Diazo-coupling Reactions of Cycloheptatrienols: a Combined Experimental and Theoretical Study

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Isomeric cycloheptatrienols **1**, **2** and **3** are found to undergo ketonizations as well as diazo-coupling reactions *via* three different pathways; experiments and *ab initio* calculations suggest that the 2-hydroxy group provides a small but effective stabilization effect on norcaradiene **11**.

Simple enols[1] are important intermediates in many organic reactions. Over the last one and half decades, many methods have been developed for the generation of these unstable species in solutions.[2] However, apart from ketonization, few of their reactions have been studied directly. Cederstav and Novak recently observed radical-initiated polymerization from a metastable solution of vinyl alcohol, the simplest enol.[3] We now report for the first time a direct investigation of the diazo-coupling reaction of three possibly homoaromatic cycloheptatrienols: **1**, **2** and **3**.

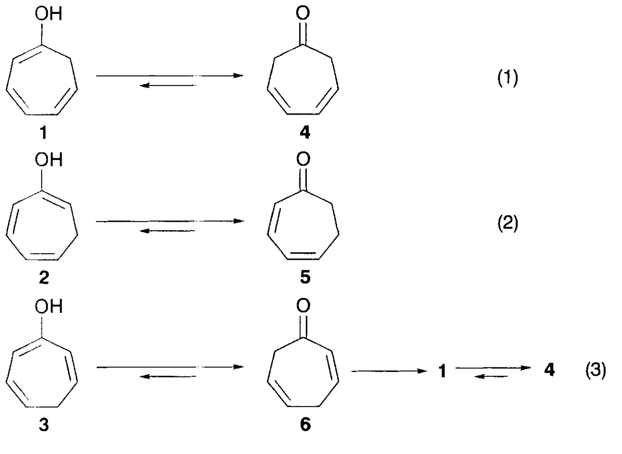
The three isomeric enols were generated by controlled acid-catalysed hydrolyses of their corresponding trimethylsilyl enol ethers in DMSO solutions.[4] Upon addition of appropriate amounts of DCl, CF_3CO_2D or HCl (*e.g. ca.* 5×10^{-4} mol dm^{-3}), ^{1}H NMR spectroscopy indicated that the hydrolyses were significantly faster than the subsequent ketonizations of the enols, and the reaction mixtures contained at least 85–95% of the enols when the hydrolyses were complete, which in general took about 2–5 min. The reaction mixtures were then used immediately or stored in liquid nitrogen to avoid further ketonization. Independent NMR experiments showed that the ketonization took place by α-protonation in all cases to give the corresponding cycloheptadienones **4**, **5** and **6**, respectively [eqns. (1)–(3)]. However, **6** is unstable at room temperature and isomerized to ketone **4** with enol **1** as an intermediate (eqn. 3).

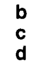
The diazo-coupling reactions were carried out by mixing a solution of freshly generated **1**, **2** or **3** with freshly prepared *p*-substituted-benzenediazonium ion **7** in water at −5 to 0 °C. When **1** was allowed to react with one equiv. of **7** for 15 min, monophenylhydrazone **9** was isolated as the major product (65%) along with a small amount of bisphenylhydrazone **10** (< 5%), which was also isolated in higher yield (45%) upon the treatment of an excess of **7** for a longer reaction time (45 min).§ Apparently, electrophilic attack of the diazonium ion **7** on **1** also took place solely at the α-position to give **8** as an initial product (Scheme 1). Further enolization of **8** followed by coupling with another equiv. of **7** led to the formation of the biscoupling product **10**. The observed first-order rate constants for the formation of the coupling product (monitoring at 400 nm) were found to be inversely proportional to [H$^+$], suggesting that the enolate anion of **1** is the actual reactive form. The second-order rate constants for coupling of the enolate anion with **7** were calculated to be close to the diffusion-controlled limit (8×10^8 to 2.8×10^9 dm^3 mol^{-1} s^{-1}), from which the reaction constant ρ_{enolate} was determined to be 1.15.

Diazo-coupling of enol **3** under similar conditions (1 equiv. of **7**, 2 h) gave the same product **9** (20%) and **10** (45%). The observed first-order rate constant for the formation of the coupling product (400 nm, 2.5×10^{-4} s^{-1}) is about 10 times less than that of the ketonization of **3** under the same conditions (2.3×10^{-3} s^{-1}). Therefore, it is concluded that **3** did not couple with **7** directly; instead, it ketonized to **6** first. The actual coupling took place *via* enol **1**, the intermediate in the isomerization of **6** to **4** (Scheme 2, *vide supra*).

Enol **2** reacted with 1 equiv. of **7d** to give **12** (60 min, 85%).§ Zero-order kinetics (400 nm) were observed for over 90% of the reaction, and these kinetics were independent of the concentration of **7d** (concentration of **3** was fixed but remained at least 10 times higher than that of **7d**). These observations are consistent with a mechanism involving rate-determining conversion of cycloheptatrienol **2** to norcaradienol **11** which then coupled with the diazonium ion (Scheme 3).

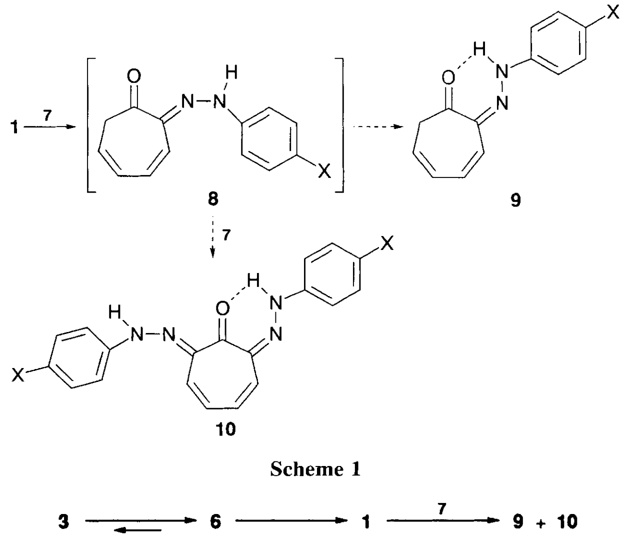
The existence of homoaromaticity in cycloheptatriene has been sometimes been claimed[5] and sometimes rejected[6,7] in the





7

	X
a	H
b	MeO
c	Me
d	Cl



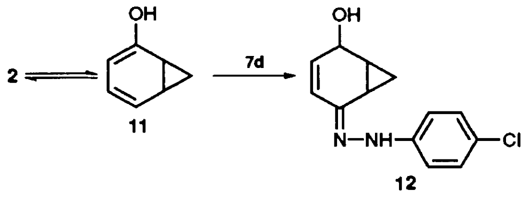
Scheme 1

$$3 \rightleftharpoons 6 \longrightarrow 1 \xrightarrow{7} 9 + 10$$

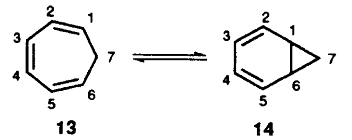
Scheme 2

literature. Our study suggests that *homoaromatic stabilization in cycloheptatriene, if any, must be very insignificant.* Evidence comes from the dramatic difference in reactivities of the three isomeric cycloheptatrienols towards electrophilic addition, including both ketonization and diazo-coupling reaction. Moreover, the reaction constant for the coupling of the enolate anion of **1** determined in this work ($\rho_{\text{enolate}} = 1.15$) is much less than that for the coupling of phenolate anion[8] ($\rho = 4.2$) and is close to that for the coupling of the enolate anion derived from acetone[9] ($\rho = 1.89$), indicating that the formation of the transition state from the aromatic phenolate anion has a much greater activation energy than formation of the transition state from the enolate anion of **1**.

There has been considerable interest in the substituent effect upon the equilibrium between cycloheptatrienes and norcaradienes both experimentally[10] and theoretically.[7,11] Klärner *et al.* has demonstrated that two trimethylsilyloxy groups substituted at the 2- and 5- positions were capable of shifting the equilibrium towards the norcaradiene side.[12] The fact that only the norcaradiene derivative **11** derived from enol **2** was trapped in this study suggests that a 2-hydroxy group possibly has a significant effect on the stabilization of the norcaradiene. We have carried out some preliminary *ab initio* calculations[13] and the topological properties of the electron density distribution have been analysed in terms of the theory of atoms in molecules[14] on the valence tautomer **2** $\rightleftharpoons$ **11**. The energy difference $\Delta E(\mathbf{2},\mathbf{11}) = E(\mathbf{2}) - E(\mathbf{11})$ (-5.26, -5.09, -1.95 and -2.79 kcal mol^{-1} at 6-31G*//6-31G*, 6-31G**//6-31G*, MP2/6-31G**//6-31G* and MP2/6-31G*//MP2/6-31G* levels of theory respectively; 1 cal = 4.184 J) is less than $\Delta E(\mathbf{13},\mathbf{14})$ for the parent unsubstituted system **13** $\rightleftharpoons$ **14** (-5.89, -5.78, -2.88 and -3.66 kcal mol^{-1} at the same level of theory, respectively), suggesting that the equilibrium concentration of **11** is higher than that of **14**. In addition, at the MP2/6-31G*//MP2/6-31G* level of theory, the electron density at the bond critical point of the C(1)–C(6) bond (ρ_b) for **11** (0.2202 a.u.) is higher than that of **14** (0.2129 a.u.). This, according to our previous finding that the electron density at the bond critical point of the C(1)–C(6) bond (the homoaromatic bond) correlates well with the relative stabilities of norcaradienes over cycloheptatrienes,[11] indicates that the 2-hydroxy group does provide a small but effective stabilization effect on the norcaradiene **11**, probably by acting both as a σ-acceptor and a π-donor.[11] Such a stabilization effect may become much more significant in polar solvents capable of acting as H-bonding acceptors, since upon deprotonation the resultant hydroxide group becomes a much more effective π-electron donor.



Scheme 3



In summary, we have shown that the ketonization and diazo-coupling reactions of three cycloheptatrienols **1**, **2** and **3** proceed *via* three different pathways. Further experimental and theoretical investigations on the substituent effect of hydroxy groups are currently in progress.

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Footnotes

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§ Compounds **9**, **10** and **12** were isolated by extraction of the reaction mixtures with ether and purified by column chromatography, and were characterized by spectroscopic (^{1}H, ^{13}C and ^{15}N NMR, MS and HRMS) and elemental analyses.

References

1 H. Hart, *Chem Rev.*, 1979, **79**, 515; H. Hart and M. Sasaoka, *J. Chem. Educ.*, 1980, **57**, 685.
2 B. Capon, in *The Chemistry of Enols*, ed. Z. Rappoport, Wiley, Chichester, 1990, ch. 5, p. 307; J. R. Keeffe and A. J. Kresge, in *The Chemistry of Enols*, ed. Z. Rappoport, Wiley, Chichester, 1990, ch. 7, pp. 418–423.
3 A. K. Cederstav and B. M. Novak, *J. Am. Chem. Soc.*, 1994, **116**, 4073.
4 B. Capon, B.-Z. Guo, F.-C. Kwok and Z.-P. Wu, *Pure Appl. Chem.*, 1987, **12**, 1557.
5 R. B. Turner, W. R. Meador, W von E. Doering, L. H. Knox, J. R. Mayer and D. W. Wiley, *J. Am. Chem. Soc.*, 1957, **79**, 4127; A. G. Harrison, L. R. Honnen, H. J. Dauben and F. P. Lossing, *J. Am. Chem. Soc.*,1960, **82**, 5593; R. B. Turner, B. J. Mallon, M. Tichy, W von E. Doering, W. R. Roth and G. Schroder, *J. Am. Chem. Soc.*, 1973, **95**, 8605; H. J. Lindner, *Tetrahedron*, 1981, **37**, 535; W. C. Herndon and C. Parkanyi, *Tetrahedron*, 1981, **38**, 2551; W. R. Roth, M. Böhm, H. W. Lennartz and E. Vogel, *Angew Chem., Int. Ed. Engl.*, 1983, **22**, 1007.
6 K. Conrow, *J. Am. Chem. Soc.*, 1961, **83**, 2958; R. F. Childs and I. Pikulik, *Can. J. Chem.*, 1977, **55**, 259; K. N. Houk, R. W. Gandour, R. W. Strozier, N. G. Rondan and L. A. Paquette, *J. Am. Chem. Soc.*, 1979, **101**, 6797.
7 J. M. Schulmann, R. L. Disch and M. L. Sabio, *J. Am. Chem. Soc.*, 1984, **106**, 7696; E. Kraka and D. Cremer, in *The Concepts of the Chemical Bond*, ed. Z. B. Maksic, Part 2, Springer-Verlag, New York, 1990, pp. 452–542.
8 V. Šterba and K. Valter, *Coll. Czech. Chem. Commun.*, 1971, **36**, 282.
9 V. Machácek, O. Machácková and V. Šterba, *Coll. Czech. Chem. Commun.*, 1970, **35**, 2954.
10 G. Maier, *Angew Chem., Int. Ed. Engl.*, 1967, **6**, 402; J. F. Liebman and A. Greenberg, *Chem. Rev.*, 1989, **89**, 1225.
11 T-H. Tang, C. S. Q. Lew, Y-P. Cui, B. Capon and I. G. Csizmadia, *J. Mol. Struct. (Theochem)*, 1994, **305**, 149.
12 F.-G. Klärner, E. K. G. Schmidt and M. A. Rahman, *Angew. Chem., Int. Ed. Engl.*, 1982, **21**, 138.
13 Computation methods can be found in ref. 11.
14 R. F. W. Bader, *Atoms in Molecules: A Quantum Theory*, Clarendon, Oxford, 1990.