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REMARKABLY FAST [2+2]CYCLOREVERSION IN METHOXY SUBSTITUTED COOKSON'S CAGE KETONES ASSISTED BY THE CAPTO-DATIVE SUBSTITUENT EFFECT AND BY THE THROUGH-BOND INTERACTION

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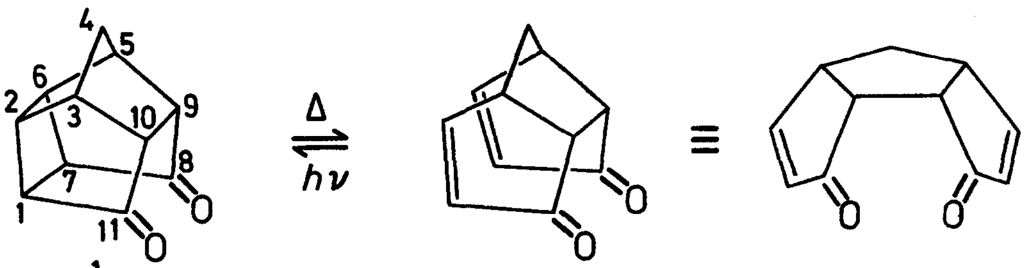
Abstract: 1,7-Dimethoxy groups in Cookson's pentacyclic cage ketone derivatives (2 and 5) accelerate the thermal [2+2]cycloreversion, possibly by means of the unusual lengthening of C_1-C_7 bond and the synergetic capto-dative stabilization of 1,4-diradical (7 and 8).

Thermal [2+2]cycloreversion of Cookson's one-winged birdcage diketones 1 (eq. 1) is recently attracting considerable attention as the key step in the solar energy utilization[1] and in the synthesis of polyquinanes.[2] The reaction is, however, slow and requires extremely high temperatures of up to 625°.[2a] We found that the substitution with methoxy group at C_1 and C_7 positions of 1 remarkably accerelated the cycloreversion.

Cage compounds 2 to 6 were prepared by the known procedure.[3] As shown in Table I, methoxy-bearing 2 and 5 showed high propensity to the thermally forbidden ring opening reaction even at 90° to give tricyclic dienes[4], whereas compounds 3, 4 and 6 underwent the reversion only very slowly at much higher temperatures (eq. 2 to 4). The most naive explanation for the observed substituent effect would be to invoke the large stabilization of carbon radical by methoxy group (7).[5] However, a closer examination of the reaction rates revealed the presence of other, extraordinary effect. First, the difference in activation enthalpies ($\Delta\Delta H^{\ddagger}$) between 2 and 3 is abnormally large. The three rate data for 2 gave a reasonably straight line in the Arrhenius plot, yielding a $\Delta H^{\ddagger}$ of 35.2 kcal/mol. Assuming the same A factor, one estimates a $\Delta H^{\ddagger}$ of 49.5 kcal/mol for 3. On the other hand, it is known that a methoxy group stabilizes a carbon radical by 4 to 5 kcal/mol more than a methyl.[5] Given that there are two methoxy groups on the C_1-C_7 bond of 2, the observed $\Delta\Delta H^{\ddagger}$ (14 kcal/mol) for the 2/3 pair is 4 to 6 kcal/mol larger than expected. Hence, either 2 is unusually reactive or 3 is abnormally unreactive.



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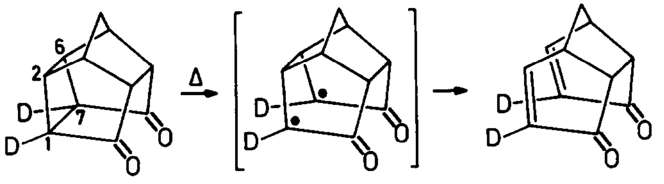
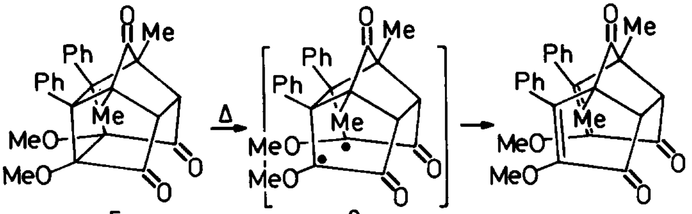
(1)



2(D=OMe)
3(D=Me)
4(D=H)

7

(2)



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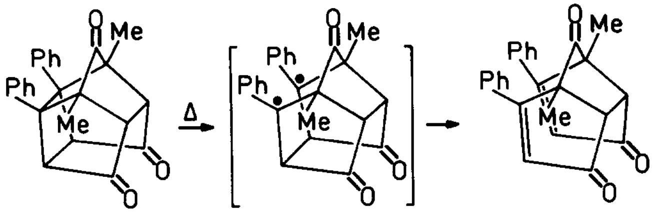
8

(3)



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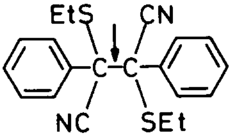
(4)



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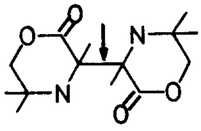

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A dramatic case of the large methoxy effect is demonstrated by the relative reaction rate between 5 and 6 (eq. 3 and 4). Since 5 cyclorerverses at about the same rate as 2, the biradical (8) must have been the intermediate. 6 reacts slower than 5 but much faster than 4, hence the benzyl type biradical (9) must have been formed.[6] The inevitable conclusion is that 8 is much more stable than 9, and this relative order does not agree with the well-known fact that the phenyl group stabilizes a carbon radical by 11-12 kcal/mol than the methoxy group.[5]

We suggest that the remarkably enhanced stabilization of 7(D=OMe) over 7(D=H) and that of 8 over 9 is the result of synergetic effect of dative (methoxy) and captive (carbonyl) substituents known to efficiently stabilize the radical to which they are geminally attached.[7]

Table I. Rates of Cycloreversion of Cage Ketones **2** - **6**

compd	temp °C (±0.1)[a]	solvent	k_1 10^5 sec^{-1}
2	85.1	ETOH	1.54
	98.8	ETOH	16.6
	90.5	C_6D_6	3.05
3	248.5	EG[b]	7.83
4	260.5	EG[b]	undetectable[c]
5	90.6	$CDCl_3$	1.89
6	230.0	DPE[d]	43.4

[a] Measured by the ampul technique. [b] Ethylene glycol. [c] No cycloreversion product was observed at this temperature. Thermal decomposition of **4** required severer conditions (500°C under 1 Torr). [d] Diphenyl ether.

Table II. Calculated Bond Lengths by MO (MNDO) and molecular mechanics (MM2')

compd	bond length (Å)			
	C_1-C_7		C_2-C_6	
	MNDO	MM2'	MNDO	MM2'
2	1.6266	1.5672	1.5677	1.5573
3	1.6036	1.5563	1.5726	1.5589
4	1.5726	1.5553	1.5754	1.5526
5[a]	1.6268	1.5779	1.6191	1.5738
6[a]	1.5666	1.5600	1.6187	1.5662

[a] Calculations of **5** and **6** were done on model structures without C-methyl groups.

Even if the powerful capto-dative radical stabilization is admitted, the observed preferential cleavage of C_1-C_7 over C_2-C_6 bond in **5** is still surprising. This is because the latter bond (as well as the corresponding bond of **6**) should be elongated to about 1.64 Å[6] due to the through-bond interaction between π-orbitals[8] of two phenyl groups assisted by the pre-strain in the mediating cyclobutane ring,[1a,9] and hence this bond should be inherently susceptible to the thermal cleavage. MNDO[10] calculations indicate that the C_1-C_7 bonds of **2** and **5** are also significantly lengthened in the ground state (Table II). Note that the C_2-C_6 bond is indeed calculated to be abnormally long when these carbon atoms bear phenyl group (**5** and **6**).[1a,5,9] The elongation in these bonds is not due to steric reasons like the repulsion between vicinal methoxy, phenyl and carbonyl groups, since MM2'[11] calculations showed more or less normal lengths for these bonds (Table II).

The reason for the predicted lengthening of the C_1-C_7 bond in **2** and **5** is not clear as yet. The enhanced through-bond interaction between the lone-pair electron of methoxy group[9] is certainly likely, but the possibility of this interaction involving π orbitals of the captive as well as the dative groups cannot be excluded. Indeed, two open-chain dimers of capto-dative radicals (**10**, **11**) have very long central bonds of about 1.6 Å,[12,13] but in these cases it is not clear if the bond lengthening is the result of steric repulsion common to the fully substituted ethanes.

Studies aimed at obtaining more thermodynamic parameters of cycloreversion reactions and molecular structure determination of **2** and related molecules are in progress.

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(3) The derivatives of p-benzoquinone were synthesized by essentially the same manner as previously reported: 2,3-Dimethyl-p-benzoquinone; Conant, J.B.; Fieser, L.F. *J. Am. Chem. Soc.* **1923**, *45*, 2194-2218. 2,3-Dimethoxy-p-benzoquinone; Catlin,J.C.; Daves Jr., G.D.; Folkers, K. *J. Med. Chem.* **1971**, *14*, 45-48. The preparation of cage compounds followed the general procedure cited in ref. 1b.

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