derivatives has a strong tendency to occupy the sterically less crowded equatorial or quasiequatorial position. [1]

We now report the first exception,[2] to our best knowledge: 3-*C*-nitro-D-gulal **13** having the quasiaxial nitro group is thermodynamically more stable than its 3-epimer **14**.

Vasella, *et al*, [3] proved that the anomeric nitro group predominantly occupies the axial position (anomeric effect[4]). This is explained, at least partly, in terms of stabilization of resonance structures originating from n_{O5}-$\sigma^*_{C\text{-}N}$ hyperconjugative electron delocalization. Similar hyperconjugation through the carbon-carbon double bond should stabilize the 3-nitro-D-allal **1** more effectively than the 3-nitro-D-glucal **5** (Fig. 1). In fact considerable amount of allal **1** is formed in equilibrium (the ratio of **1** : **5** = 1 : 2.5).[5] If this is the case, the ratio of glucal to allal in the 5a-carba 3-nitro sugar (the ring oxygen atom is replaced by a methylene group) should be higher than that in the 3-nitro sugars. This speculation is proved as follows. Treatment of 3-*C*-nitro-5a-carba-DL-allal **3**[6] with *N*,*N*-dimethylaminopyridine in $CDCl_3$ afforded a ~ 1 : 8.7 mixture of **3** and **7**[7]. Almost the same equilibrium mixture was obtained by similar treatment of the glucal **7**.

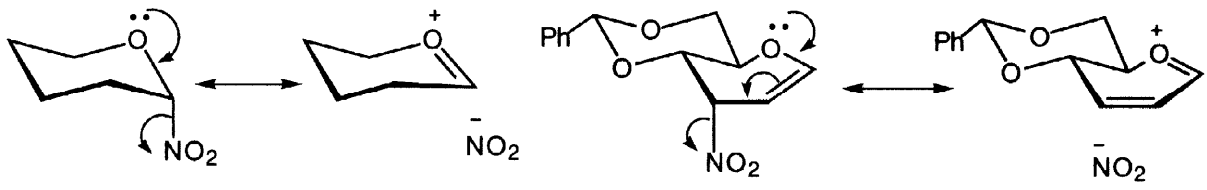


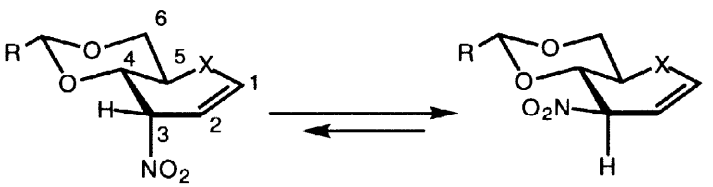
Fig. 1

Contribution of this hyperconjugative stabilization is supported by *ab initio* calculation[8] (6-31G* with full optimization in $CHCl_3$). 3,4-Dihydro-4-nitro-2*H*-pyran **9** having the quasiaxial nitro group was more stable than its 3-epimer **10** by 7.1 kJ/mol. The difference decreased to 1.1 kJ/mol in the case of 3-nitrocyclohexenes **11** and **12**.

0040-4039/98/$19.00
PII: S0040-4039(97)10652-9

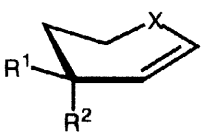
Similar *ab initio* calculations reproduced the equilibria by the use of nitro sugars **2** and **6** and 5a-carba nitro sugars **4** and **8** as model compounds. The difference of heat of formation between **2** and **6** was 1.9 kJ/mol and that between **4** and **8** is 6.3 kJ/mol, while the free energy calculated from its equilibrium (at 25℃) was 2.3 kJ/mol and 5.3 kJ/mol, respectively. Bond length[9] and NBO analyses[10] support the different degree of hyperconjugation between the ring oxygen atom and the β-nitroolefin moiety (Table 1).

Why is the glucal **6** slightly more stable than its 3-epimer **2**, in spite of the hyperconjugation? In the optimized conformations of 2*H*-dihydropyran derivatives **9** and **10**, one of the N-O bond in the nitro group was almost eclipsed to the C3 - C4 bond (sugar numbering) (Table 1). On the other hand, in the allal **2**, the conformation of the nitro group largely deviated from the eclipsed one (Table1), undoubtedly to reduce the steric and electrostatic repulsion due to O4. If the dihedral angle (ONC3C2) was fixed to the value (106° for **2** and 112° for **6**) obtained in the corresponding 2*H*-dihydropyran and others were optimized, **2** and **6** became less stable than the fully optimized ones by 7.1 and 1.1 kJ/mol, respectively. This should be the main reason why the glucal **6** is slightly more stable than its 3-epimer **2**.



1 X = O, R = Ph
2 X = O, R = H
3 X = CH_2, R = Ph
4 X = CH_2, R = H

5 X = O, R = Ph
6 X = O, R = H
7 X = CH_2, R = Ph
8 X = CH_2, R = H

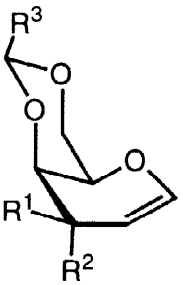


9 X = O, R^1 = H, R^2 = NO_2
10 X = O, R^1 = NO_2, R^2 = H
11 X = CH_2, R^1 = H, R^2 = NO_2
12 X = CH_2, R^1 = NO_2, R^2 = H

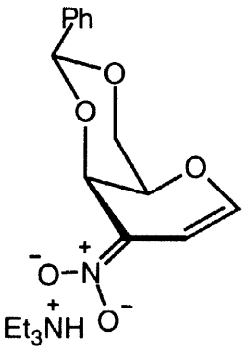
From these results, the 4-epimer of **2**, i.e. the gulal **15**, should be much more stable than the galactal **16**, because the former is favorable owing to the hyperconjugation and the latter is unfavorable due to the steric and electrostatic repulsion between the nitro group and O-4. In fact the calculation indicated that the gulal **15** was more stable than the galactal **16** by 8.3 kJ/mol.

Table 1. Heat of formation (HF), bond length, dihedral angle, and NBO analysis of nitro compounds calculated by 6-31G* including solvent via the Onsager reaction model (ε=4.81)

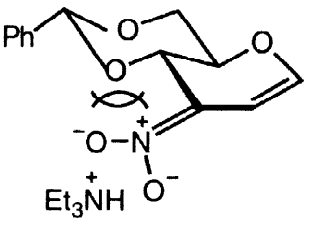
Comp.	HF (Hartree)	Bond length (Å) (sugar numbering) O5-C1	C1-C2	C2-C3	Dihedral angle ∠ONC3C2	π-σ^*_{CN} kJ/mol (n_{O5}-$\pi^*_{C=C}$)
2	-698.9167774	1.3398	1.3244	1.4997	58°	49.7 (191.6)
6	-698.9175006	1.3436	1.3221	1.5077	90°	27.0 (169.0)
4	-663.1031828	1.5073	1.3210	1.5047	58°	43.4
8	-663.1055711	1.5079	1.3200	1.5099	85°	22.8
9	-472.3100788	1.3329	1.3244	1.5005	106°	47.0 (204.1)
10	-472.3073888	1.3372	1.3223	1.5048	112°	27.8 (182.1)
11	-436.4965405		1.3207	1.5088	109°	39.1
12	-436.4961075		1.3200	1.5107	107°	22.3
15	-698.9174007	1.3328	1.3217	1.4971	100°	47.2 (200.7)
16	-698.9142333	1.3399	1.3192	1.4938	183°	31.3 (176.1)



13 $R^1 = H, R^2 = NO_2, R^3 = Ph$
14 $R^1 = NO_2, R^2 = H, R^3 = Ph$
15 $R^1 = H, R^2 = NO_2, R^3 = H$
16 $R^1 = NO_2, R^2 = H, R^3 = H$

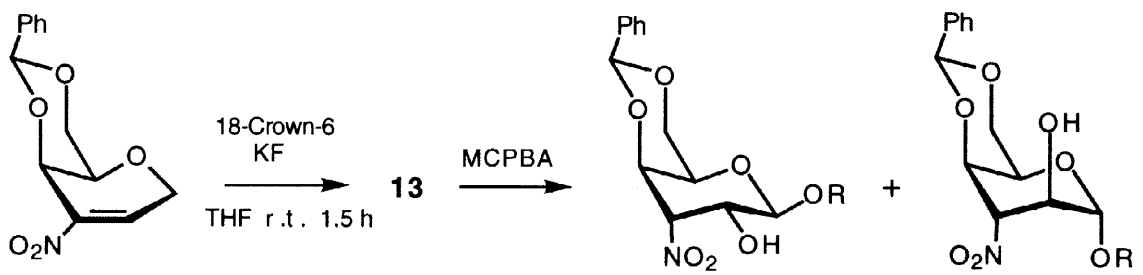


17



18

As had been already reported,[5] however, reaction of the D-*threo* isomer **19** with Et_3N in CH_2Cl_2 (employed for the double bond migration of the corresponding D-*erythro* isomer) stopped at the step of the nitronate **17**. Different from the case of the nitronate **17**, the nitronate **18** should be destabilized by $A^{(1,3)}$ strain[11] and smoothly protonated. Expecting that removal of the counter ion should be so destabilized the nitronate **17** as to promote the protonation, we have performed the reaction in the presence of potassium fluoride and 18-crown-6 instead of Et_3N and obtained the D-gulal **13** in high yield[12] as judged from its ^1H NMR spectrum. The D-gulal structure for **13** was chemically confirmed as follows. Treatment of **13** with *m*- chloroperoxybenzoic acid in CH_2Cl_2 afforded a mixture mainly consisting of two products, from which 4,6-*O*-benzylidene-1-*O*-*m*-chlorobenzoyl-3-deoxy-3-*C*-nitro-β-D-gulopyranose (**20**) and -α-D-idopyranose (**21**)[13] were isolated after HPLC. The present calculation determined only thermodynamic stability of model compounds. Therefore, in order to prove whether the experimental results are agreed with the calculation or not, it is necessary to confirm that the epimerization at C-3 occurred under the reaction conditions employed. When the D-gulal **13** was treated with KF under the same conditions except the addition of small amounts of CH_3COOD, complete deuteration at C-3 of **13** took place, indicating that H-3 was acidic enough for abstraction and probably epimerization occurred. Under the same conditions, the double bond migration and deuteration occurred from the nitroolefin **19**.



19 **20** **21**

Acknowledgment

This work is partially supported by Grant-in-Aid for Scientific Research (No.07640727) from the Ministry of Education, Science and Culture in Japan.

References and Notes

1. For example, P. A. Wade and R. M. Giuliano, *Nitro Compounds: Recent Advances in Synthesis and Chemistry, Organic Nitro Chemistry Series,* Ed. by H. Feuer and A. T. Nielsen, VCH Publishers, New York, 1990, Chap.2.
2. 4-Acetyl-2,3-dihydro-5-methyl-(4,6-*O*-benzylidene-2,3-dideoxy-3-*C*-nitro-β-D-altropyranosido)[1,2-*b*] furan, having the axial nitro group was proved to be thermodynamically more stable than its 3-epimer. However, the axial position is a sterically less crowded *exo* position. T. Sakakibara, A. Seta, and T. Nakagawa, *Carbohydr. Res.*, **1991**, 212, 119.
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6. Physical data of **3**: mp 116.0-116.5℃, ν_{max} 1550 cm^{-1} (NO_2); ^{1}H-n.m.r.: δ 6.26 (broad d and dd, 1 H, $J_{1,2}$ 7.9, $J_{1,5aa}$ 2.3, $J_{1,5ae}$ 5.6 Hz, H-1), 5.83 (dddd, 1 H, $J_{2,3}$ 5.0, $J_{2,5aa}$ 2.3, $J_{2,5ae}$ 1.0 Hz, H-2), 5.32 (broad t, 1 H, $J_{3,4}$ 5.4, H-3), 4.03 (dd, 1 H, $J_{4,5}$ 11.4 Hz, H-4).
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8. Gaussian 94, Revision C.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, and J. A. Pople, Gaussian, Inc., Pittsburgh PA, 1995.
9. One exception was observed in C2 - C3 bond length between **15** and **16**.
10. Hyperconjugative stabilization energies were calculated by second-order perturbation theory analysis of the off-diagonal Fock matrix elements in the natural bond orbital (NBO) basis: E. D. Glendening, A. E. Reed, J. E. Carpenter, and F. Weinhold, *NBO version 3.1*.
11. E. Johnson, *Chem. Rev.*, **1968**, 68, 376.
12. The isolated yield of **13** was ca. 50% after silica gel column chromatography, because **13** was partially decomposed to an ulose during the purification as judged from IR and ^{1}H NMR spectroscopy. Physical data of **13**: m.p. 151-153℃, $[\alpha]_D^{25}$ 306° (*c* 0.9, CH_2Cl_2), ^{1}H-n.m.r.($CDCl_3$): δ=6.81 (d, 1 H, $J_{1,2}$=6.3 Hz, H-1), 5.11 (ddd, 1 H, $J_{2,3}$=5.3, $J_{2,4}$=1.7 Hz, H-2), 4.90 (dd, 1 H, $J_{3,4}$=1.3, H-3), 4.70 (ddd, 1 H, $J_{4,5}$=3.0 Hz, H-4).
13. Physical data of **20**: syrup, $[\alpha]_D^{25}$ -9° (*c* 1.0, $CHCl_3$), ^{1}H-n.m.r.($CDCl_3$): δ=6.54 (d, 1 H, $J_{1,2}$=7.9 Hz, H-1), 4.47 (dd, 1 H, $J_{2,3}$=5.6, H-2), 5.21 (dd, 1 H, $J_{3,4}$=2.0, H-3), 4.59 (t, 1 H, $J_{4,5}$=2.0 Hz, H-4). Physical data of **21**: syrup, $[\alpha]_D^{25}$ 36° (*c* 0.3, $CHCl_3$), ^{1}H-n.m.r.($CDCl_3$): δ=6.71 (d, 1 H, $J_{1,2}$=3.6 Hz, H-1), 4.99 (dd, 1 H, $J_{2,3}$=2.0, H-2), 4.93 (dd, 1 H, $J_{3,4}$=1.0, H-3), 5.01 (d, 1 H, $J_{4,5}$=0 Hz, H-4).