J|A|C|S
COMMUNICATIONS

Aromatic 4-Tetrahydropyranyl and 4-Quinuclidinyl Cations. Linking Prins with Cope and Grob

Roger W. Alder,* Jeremy N. Harvey, and Mark T. Oakley
School of Chemistry, University of Bristol, Bristol, United Kingdom BS8 1TS

Received February 12, 2002

We report B3LYP/6-31G* density functional calculations[1] on the chair 4-tetrahydropyranyl cation **1a** and the 4-quinuclidinyl cation **2**, which show these species to be energy minima, but with unusual geometries associated with extensive delocalization. In both species, the $CH_2{-}CH_2$ bonds are exceptionally long, while the C−C bonds to the carbocation center and the C−X bonds are shortened (Figure 1). In **1a** the $C^+{-}H$ is semi-axial to provide better overlap of the empty orbital with the $CH_2{-}CH_2$ bond orbitals[2] and the equatorial lone pair on oxygen, creating a 6-electron system in the equatorial plane of the ring. Calculation of nucleus-independent chemical shifts (NICS)[3] gives values of −14.2 at the center of the ring in **1a**, and −25.6 at the center of the bicyclic system in **2**, strongly indicative of aromaticity in both species. Through-bond coupling has been extensively explored,[4] but species such as **1a** or **2** represent a novel type of delocalized cation; moreover these findings have important implications for the Prins cyclization[5−7] and Grob fragmentation[8,9] reactions, and for the continuing debate about transition states and intermediates in Cope rearrangements.

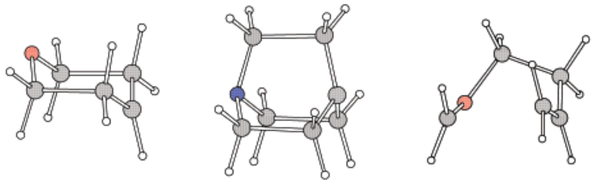

(a) (b) (c)

Figure 1. (a) The 4-tetrahydropyranyl cation **1a**: $CH_2{-}CH_2$ 1.673 Å; $CH_2{-}CH^+$ 1.433 Å; C−O 1.379 Å; $C{-}C^+{-}C$ 120.2°; $C{-}C^+{-}H$ 118.7°. (b) 4-Quinuclidinyl cation **2**: $CH_2{-}CH_2$ 1.719 Å; $CH_2{-}C^+$ 1.448 Å; C−N 1.425 Å; $C{-}C^+{-}C$ 115.8°; C−N−C 111.6°. (c) Partially open twist structure **4**.

Cation **1a** is 56 kJ/mol more stable (41 kJ/mol in water[1]) than the best conformation of open cation, **3**, which cyclizes without activation once it achieves the appropriate conformation (see Figure 2). This is the prototypical Prins cyclization, and intermediates related to **1** should now be considered for many cyclizations leading to 4-substituted tetrahydropyrans (eq 1). It has previously been assumed that cyclization is concerted with nucleophilic capture although this might be expected to lead to unfavorable entropies of activation.[10]

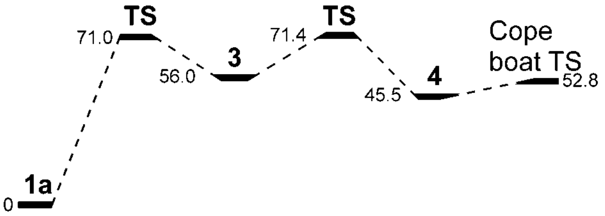
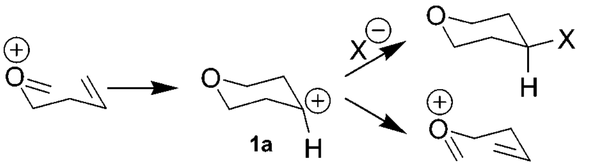


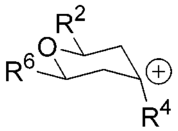
Figure 2. Gas-phase relative energies (kJ/mol) of **1a**, **3**, **4**, the transition states (TS) connecting them, and the TS for the oxonia-Cope rearrangement in the boat series.



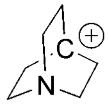
(1)

The Prins cyclization has attracted attention recently from synthetic chemists because the stereochemistry of substituted products is well-controlled and can be rationalized through a chairlike transition state (or intermediate).[6,7] The boat analogue of **1a** is 52.8 kJ/mol less stable, and is the transition state (TS) for rapid, degenerate, oxonia-Cope rearrangement of the π-complex twist like structure **4** (see Figure 1c). Note that the energy difference between **1a** and **4** is almost twice the calculated difference between the chair and twist forms of tetrahydropyran or cyclohexane (24.9 and 27.2 kJ/mol, respectively).

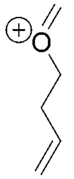
Prins cyclizations may be accompanied by oxonia-Cope rearrangements,[7,11] and species related to **1** can be intermediates in these processes (eq 1). There has been extensive debate concerning the chameleonic[12] (or centauric[13]) nature of the Cope transition state, and a continuing search for intermediates. Using isotopic perturbation methods, Quast et al.[14] have made a strong case for co-occurrence of both localized and delocalized species in 2,4,6,8-tetrasubstituted barbaralanes. In these examples, the transition state resembles two allyl radicals due to the release of cyclopropane ring strain. The transition state **5** for Cope rearrangement of 1,5-hexadiene is still much more open than **1a** with partial $CH_2{-}CH_2$ bonds 1.97 Å long,[12] but B3LYP/6-31G* calculations for 2,5-dicyano-1,5-hexadiene predict an intermediate resembling cation **1**, with even shorter $CH_2{-}CH_2$ bonds (1.575 Å).[12] Finally, the role played by **1a** is reminiscent of the zwitterion intermediates identified by Gompper's group in the reactions of 2-donor 5-acceptor substituted hexa-1,5-dienes.[15]



1a, R^2 R^4=R^6=H
1b, R^2=R^6=H, R^4=Me
1c, R^2=R^6=Me, R^4=H
1d, R^2=Me, R^4=R^6=H

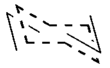


2



3

4



5

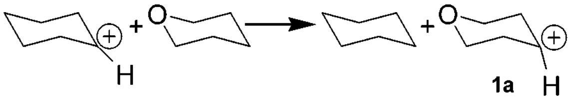
It is interesting to note that the NICS value for **5** (−27)[16] is significantly higher than that for **1**. Aromaticity in these species is gained *at the expense* of σ-bonding in the $CH_2{-}CH_2$ bonds, and

---

* Corresponding author. E-mail: rog.alder@bris.ac.uk.

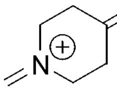
10.1021/ja025902+ CCC: $22.00 © 2002 American Chemical Society

extraordinary thermodynamic stability should not be expected for **1**. The solvolysis rate of 4-tetrahydropyranyl *p*-toluenesulfonate in acetic acid at 85 °C is only 0.03 that of cyclohexyl *p*-toluenesulfonate,[17] and we calculate that the isodesmic reaction in eq 2 is endothermic by 2.4 kJ/mol (8.2 kJ/mol in water) in satisfactory agreement with this.

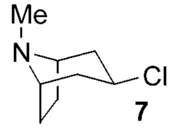


(2)

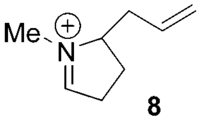
Cations related to **1** are subject to the usual strong effects of alkyl substitution on carbocation stability. Thus 4-methyl ion **1b** is 97 kJ/mol more stable than open forms, whereas 2-methyl and 2,6-dimethyl substitution stabilize open forms. *cis*-2,6-Dimethyl-4-tetrahydropyranyl cation **1c** is 13.4 kJ/mol less stable than the most stable opened form, a π-complex that retains interaction between the electrophilic $O-CH_2^+$ group and the alkene. Here we seem to have an oxonia-Cope rearrangement with a genuine intermediate, since the closed form is still protected by an activation barrier of 1.9 kJ/mol for ring opening. The closed 2-methyl cation **1d** is quite unsymmetrical, with the CHMe-CH_2 bond much longer (1.765 Å) than the CH_2-CH_2 bond (1.633 Å). This cation is still an energy minimum, but is unstable with respect to the opened form by 15.1 kJ/mol, and the activation energy for opening in this direction is extremely small (less than 1 kJ/mol).



6

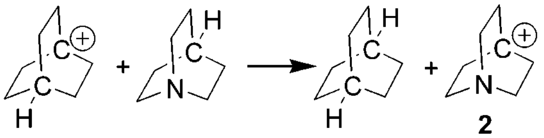


7

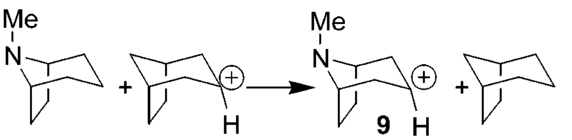


8

The Prins cyclization is the reverse of a Grob fragmentation, and the identification of an intermediate in the former raises the question of similar intermediates being involved in the latter. In his classic studies,[9] Grob distinguished stepwise and synchronous fragmentations, with the latter involving perfect alignment for through-bond coupling in the transition state, and being subject to what was termed frangiomeric acceleration. 4-Chloroquinuclidine reacts 5 × 10^4 times faster than 1-chlorobicyclo[2.2.2]octane; the frangiomeric effect (estimated to be 10^5) in this case is the largest recorded. However, B3LYP/6-31G* calculations find **2** to be an energy minimum, with a small, but real, activation energy (4.0 kJ/mol; 4.7 kJ/mol in water) for fragmentation to **6** (exothermic by 80.1 kJ/mol). Moreover, the isodesmic reaction in eq 3 is exothermic by 37 kJ/mol, corresponding to an equilibrium constant of $10^{6.5}$ neglecting symmetry and entropy effects. Thus the Grob fragmentation may be stepwise even in this highly favorable case.



(3)



(4)

However, we do *not* claim that all Grob fragmentations are stepwise; in fact the solvolysis of **7** leading to **8** may be a real case of synchronous fragmentation, since B3LYP/6-31G* calculations indicate that **9** (see eq 4) is a transition state for the Cope rearrangement of **8** (activation energy 85.3 kJ/mol), and not an intermediate. Grob reports that solvolysis of **7** is 1.35 × 10^4 faster than solvolysis of the corresponding chloride with NMe replaced by CH_2; this system has the second highest frangiomeric acceleration after the quinuclidinyl system. However, the B3LYP calculations suggest that the fragmentation process is only incidental to the acceleration; the isodesmic reaction shown in eq 4 is exothermic by 84 kJ/mol, so that through-bond stabilization is more than enough to explain the acceleration.

In summary, 4-oxa- and 4-aza-cyclohexyl cations such as **1** and **2** in which a lone pair on the heteroatom and the carbocation center can interact via the CH_2-CH_2 bonds represent a novel type of aromatic system, and can be intermediates in Prins cyclizations, Grob fragmentations, and Cope rearrangements. Ions such as **2** might be detected by trapping experiments and NMR observation of suitably substituted derivatives of **1** may be possible if 1,2-shifts leading to more stable species can be blocked (**1** is 100 kJ/mol less stable than the well-known 2-tetrahydropyranyl cation).

Acknowledgment. We thank EPSRC for a studentship under grant GR/L75191.

Supporting Information Available: Cartesian coordinates and energies for **1a**−**d**, **2**, **4**, **8**, and **9** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Unless mentioned otherwise, all calculations were carried out using Jaguar 4.1 (Schrödinger, Inc.: Portland, OR, 2000). All species were characterized using full geometry optimization followed by frequency calculations at the B3LYP/6-31G* level. Calculations simulating water solvation used the Poisson−Boltzmann continuum model as implemented in Jaguar. Sample calculations using larger basis sets and other density functionals did not lead to significantly different geometries or energies. Unlike the biradical-like Cope transition states, ions such as **1a** can be described by a single Lewis structure with all electrons in pairs; accordingly, restricted singlet "wavefunctions" were used throughout.

(2) For a discussion of "hyperconjomers" see: Rauk, A.; Sorensen, T. S.; Schleyer, P. V. *J. Chem. Soc., Perkin Trans. 2* **2001**, 869.

(3) Schleyer, P. V.; Maerker, C.; Dransfeld, A.; Jiao, H. J.; Hommes, N. *J. Am. Chem. Soc.* **1996**, *118*, 6317. NICS calculations were carried out at the B3LYP/6-31G* level of theory at the optimized geometries, using the simple GIAO method as implemented in Gaussian 98 (Revision A.7; Gaussian, Inc.: Pittsburgh, PA, 1998).

(4) Hoffmann, R. *Acc. Chem. Res.* **1971**, *4*, 1. Gleiter, R. *Pure Appl. Chem.* **1987**, *59*, 1585. Gleiter, R.; Schafer, W. *Acc. Chem. Res.* **1990**, *23*, 369.

(5) Snider, B. B. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: New York, 1991; Vol. 2, p 527; Winstead, R. C.; Simpson, T. H.; Lock, G. A.; Schiavelli, M. D.; Thompson, D. W. *J. Org. Chem.* **1986**, *51*, 275. Bunnelle, W. H.; Seamon, D. W.; Mohler, D. L.; Ball, T. F.; Thompson, D. W. *Tetrahedron Lett.* **1984**, *25*, 2653.

(6) Al-Mutairi, E. H.; Crosby, S. R.; Darzi, J.; Harding, J. R.; Hughes, R. A.; King, C. D.; Simpson, T. J.; Smith, R. W.; Willis, C. L. *Chem. Commun.* **2001**, 835. Hu, Y. Q.; Skalitzky, D. J.; Rychnovsky, S. D. *Tetrahedron Lett.* **1996**, *37*, 8679. Jaber, J. J.; Mitsui, K.; Rychnovsky, S. D. *J. Org. Chem.* **2001**, *66*, 4679. Kopecky, D. J.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2001**, *123*, 8420. Rychnovsky, S. D.; Hu, Y. Q.; Ellsworth, B. *Tetrahedron Lett.* **1998**, *39*, 7271. Rychnovsky, S. D.; Thomas, C. R. *Org. Lett.* **2000**, *2*, 1217.

(7) Rychnovsky, S. D.; Marumoto, S.; Jaber, J. J. *Org. Lett.* **2001**, *3*, 3815.

(8) Grob, C. A.; Kostka, K.; Kuhnen, F. *Helv. Chim. Acta* **1970**, *53*, 608. Grob, C. A.; Kostka, K. *Helv. Chim. Acta* **1970**, *53*, 613.

(9) Grob, C. A. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 535.

(10) In a recent paper, "pre-folded" intermediates have been proposed for a related cyclization on the basis of B3LYP/6-31G* calculations: Kjellgren, J.; Szabo, K. *Tetrahedron Lett.* **2002**, *43*, 1123.

(11) Crosby, S. R.; Harding, J. R.; King, C. D.; Parker, G. D.; Willis, C. L. *Org. Lett.* **2002**, *4*, 577.

(12) Hrovat, D. A.; Beno, B. R.; Lange, H.; Yoo, H. Y.; Houk, K. N.; Borden, W. T. *J. Am. Chem. Soc.* **1999**, *121*, 10529.

(13) Doering, W. V.; Wang, Y. H. *J. Am. Chem. Soc.* **1999**, *121*, 10967.

(14) Quast, H.; Seefelder, M.; Becker, C.; Heubes, M.; Peters, E. M.; Peters, K. *Eur. J. Org. Chem.* **1999**, 2763. Quast, H.; Seefelder, M.; Becker, C.; Heubes, M.; Peters, E. M.; Peters, K. *Eur. J. Org. Chem.* **2000**, 691. Quast, H.; Seefelder, M. *Angew. Chem., Int. Ed.* **1999**, *38*, 1064.

(15) Gompper, R.; Wagner, H. U. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1437.

(16) Jiao, H. J.; Schleyer, P. V. *J. Phys. Org. Chem.* **1998**, *11*, 655.

(17) Tarbell, D. S.; Hazen, J. R. *J. Am. Chem. Soc.* **1969**, *91*, 7657.

JA025902+