Stabilization of the phenyl cation by hyperconjugation

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Scheme II[a]

2 $\xrightarrow[65\%]{a,b}$ **9** $\xrightarrow[79\%]{c-e}$

10 : R = Me
11 : R = H

$\xrightarrow[37\%]{f}$ **12** $\xrightarrow[98\%]{g}$

13

$\xrightarrow[55\%]{h,i}$ **14**

$\xrightarrow[42\%]{j,i,h,k,l}$ **15**
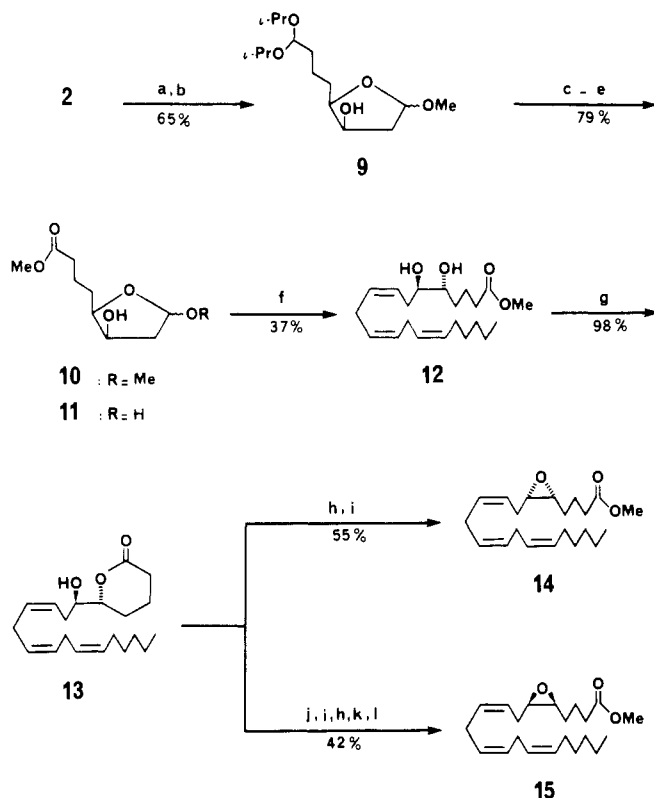
[a] 16, BuLi, THF/HMPA 4:1, –78 → 23 °C, 12 h. [b] 5% Pd/C, 1 atm H₂, EtOH, 2 h. [c] HCO₂H, MCPBA, THF/H₂O 3:1, 35 h; Me₂S, 30 min. [d] Me₂SO₄, NaHCO₃, 23 °C, 10 h. [e] HCO₂H, THF/H₂O 1:1, 65 °C, 2.5 h. [f] 17, LiN(SiMe₃)₂, THF/HMPA, 4:1, –78 → 23 °C, 12 h; MeOH, 2 h. [g] TsOH, PhCH₃, 3 Å Mol. Sieves, reflux, 0.5 h. [h] TsCl, py, DMAP, CH₂Cl₂, 12–48 h. [i] Et₃N, MeOH, 12 h. [j] DHP, PPTS, CH₂Cl₂, 12 h. [k] Amberlyst H-15, MeOH, 12 h. [l] NaOMe, MeOH, 0 °C, 1 h.

(THF/HMPA 4:1, –78 to 23 °C over 12 h) with the ylide from dodeca-(Z,Z)-3,6-dien-1-yltriphenylphosphonium bromide[20] (**17**), anhydrous methanol quench (23 °C, 2 h), and chromatography secured methyl 5(R),6(R)-dihydroxyeicosatrienoate[16] (**12**) (37%). Differentiation of the diol by lactonization to **13** (98%), tosylation, and treatment with Et₃N/MeOH afforded methyl 5(R),6(S)-epoxyeicosatrienoate (**14**)[16] (55%).

Lactone **13** was also exploited for the preparation of methyl 5(S),6(R)-epoxyeicosatrienoate[16] (**15**) by the sequence: tetrahydropyranylation, lactone methanolysis, tosylation, THP removal, and epoxide closure under the influence of NaOMe (42% from **13**).

The foregoing syntheses provide ready access to sufficient quantities of the epoxygenase metabolites for pharmacological and biological testing. Investigations into their possible physiological role and metabolic fate will be reported in due course.

Supplementary Material Available: Chromatographic, microanalytical, and spectral data for **2–7**, **9**, **10**, **12**, **14**, and **15** (2 pages). Ordering information is given on any current masthead page.

(20) Obtained in 60–65% overall yield from 2-octyn-1-ol by modification of the procedures in ref 15.

Stabilization of the Phenyl Cation by Hyperconjugation[†]

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Aryl cations **1**, have attracted considerable experimental[1,2] and theoretical interest.[3,4] In solution, **1** can be generated by the decomposition of arenediazonium ions,[1] but the numerous attempts to generate these species by the solvolysis of aryl precursors have failed.[2] These failures result from the inherent low stability of the phenyl cation (**1a**), which in the gas phase is 21–25 kcal/mol less stable than the 2-propenyl cation (**2**).[5] Ab initio calculations[6,7]

1a, R = H ; **1b**, R = CH₃
1c, R = SiH₃

2

3

4

5
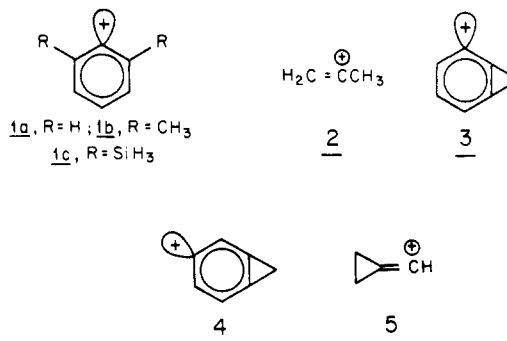
give an energy difference of 27 kcal/mol at MP2/6-31G*.[8a,b] **2** is among the least stable vinyl cations that can be generated by

(1) (a) Zollinger, H. In "The Chemistry of Triple-bonded Functional Groups"; Patai, S., Rappoport, Z., Eds.; Wiley: London, 1983; Suppl. C. (b) Szele, I.; Zollinger, H. *Helv. Chim. Acta* **1981**, *64*, 2728 and references therein. (c) Fornarini, S.; Speranza, M. *J. Chem. Soc., Perkin Trans. 2* **1984**, 171. (d) Speranza, M.; Keheyan, Y.; Angelini, G. *J. Am. Chem. Soc.* **1983**, *105*, 6377. (e) Depke, G.; Hanack, M.; Hummer, W.; Schwarz, H. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 786. (f) Haberfield, P.; Cardona, C.; Bell, M. *J. Org. Chem.* **1984**, *49*, 78.

(2) (a) Streitwieser, A.; Dafforn, A. *Tetrahedron Lett.* **1976**, 1435. (b) Subramanian, L. R.; Hanack, M.; Chang, L. W. K.; Imhoff, M. A.; Schleyer, P. v. R.; Effenberger, F.; Kurtz, W.; Stang, P. J.; Dueber, T. E. *J. Org. Chem.* **1976**, *41*, 4099. (c) Laali, K.; Szele, I.; Yoshida, K. *Helv. Chim. Acta* **1983**, *66*, 1710. (d) Note, however, the successful generation of a phenyl cation via the solvolytic cyclization of a dienynyl triflate: Hanack, M.; Holweger, W. *J. Chem. Soc., Chem. Commun.* **1981**, 713.

(3) (a) Dill, J. D.; Schleyer, P. v. R.; Binkley, J. S.; Seeger, R.; Pople, J. A.; Haselbach, E. *J. Am. Chem. Soc.* **1976**, *98*, 5428. (b) Dewar, M. J. S.; Reynolds, C. H. *J. Am. Chem. Soc.* **1982**, *104*, 3244. (c) Schleyer, P. v. R.; Kos, A. J.; Raghavachari, K. *J. Chem. Soc., Chem. Commun.* **1983**, 1296.

(4) Gleiter, R.; Hoffmann, R.; Stohrer, W. D. *Chem. Ber.* **1972**, *105*, 8.

(5) (a) Relative to the corresponding hydrocarbons. (b) Based on $\Delta H_f^\circ(C_6H_5^+)$ = 270 kcal/mol: Beauchamp, J. L. *Adv. Mass. Spectrom.* **1974**, *6*, 717. A lower value of $\Delta H_f^\circ(C_6H_5^+)$ = 266 kcal/mol was also reported: Sergeev, Y. L.; Akopyan, M. E.; Vilesov, F. I.; Kleimenov, V. I. *Opt. Spectrosc. (Engl. Transl.)* **1970**, *29*, 63. $\Delta H_f^\circ(2)$ = 230 kcal/mol: Aue, D. H.; Bowers, M. T. In "Gas Phase Ion Chemistry"; Bowers, M. T., Ed.; Academic Press: New York, 1979; Vol. 2, Chapter 9. $\Delta H_f^\circ(C_6H_6)$ = 19.8 kcal/mol, $\Delta H_f^\circ(CH_2=CHCH_3)$ = 4.9 kcal/mol: Cox, J. D.; Pilcher, G. "Thermochemistry of Organic and Organometallic Compounds"; Academic Press: New York, 1970.

(6) We used the GAUSSIAN 80 series of programs: Binkley, J. S.; Whiteside, R. M.; Krishnan, R.; Seeger, R.; DeFrees, D. J.; Schlegel, H. B.; Topiol, S.; Kahn, L. R.; Pople, J. A. *QCPE*, **1980**, *13*, 406.

(7) (a) Throughout the paper the geometries of all species were fully optimized with the 3-21G basis sets.[7b] (b) Binkley, J. S.; Pople, J. A.; Hehre, W. J. *J. Am. Chem. Soc.* **1980**, *102*, 939. Gordon, M. S.; Binkley, J. S.; Pople, J. A.; Pietro, W. J.; Hehre, W. J. *Ibid.* **1982**, *104*, 2797.

(8) (a) 6-31G*: Hariharan, P. C.; Pople, J. A. *Theor. Chim. Acta* **1973**, *28*, 213. Pietro, W. J.; Francl, M. M.; Hehre, W. J.; DeFrees, D. J.; Pople, J. A.; Binkley, J. S. *J. Am. Chem. Soc.* **1982**, *104*, 5039. (b) MP2: Frisch, M. J.; Krishnan, R.; Pople, J. A. *Chem. Phys. Lett.* **1980**, *75*, 66 and references therein. (c) Due to the size of **3** we could not carry out a 6-31G* calculation. We have therefore constructed a smaller fully polarized 3-21G* basis set by adding a set of six d-type functions taken from 6-31G*.[8a] We follow the guidelines of in ref 8a. In cases where 6-31G* and 3-21G* calculations are both available the results were uniformly close. A similarly constructed 3-21G* basis set was recently used by: Bachrach, S. M.; Streitwieser, A. *Ibid.* **1985**, *107*, 1186.

solvolysis.[9] It is therefore reasonable to expect that aryl cations which are comparable in stability to **2** can be produced via solvolysis.[10]

To achieve this goal one should design a substituted aryl cation that is more stable than **1a** by at least 25 kcal/mol. The major difficulty in reaching such large stabilization energies is obvious: The most effective substitution site—the α-position—is blocked. **1** can be stabilized only by the β- or the γ-substituents. It was suggested that meta electron-donating substituents can stabilize the phenyl cation substantially by "through bond interactions".[4] Disappointingly, aryl triflates which were prepared according to this theoretical proposal failed to produce the desired **1**.[2b] It was concluded that "substituents are not very effective in providing significant stabilization of singlet aryl cations".[2b]

We use here ab initio calculations to point out two substitution patterns that stabilize the phenyl cation sufficiently to allow its generation by solvolysis.[10] One of these theoretical predictions has been verified as described in the accompanying paper[11] and the other is under active investigation.

Hyperconjugation between the empty $2p(C^+)$ orbital and the β-C–R bonds is the key to stabilizing the phenyl cation. According to PMO theory the hyperconjugative stabilization (ΔE) is proportional to $S^2/\Delta\epsilon$, where $\Delta\epsilon$ is the energy difference between the interacting orbitals and S is their overlap.[12] A β-C–R orbital that lies higher in energy than a C–H orbital is expected (due to a smaller $\Delta\epsilon$) to stabilize the phenyl cation. In agreement with this qualitative argument **1b** is more stable than **1a** by 10 kcal/mol at 3-21G.[5a] C–Si bond orbitals are generally higher in energy than C–C bond orbitals so that β-silyl substituents are likely to be even more stabilizing than β-alkyl groups.[13,14] Indeed, **1c** is more stable than **1b** by 15 kcal/mol and comparable in stability to **2** (3-21G). Furthermore, correlation energy (CE) stabilizes β-silyl cations (e.g., $H_3SiCH{=}CCH_3^+$) relative to the corresponding β-alkyl cations (e.g., $H_3CCH{=}CCH_3^+$) by 7–10 kcal/mol. Using this correction for the CE, we conclude that **1c** is by a few kilocalories per mole more stable than **2**, and it is therefore amenable to generation by solvolysis.[10] This prediction has recently been verified by Sonoda et al. who showed that the solvolysis of 2,6-bis(trimethylsilyl)phenyl triflate in TFE proceeds via an aryl cation intermediate.[11,15] The same should hold also for the corresponding tin derivatives.[16] 2-(Trimethylsilyl)- and 2,6-dimethylaryl triflates (yielding **1b**) are unreactive[11] in complete agreement with the calculations.

Alternatively, the phenyl cation can be stabilized through hyperconjugation with high-lying strained carbon–carbon bonds[17] as in **3**. The major stabilizing interaction, that between the empty $2p(C^+)$ orbital and the highest occupied Walsh orbital of the fused cyclopropene ring, is shown schematically in **6**. The resulting stabilization is indeed large; **3** is more stable than **1a** by 23 kcal/mol at 3-21G*.[8c] Similarly, **3** is by 22 kcal/mol (3-21G*) more stable than the isomeric **4** where hyperconjugation with the cyclopropene ring is prohibited. Experience with the analogous
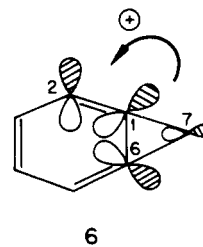
6

5 suggests that the addition of correlation energy should stabilize **3** further. As **5** is more stable than **2** by 8 kcal/mol at 6-31G* but by 14 kcal/mol at MP2/6-31G* we estimate that **3** is by 5 kcal/mol more stable than **2**. Thus, **3** is well within the stability range which is suitable for solvolytic generation. Interaction **6** induces interesting structural deformations. Relative to the corresponding bonds in cyclopropabenzene[18] the C_1–C_6 bond in **3** is drastically elongated (by 0.34 Å), while the C_1–C_2 bond is shortened by 0.14 Å.[19] The exceptionally long C_1–C_6 distance of 1.67 Å stabilizes **3** because it partially relieves the strain in the cyclopropabenzene skeleton.[18] Severe distortions in the bond angles, such as flatening at C_2, also occur. Experiments aimed at generating **3** by solvolysis, in superacid media and in the gas phase, are in progress.

Note Added in Proof. While this paper was in press an important paper on the magnitude and origin of the β-silicon effect on carbenium ions was published.[20] The reader is refered to this paper for a more complete discussion (than possible in a communication) on the hyperconjugative stabilization by silicon. The conclusions of Jorgensen et al. regarding the magnitude and effect of correlation on the β-silicon effect are similar to ours.

Registry No. 1a, 17333-73-2; **1c,** 97521-77-2; **3,** 97521-78-3.

(18) Apeloig, Y.; Arad, D., manuscript in preparation.
(19) The C_1–C_7 bond length remains essentially unchanged, and the C_6–C_7 distance is shortened by 0.05 Å.
(20) Wierschke, S. G.; Chandrasekhar, J.; Jorgensen, W. L. *J. Am. Chem. Soc.* **1985**, *107*, 1496.

A First Example of Generating Aryl Cations in the Solvolysis of Aryl Triflates in Trifluoroethanol[1]

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The solvolytic generation of aryl cations has long been an unrealized goal. The method of generating these cations in solution so far is restricted (except for a novel example of the solvolysis of dienynyl triflates[2]) to the dediazoniation of arenediazonium ions.[3] Several research groups have attempted to generate these cations in the solvolysis of aryl substrates by using various "super"

(9) Stang, P. J.; Rappoport, Z.; Hanack, M.; Subramanian, L. R. "Vinyl Cations"; Academic Press: New York, 1979.
(10) The calculations hold strictly only in the gas phase. However, numerous studies have shown the existence of a linear correlation between the free enthalpies (or rates) of solvolysis and the gas-phase stabilities (either experimental or calculated) of the corresponding cations. E.g.: Mayr, H.; Schneider, R.; Wilhelm, D.; Schleyer, P. v. R. *J. Org. Chem.* **1981**, *46*, 5336.
(11) Himeshida, Y.; Kobayashi, H.; Sonoda, T., following paper in this issue.
(12) Fleming, I. In "Frontier Orbitals and Organic Chemical Reactions"; Wiley: New York, 1976; pp 80–85.
(13) Apeloig, Y.; Schleyer, P. v. R.; Pople, J. A. *J. Am. Chem. Soc.* **1977**, *99*, 5901. Apeloig, Y.; Schreiber, R. *Tetrahedron Lett.* **1978**, 4555.
(14) The ability of β-silyl substituents to stabilize carbenium ions is known but the degree of stabilization has not yet been evaluated quantitatively. See: Lambert, J. B.; Finzel, R. B. *J. Am. Chem. Soc.* **1982**, *104*, 2020 and references therein.
(15) The relief of ground-state strain upon solvolysis of 2,6-bis(trimethylsilyl)phenyl triflate is probably small. However, this factor may be more important in other 2,6-disubstituted aryl triflates.
(16) Cauletti, C.; Furlani, C.; Granozzi, G.; Sebald, A.; Wrackmeyer, B. *Organometallics* **1985**, *4*, 290.
(17) (a) Gleiter, R. *Top. Curr. Chem.* **1979**, *86*, 197. (b) Gleiter, R.; Jahne, G.; Oda, M.; Iyoda, M. *J. Org. Chem.* **1985**, *50*, 678.

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‡ Research Institute of Industrial Science.
(1) Presented at the VII IUPAC Conference on Physical Organic Chemistry, Auckland, New Zealand, August 1984, Abstr. A17.
(2) (a) Hanack, M.; Michel, U. *Angew. Chem.* **1979**, *91*, 928. (b) Hanack, M.; Holweger, W. J. *J. Chem. Soc., Chem. Commun.* **1981**, *713*.
(3) Reviews: (a) Hegarty, A. F. In "The Chemistry of Diazonium and Diazo Groups"; Patai, S., Ed.; Wiley: London, 1978; p 511. (b) Zollinger, H. In "The Chemistry of Triple-Bonded Functional Groups"; Patai, S., Rappoport, Z., Eds.; Wiley: London, 1983; Suppl. C, p 603.