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Electron Loss from 1,3,3-Trimethyl-2-azabicyclo[2.2.2]octane Derivatives. Is σ Coupling Thermodynamically Important?

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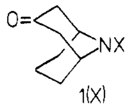
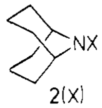
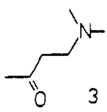
The ease of one-electron oxidation was compared for σ coupled and non-σ-coupled γ-oxopiperidine nitroxides and their saturated analogues (CO → CH_2). For the non-σ-coupled pair, 1,3,3-trimethyl-2-oxyl-2-azabicyclo-[2.2.2]octan-5-one (**9**) has IP_v = 7.29 eV, $E^{\circ\prime}$ = 0.73 V and its CO → CH_2 analogue **11** IP_v = 6.88, $E^{\circ\prime}$ = 0.52 V. The σ-coupled pair 9-oxyl-9-azabicyclo[3.3.1]nonan-3-one (**12**) has IP_v = 7.78 eV, $E^{\circ\prime}$ = 0.83 V and its CO → CH_2 analogue **13** IP_v = 7.39 eV, $E^{\circ\prime}$ = 0.58 V. Replacement of CO by CH_2 in the non-σ-coupled example has as large an effect of IP_v and only a 13% smaller effect on $E^{\circ\prime}$ than in the σ-coupled example, making it appear that a σ-coupled transmission of positive charge from the nitrogen to the carbonyl in the radical ccation is unimportant.

Cookson and co-workers[1] first pointed out that when two π systems and/or lone pairs both overlap with an intervening CC σ bond, a new band appears in the electronic spectrum, and they christened the effect of σ coupling. An example of a σ-coupled γ-keto amine is the 9-azabicyclo-[3.3.1]nonan-3-one system **1**(X). Our interest in this particular system arose from the fact that the radical cations of 9-azabicyclo[3.3.1]octane derivatives **2**(X) are long-lived when X cannot deprotonate,[2] so that the thermodynamics for electron loss can be determined by cyclic voltammetry (CV). The difference in formal potential ($E^{\circ\prime}$) for one-electron transfer for two compounds is proportional to the difference in ΔG° for their electron-transfer equilibria: $23.06\Delta(E^{\circ\prime}, V) = \Delta(\Delta G^\circ_e, \text{kcal/mol})$. We expected that $E^{\circ\prime}$ would be especially sensitive to the presence of the γ-keto group, as the electron-withdrawing effect to the presence of the carbonyl carbon would be transmitted through the CC σ bonds (C_1C_2 and C_4C_5) to the nitrogen, which is highly electron deficient in the radical cation. We expected then, that comparison of $\Delta(E^{\circ\prime}) = E^{\circ\prime}(1) - E^{\circ\prime}(2)$ with that of suitable non-σ-coupled models could establish the thermodynamic importance of σ coupling in these compounds.


1(X)


2(X)

The thermodynamic effect of CO → CH_2 replacement comparing **1**(X) with **2**(X) did prove to depend on the amount of positive charge at the nitrogen to the cation.[3] $\Delta E^{\circ\prime}$ varied from 0.32 δ ($\Delta(\Delta G^\circ_e)$ = 7.4 kcal/mol) for X = *t*-Bu to 0.14 V ($\Delta G^\circ_e)$ = 3.2 kcal/mol) per keto group for the *p*-phenylenediamine derivatives, and for the dimethylamino hydrazines (X = NMe_2), $\Delta E^{\circ\prime}$ was 0.21 V ($\Delta(\Delta G^\circ_e)$ = 4.8 kcal/mol). As model compounds to see whether σ coupling was important in determining $\Delta(\Delta G^\circ_e)$, we compared **3** and **4**, finding that $\Delta(E^{\circ\prime})$ here was only 0.02 V (0.5 kcal/mol).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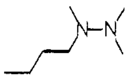
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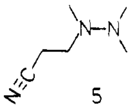
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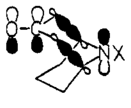
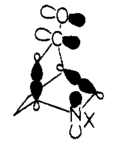
The vapor phase vertical measurement of how hard it is to remove an electron given by photoelectron (PE) spectroscopic IP_v values gave very similar changes for the CO → CH_2 structural change: ΔIP_v was 0.50 V for **1**-(NMe_2) vs. **2**(NMe_2) and 0.47 V for **3** vs. **4**. When a similar comparison was made with the more electron-withdrawing cyano group as the substituent, comparing **5** with **4**, ΔIP_v increased 87% to 0.88 V, but $\Delta E^{\circ\prime}$ was over 10 times as large, 0.23 V (5.3 kcal/mol). Because the cyano group has cylindrical symmetry, σ_{CC} cyano group, π system interaction cannot be "turned off" by CH_2–CN rotation. These experiments were interpreted to imply that σ coupling is very significant in determining the rather large $\Delta E^{\circ\prime}$ values found for CO → CH_2 substitution in comparing **1** with **2**.[3]

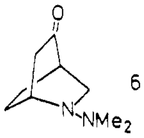
It must be admitted, however, that **3** → **4** is not an especially convincing model for the CO → CH_2 change in **1** → **2**. A much better model would be a non-σ-coupled γ-oxopiperidine. As shown diagramatically in the structures below, the 2-azabicyclo[2.2.2]octan-5-one system is a bicyclic γ-oxopiperidine in which the keto and amino functionalities are held in a non-σ-coupled geometry. In this paper we report PE and CV data on nitroxides in these two geometries and comment on the reasons for different IP_v and $E^{\circ\prime}$ values for these compounds.


9-ABN-3-one
CO, N
σ-coupled


2-ABO-5-one
CO, N
not σ-coupled

Results

To make the thermodynamically significant $E^{\circ\prime}$ measurements, we require radical cations that have long lifetimes under CV conditions (approximately 1 mM in neutral form). For most substituents on nitrogen, this requires Bredt's rule protection because the neutral form deprotonates the radical cation so rapidly. We had initially envisaged carrying out the comparison on **6** and its non-keto analogue, because tetralkylhydrazines do not require Bredt's rule stabilization, but our efforts at making **6** failed. We decided to turn our attention to X groups at nitrogen that require Bredt's rule protection for $E^{\circ\prime}$ measurement.


6

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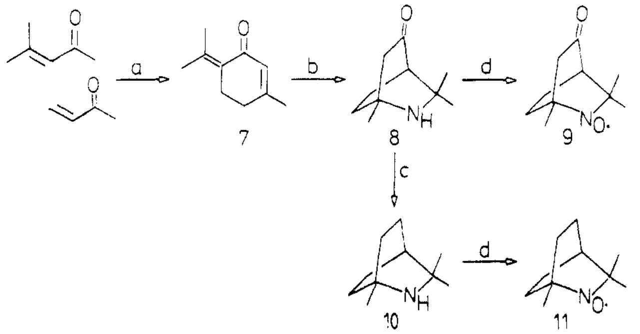
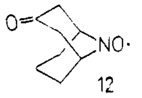
Scheme I

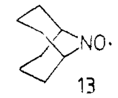


Replacement of the two C_3 hydrogens by methyl groups is required to convert the 2-ABO system into a Bredt's rule protecting group.[4] We first tried to make the keto substitution comparison on chloroamines, which would have had the advantage of an especially large nitrogen charge density in the radical cation, maximizing the effect of the keto group. Once again, we found ourselves incapable to preparing the necessary compounds, however. Several attempts at making **1**(Cl) at various temperatures and with various chlorinating agents failed completely; we apparently were having problems with halogenation α to the keto group.

Rassat and Rey's bis Michael addition of ammonia to piperitenone (**7**) has made keto amine **8** and hence nitroxide **9** easily available[5] (see Scheme I). We carried **8** to the saturated nitroxide **9** by the obvious route of Wolff–Kishner reduction, which has its difficulties; considerable cleavage back to **7**, which was reduced under the reduction conditions, occurred. Rassat and co-workers have apparently not reported the conversion of **8** to **11**, and made **11** from 1,8-diamino-*p*-menthane.[6] Because Bredt's rule protected nitroxides show electrochemically reversible oxidation,[2] we made our comparison of σ-coupled and non-σ-coupled systems with nitroxides **12** and **13**, also



12



13

well-known from the work of Rassat and co-workers.[7] For nitroxides the neutral form is the paramagnetic species and the cation is diamagnetic, but these nitroxides are easy to handle, and a charge density change similar to that for hydrazine oxidation is expected upon electron removal. The spin densities at O and N for dialkyl nitroxides are believed to be very similar,[8] making the formal nitrogen charge density close to $+ {}^1/_2$ in the neutral radical, while that in the oxidized $(R_2N{=}O)^+$ form is +1.

The PE and CV data for the nitroxides are collected in Table I.

Table I. PE and CV Data for γ-Keto Nitroxides and Their C=O → CH_2 Analogues

compd	IP_v, eV	$E^{\circ\prime}(\Delta E_{pp})$,[a] V
12	7.78, 9.43	0.83_2 (0.063)
13	7.39, 9.45	0.58_2 (0.072)
9	7.29, 9.12	0.73_2 (0.073)
11	6.88, 8.73	0.51_5 (0.073)

[a] Conditions: acetonitrile containing 0.1 M *n*-Bu_4NClO *n*-Bu_4NClO_4, at gold, vs. SCE, 23 ± 1 °C, 200 mV/s scan rate.

Table II. Effect of Replacing CO by CH_2 in γ-Keto Amine Derivatives on the Ease of Electron Removal

keto compd	CO → CH_2 analogue	$\Delta(IP_v)$, eV	$\Delta(E^{\circ\prime})$, V
1	2	0.50[a]	0.21[a]
3	4	0.47[a]	0.02[a]
12	13	0.39[b]	0.25[b]
9	11	0.41	0.22[b]

[a] Reference 3. [b] This work.

Discussion: The σ-Coupling Effect

Data pertinent to considering the effect of CO → CH_2 substitution on the ease of electron removal are collected in Table II. It may be seen that the non-σ-coupled ABO pair **9**,**11** has as large a $\Delta(IP_1)$ as the σ-coupled pair **12**,**13**. Furthermore, $\Delta(E^{\circ\prime})$ for the non-σ-coupled pair is only 13% smaller than that for the σ-coupled pair, in contrast to the acyclic examples **3**,**4** compared to **1**,**2**. There clearly is an electrostatic component to $\Delta(E^{\circ\prime})$ that depends only on CO,N distance, not σ overlap. In the crudest approximation, one might argue that the electron loss involves increasing the nitrogen charge density by roughly $+{}^1/_2$, and when a γ-carbonyl is present, there is about a $+{}^1/_2$ charge at the carbonyl carbon. The N,C=O distance in both **12** and **9** is measured off a Dreiding model to be about 2.9 Å, leading to a zeroth order approximation to a charge repulsion effect of $166q_1q_2/\epsilon r$ kcal/mol, or 14 kcal/mol (0.6 eV) if $\epsilon = 1$ is employed, and half that if the dielectric constant of cyclohexane ($\epsilon = 2.02$) is employed to represent the σ framework. This is about the size of the CH_2 → CO substitution effect on both these nitroxides. If a significantly different N,CO distance was present for $\mathbf{9}^{+\cdot}$ and $\mathbf{12}^{+\cdot}$, it would affect the $E^{\circ\prime}$ values observed, although Dreiding models suggest that Δr is less than 0.1 Å. The CO dipole is held in a more favorable position in 2-ABO derivative $\mathbf{9}^{+\cdot}$ than in $\mathbf{12}^{+\cdot}$, which is not going to explain a higher $\Delta(E^{\circ\prime})$ for **9** compared to **12** than in the acyclic example **3**. The principal difference between the acyclic and the bicyclic comparison of non-σ-coupled systems in Table II is that only the acyclic case can undergo substantial bond rotation change upon electron loss. Because **9** is held in a conformation minimizing σ coupling, it is difficult for us to come to any conclusion but the one that σ coupling is rather unimportant in determining how destabilizing the introduction of a γ-keto group is on electron loss from piperidines. It is not clear, of course, why **3** is so far out line in its $E^{\circ\prime}$ value compared to the other compounds studied. It is true that **3** can undergo much greater conformational change upon electron loss and also has much less hindered carbonyl and hydrazine groups than the bicyclic compounds, so perhaps there is a differential solvation effect causing the anomaly.

Conclusion

In comparison of the γ-keto nitroxides **9** and **12** with their non-keto analogues, only a 13% lowering of $\Delta(E^{\circ\prime})$ was observed for the non-σ-coupled example, suggesting that the effect of σ coupling in destabilizing $\mathbf{12}^{+\cdot}$ by through-bond interaction of the partial positive charges at the carbonyl carbon and the nitrogen is quite modest, under 1 kcal/mol.

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Experimental Section

1,3,3-Trimethyl-2-oxyl-2-azabicyclo[2.2.2]octan-5-one (9). Piperitenone (7) was prepared by the method of Beerebom[9] from 178 g of methyl vinyl ketone and 686 g of mesityl oxide, giving 112 g of crude petroleum [90–125 °C bp (10 mm)], which was stirred with 28% aqueous ammonium hydroxide for 120 h at room temperature, saturated with sodium chloride, extracted in ether, extracted with 3 M HCl, dried, and concentrated to a 22% yield (based on MVK) of ca. 90% pure 8. Pulverized 85% potassium hydroxide (20 g) was dissolved in 200 mL of diethylene glycol by heating to 70 °C, and after the solution cooled to 35 °C, 14 g of hydrazine hydrate and 14 g of crude 8 were added. The solution was heated at 230 °C for 3 h and while the distillate produced was collected and cooled to room temperature. After addition of 250 mL of water, the pot solution was extracted three times with 250 mL of ether. Concentration, extraction into 3 M HCl, basification, extraction into ether, drying, concentration, and Kugelrohr distillation gave 2.24 g (19%) 9 as an oil: ^{1}H NMR ($CDCl_3$) δ 0.98 (s), 1.22 (s), 1.50 (s); ^{13}C NMR ($CDCl_3$) δ 23.15, 28.72, 30.90, 32.94, 33.78, 48.52, 51.55; high-resolution mass spectral peak match for $C_{10}H_{19}N$.

Nitroxides 9, 11, 12 and 13 were prepared by use of sodium tungstate dihydrate, hydrogen peroxide oxidation of their amines,[5c] and purification by column chromatography on neutral alumina. All showed the expected ESR spectra.[5-7]

Physical Measurements. The PE, CV, and ^{13}C NMR measurements and data workup have been previously described.[2,4]

Acknowledgment. We thank the National Institutes of Health for support of this research under Grant GM 25428.

Registry No. 7, 491-09-8; 8, 33069-72-6; 9, 83291-33-2; 11, 34122-41-3; 12, 7123-92-4; 13, 31785-68-9.

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Coupling of Diazopurines, a Curious Steric Effect in a Free Radical Reaction

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The reaction of adenine derivatives with nitrite esters in the presence of arenes was examined and found to give 6-arylpurines in good (83%) to poor (11%) yield. The arylated products consisted only of the meta and para isomers; none of the anticipated ortho isomers were found. The predominance of meta- and para-substituted products is attributed to steric effects. The evidence that the reaction proceeds via a purine radical includes light stimulation, relative insensitivity to electronic factors, and the facile reaction of the purine intermediate with pyridine *N*-oxide. Photolysis of 6-iodo-9-benzylpurine in the presence of anisole gave the same mixture of 6-(*m*-methoxyphenyl)- and 6-(*p*-methoxyphenyl)purine as did diazotization, suggesting that both reactions involve the same purine radical.

The coupling of phenyl diazo compounds with arenes to produce mixed biphenyls is well-known,[1] but coupling of the unstable diazo derivatives of electron-deficient heterocycles[2] has not been reported. Such a reaction would be valuable for it would allow the ready synthesis of unnatural nucleosides, analogues of the antitumor antibiotics like puromycin,[3] and analogues of the postulated endogenous antianxiety substance hypoxanthine.[4] An advantage of using heterocyclic diazo compounds to couple to a benzene, rather than adding phenyl radicals to the heterocycle, is that one can control, a priori, the position of substitution on the heterocyclic ring. Furthermore, a large number of compounds with different substituents and different substitution patterns may be prepared from one intermediate.

The hydrolysis of adenine to hypoxanthine by using aqueous nitrous acid was reported in the last century,[5] but the presumed purinediazonium salt intermediate has never been isolated. Purinediazonium compounds probably have only a transitory existence as few[6] reports exist of their synthetic utility. We report the coupling of the diazo derivatives of N-9-alkylated adenine with other aromatic compounds and discuss possible mechanistic implications arising from the lack of ortho-coupled products in this reaction.

Table I. **Partial Rate Factors for the Coupling of Radicals to Substituted Benzenes**[a]

	purinyl radical			phenyl radical		
R	ortho	meta	para	ortho	meta	para
OCH3		0.9	5.6	2.4	0.6	1.1
CF3		0.32	0.29	0.6	1.2	2.4
pyridine	0.29	0.14	0.46	1.9	0.9	1.0

[a] The benzene values refer to the coupling of phenyl radicals derived from benzoyl peroxide at 80 °C and are taken from: Walling, Cheves. "Free Radicals in Solution"; Wiley: New York, 1957; p 484.

The readily available[7] substituted adenines 1 were diazotized in situ and coupled to an arene which was present

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