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Studies on Cyclobutyl Bond Cleavage by Adjacent Ketyl Radical Generated Under PET Conditions

Bipin Pandey*, Ashok T.Rao, Pramod V.Dalvi and Pradeep Kumar

Division of Organic Chemistry: Technology,
National Chemical Laboratory, Pune-411008, India

Abstract: *A variety of adjacent cyclobutyl ketones have been subjected to a new photoelectron transfer (PET) conditions, i.e., photolysis in a protic and polar solvent EtOH with triethyl amine. The cleavage of cyclobutane ketyl radical is highly substrate specific. An interesting wavelength dependence (irradiation at 254nm vs 300nm) phenomenon has been uncovered. The nature of chemical transformation has been shown to be a function of mode of generation of ketyl radicals. In continuation, the cleavage of even adjacent cyclopentane ring is postulated to account for our recently discovered novel isomerization of Diels-Alder endo-isomers to exo-adducts under PET conditions, which is quite unprecedented.*

Control and prediction of stereochemistry in medium cyclic rings is quite a complex and challenging concern of current synthetic organic chemists.[1,2] As part of a programme for the synthesis of stereocontrolled medium cyclic rings, e.g., 10, 11, 12 and 13-membered rings **1-4**, the locked cage diones **5** and **6** are envisaged as an intermediate, offering considerable opportunity for stereochemical manipulation (Scheme 1).[3-8] Recently, we[4,8] and Coxon et al.[9] have shown that hexacyclo [10.2.1, $0^{2,11}$, $0^{4,9}$ $0^{4,14}$, $0^{9,13}$] pentadeca-5,7-diene-3,10-dione **6** can react exclusively either from cyclobutane face or, from ketone face of the diene, depending on the nature of dienophiles. To unlock the cage dione, we have employed various methods e.g.,Baeyer-Villiger oxidation,[3,7,10] and photochemical α-cleavage[5,7] etc. to cleave cyclobutyl-carbonyl bond, with limited success.

Dauben et al. have proposed that during the electron transfer conditions by lithium in liq. ammonia, the regiochemistry of cyclopropane bond cleavage is governed by the concept of maximum overlap of one of the bond with the π-orbitals of carbonyl group.[11,12] Since the ß-bonds C_4-C_9 and C_2-C_{11} should have more overlap with carbonyl π^*-orbital in **5** and **6**, a study of photochemical electron transfer (PET) with cage dione was undertaken with a view to cleave these bonds and with a view to understand the nature of PET-generated radical anions vs other modes of generating these species, in these systems.

Initially the reaction of **6** with triethylamine (TEA) and ethanol in photolytic conditions[13,14] was examined and a quantitative conversion to exo-**8** was accomplished. Understandably, the ß-clea-

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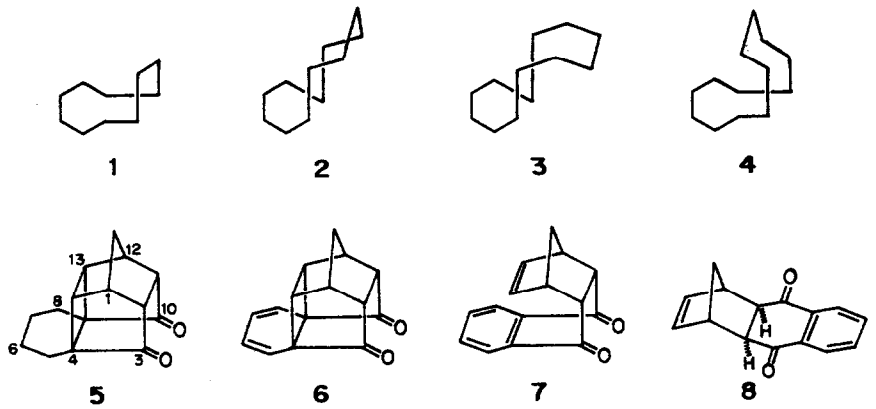
Dedicated to Dr. S.Rajappa on the occasion of his 60th birthday.

vage of unexpected cyclobutyl bond (i.e., C_4-C_{14} and C_9-C_{13}) was triggered by adjacent PET-generated radicals leading to endo-**7**, which subsequently isomerized to the exo-**8**. Notably, the ß-cleavage of cyclobutyl bonds by PET-generated radical ions have recently been proposed in the biological systems as well.[15-16] While we preferred to examine the generality of unprecedented Diels- Alder endo-exo isomerization under PET-conditions,[13,14] the generality of equally important and unprecedented ß-cleavage of cyclobutane ring cleavage remained to be studied.[17] This study reports that the cleavage of cyclobutyl bonds adjacent to PET-generated ketyl radicals is a highly substrate specific reaction and not a general reaction. We also emphasize that the method of generating ketyl radicals, i.e., either by exciting TEA at 254nm or by exciting ketone at 300nm matters in regulating efficiency of bond cleavage. In continuation, we suggest that the nature of chemical transformations from radical anions generated by various PET reactions and by other methods, is not necessarily same.

Scheme-1



The various cyclobutyl ketones utilized in our studies e.g., hexacyclo [10.2.1.$0^{2,11}$.$0^{4,9}$.$0^{4,14}$.$0^{9,13}$] pentadeca-3,10-dione (**5**)[3], hexacyclo [10.2.1.$0^{2,11}$.$0^{4,9}$.$0^{4,14}$.$0^{9,13}$] pentadeca-5,7-diene-3,10-dione (**6**)[18], *endo* tetracyclo [10.2.1.$0^{2,11}$.$0^{4,9}$] pentadeca-4,5,7,13-tetraene-3,10-dione (**7**)[13], pentacyclo [6.2.1.$0^{2,7}$.$0^{4,10}$.$0^{5,9}$] undecane-3,6-dione (**11**)[19] were prepared as per literature precedences, whereas the preparation of 2-methyl hexacyclo [10.2.1.$0^{2,11}$.$0^{4,9}$,$0^{4,14}$.$0^{9,13}$] pentadeca-5,7-diene-3,10-dione (**9**), *endo* 2-methyl tetracyclo [10.2.1.$0^{2,11}$.$0^{4,9}$] pentadeca-4,5,7,13-tetraene-3,10-dione, 1,12,13,14,15,15'-hexachlorohexacyclo [10.2.1.$0^{2,11}$.$0^{4,9}$.$0^{4,14}$.$0^{9,13}$] pentadeca-5,7-diene-3,10-dione (**10**), *endo* 1,12,13,14,15,15'-hexachlorohexacyclo [10.2.1.$0^{2,11}$.$0^{4,9}$] pentadeca-4,5,7,13-tetraene-3,10-dione (**13**) and 1,12,13,14,15,15'-hexachlorotetracyclo [10.2.1.$0^{2,11}$.$0^{4,9}$] pentadeca-2,4,5,7,13-pentaene-3,10-dione (**14**) are reported in the experimental section of this publication.

For the development of appropriate reaction conditions needed for PET experiments, we varied the solvent system, concentration of triethylamine, nature of photoelectron donor e.g., HMPA, DABCO etc., excitation wavelength and duration of photolysis etc. During the optimization studies for efficient transformation of endo-**7** to exo-**8**,[13,14] and a broad understanding of various parameters was obtained. Thus, a 0.02M solution of substrate in 5-20% of triethylamine in ethanol (by volume)

was irradiated at suitable wavelength in Rayonet (at 254nm in quartz or 300nm in pyrex vessel) and successful cleavage of cyclobutane was accomplished. As the Table-1 indicates, a variety of cyclobutyl ketones (entry 1-12) were subjected to PET conditions either by exciting the ketones at 300nm or by exciting the donor molecule TEA at 254nm.[20] It is well established that an efficient electron transfer can occur from the amines to the excited ketones[21]. Thus, the cyclobutyl ketones accompanied by the diene frame e.g., in **6**, **9** and **10** (scheme 1 & 2) gave efficient cleavage products, but with saturated analogues **5** and **11**, no reaction was observed. It is reasonable to assume that the cleavage of unexpected C_4-C_{14} and C_9-C_{13} bond, instead of C_4-C_9 or C_2-C_{11} bond, is governed by the force of aromatization and release of strain criteria. Similar phenomenon was the driving force behind unexpected bond reorganisation, during the Baeyer-Villiger oxidation studies of **6**.[3] While the final products from **6** and **10** were the exo type **8** and **14**, the 2-methyl substituted **9** gave only the endo-**12**.[22] The total absence of any reactivity under PET conditions in the saturated analogues e.g., **5** and **11**, was indeed very surprising to us.[17] Mechanistically, one can postulate varied interesting possi-

Table 1:

Entry	Starting Material	Reaction Condition[a]	Irradiation[b] (nm)	Duration (h)	Product (Yield %)
1	**6**	A	300	2	**8** (76)
2	**7**	A	300	2	**8** (95)
3	**9**	A	300	7	**12** (45)
4	**12**	A	300	50	**12** (95)
5	**10**	A	300	4	**13** (85)[c]
6	**5**	A	300	24	**5** (95)
7	**11**	A	300	25	**11** (95)
8	**6**	A	254	6	**6** (90)
9	**6**	B	254	8	**8** (10)[d]
10	**11**	A	254	25	**11** (92)
11	**9**	A	254	25	**9** (94)
12	**10**	A	254	25	**10** (90)

a: A: Reaction condition implies that substrates (0.02M) were dissolved in 5% TEA/EtOH, degassed for 10 min and irradiated as indicated.

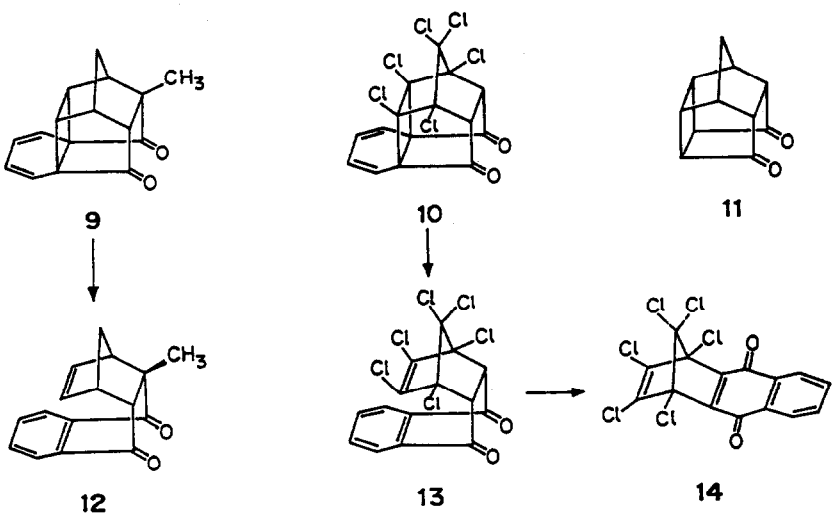
B: No TEA was added.

b: Rayonet Reactors with either 300nm or 254nm lamps were used.

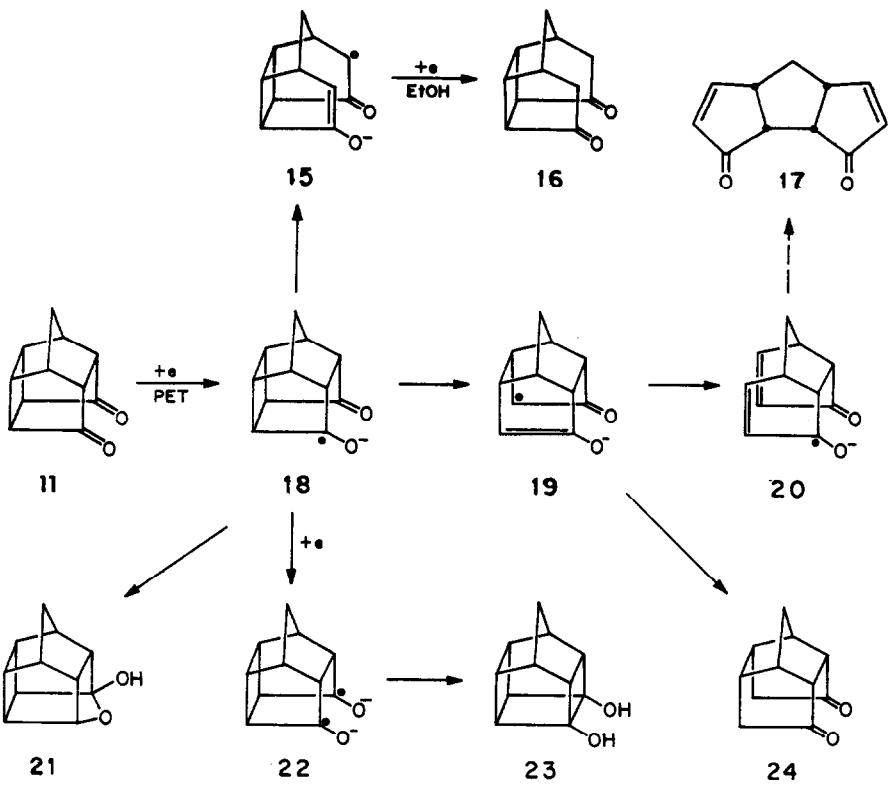
c: On prolonged irradiation, oxidized product **14** is obtained.

d: For other side products, see ref. 5.

Scheme-2



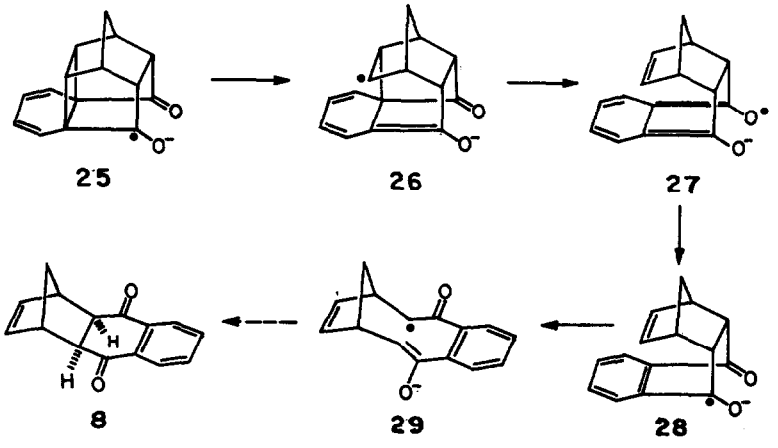
Scheme-3



bilities as shown in scheme 3. The transformation from **11** to **17** via **18**, **19** and **20** at room temp, which is normally accomplished by flash thermolysis[23] would have been an interesting reaction. Although the possibility of recombination of radicaloid species e.g., **19** & **15** in cage compounds should be high, but the release of strain from **11** to **17** or **11** to **16** or **11** to **24** could as well have been the driving force for such transformation. There are precedences for the formation of cleaved ß-bonds e.g., **16**[24] and **24**[25], cyclized hemiacetal **21** and coupled diol **23**[26] under various reductive conditions from **11**, but none of these possibilities materialised from saturated analogues under PET conditions. This clearly indicates that the nature of radical anions formed from PET-reactions and other reductive processes e.g., Zn-Acetic acid[25,26] and Na-K alloy[24] etc. are different.

Dauban etal[27] have reported efficient dechlorination due to low lying C-Cl σ-σ^* by sodium/t-BuOH. However, under PET conditions no dechlorination occured (entry 5). Although in our earlier studies, debromination α to carbonyl is a facile process.[13,14] Another notable feature of halo compounds is the quick autooxidation of exo-**13** to **14**, whereas endo **7** and **12** and many related substrates[13,14] have been found to be fairly stable under PET conditions. The probable mechanism of autooxidation may be visualised through the interaction of oxygen from solvent with species such as **27** and **28**. We have also noted that the wavelength of excitation e.g., Rayonet 254nm vs 300nm, matters in governing reactivity and selectivity. Thus, while 300nm irradiation was quite efficient for cyclobutyl cleavage, the same was not true at 254nm (entry 8-12).[28]

Scheme-4



One interesting feature of our PET-experimental condition is that it does not lead to the reduction of ketones, which is a common side reaction in ground state electron transfer reactions. Similar to the cleavage of cyclopropyl[28] and cyclobutyl group adjacent to PET-generated ketyl radicals, one wonders whether the efficient isomerization of endo-**7** to exo-**8** was the outcome of even cyclopentane ring cleavage adjacent to ketyl radicals as shown in Scheme 4.[29] Notice the possible transformation of **28** to **29**, which can subsequently cyclise to give thermodynamically stable exo-**8**. In fact, the cleavage of central bond has been indicated in Lithium/liquid ammonia studies by Gassman.[30]

In conclusion, this study examines the generality and limitations of regioselective cyclobutyl bond cleavage adjacent to ketyl radicals generated under a new PET-conditions in a protic solvent EtOH, which appears to be highly substrate specific. Thus, only those cyclobutanes, which had diene frame with a possibility of aromatization could be cleaved. Saturated cyclobutyl ketones did not lead to any product formation. In continuation, the cleavage of even adjacent cyclopentane has been proposed for efficient endo to exo isomerization under PET-conditions. The nature of chemistry generated by ketyl radicals is shown to be a function of methodology of generating these radicals. This phenomenon has been shown repeatedly by wavelength effect (254nm vs 300nm) observed in our reactions and in comparison to other methods of ground state electron transfer reactions.

Experimental Section

General information

Melting points were determined with a Mel-Temp apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 683 grating infrared spectrophotometer. Proton and ^{13}C NMR spectra were recorded on various FT-80A, Brucker WH-90 FTNMR, and Brucker AC-200 NMR spectrometers. The chemical shifts are reported in parts per million(δ) with tetramethyl silane as internal standard. Mass spectra were obtained with a Finnigan MAT-1020-B-70-eV mass spectrometer.

Experimental Procedure for ß-cleavage

Cyclobutyl ketones (0.02M) were dissolved in appropriate concentration of ethanol:triethylamine as indicated in Table-1. The solution was purged with a slow stream of nitrogen gas for 10min and then irradiated in Srinivasan Rayonet photochemical reactor at 254nm in a quartz vessel or 300nm in pyrex tube for 2 to 50 h (Table-1). The progress of the reaction was monitored by GC/TLC. The solvent and TEA were evaporated under reduced pressure and the crude product obtained was purified on silica gel column using pet. ether:acetone as eluent.

Preparation of 2-methyl hexacyclo [10.2.1.$0^{2,11}$.$0^{4,9}$.$0^{4,14}$.$0^{9,13}$] pentadeca-5,7-diene-3,10-dione (9)

Endo 2-methyltetracyclo[10.2.1.$0^{2,11}$.$0^{4,9}$] pentadeca-4,5,7,13-tetraene-3,10-dione (2g, 0.008mol) was dissolved in P_2O_5 dried acetonitrile (2000ml) and solution was purged with a slow stream of nitrogen gas for 10 min. The solution was irradiated in a pyrex tube with Srinivasan Rayonet photochemical reactor at 300nm for 2.5h. Excess acetonitrile was removed under vacuo and product mixture was separated on silica gel column using pet ether:acetone (94:6) solvent mixture to give solid of cage dione which on recrystallization from ethanol afforded **9**; 729mg (36%), m.p.104°C, IR($CHCl_3$), 3060, 2980, 2860, 1750, 1470, 1390, 1310, 730cm^{-1}; ^1H NMR, ($CDCl_3$) δ : 1.15(s,3H), 1.5-1.8(m,2H), 2.2-2.3(d,1H), 2.4-2.6 (m,1H), 2.9-3.06(m,1H), 3.2-3.4(m,2H), 5.2-5.5(m,2H), 5.8-6.1(m, 2H); ^{13}C NMR ($CDCl_3$) δ: 212.63(s), 210.23(s), 124.37(d), 124.25(d),120.01(d), 119.57(d), 61.88(d), 58.23(d), 50.65(s), 50.13(s), 49.64(d), 49.59(d), 49.24(d), 44.27(d), 37.20(t), 16.98(q); MS, m/e: 238 (M^+, 12%), 173 (25%), 80 (45%), 66(100%).

Preparation of 1,12,13,14,15,15'-hexachlorohexacyclo [10.2.1.$0^{2,11}$.$0^{4,9}$.$0^{4,14}$.$0^{9,13}$] pentadeca-5,7-diene-3,10-dione(10)

Compound **10** was prepared as described for **9** from *endo* 1,12,13,14,15,15'-hexachlorotetracyclo [10.2.1.$0^{2,11}$.$0^{4,9}$] pentadeca-4,5,7,13-tetraene- 3,10-dione, (2g, 0.004mol), and was recrystallised from methanol, 1.8g (90%), m.p. 196°C; IR (Nujol), 2920, 2890,, 1740, 1440 cm^{-1}, ^1H NMR ($CDCl_3$) δ: 2.44-2.6(m, 2H), 6.1-6.6(m, 4H): ^{13}C NMR ($CDCl_3$) δ: 213.35(s), 128.28(d), 115.90(d), 96.37(s), 83.54(s), 80.58(s), 52.23(d), 42.01(s); MS, m/e: 430(M^+, 7%), 393(100%), 358(70%), 265(40%).

Preparation of 2-methyl tetracyclo [10.2.1.$0^{2,11}$.$0^{4,9}$] pentadeca-4,5,7,13-tetraene-3,10-dione (12)

A solution of 2-methy-1,4-naphthoquinone(5g, 0.029mol) in ethanol (80ml) was added to freshly distilled cyclopentadiene (2.3ml, 0.034mol) with stirring and mixture was refluxed for 8 to 10 hrs. After evaporation of the solvents, the resulting crude product was purified by silica gel column chromatography using pet. ether: acetone (98:2) as eluent to furnish pure endo adduct **12**, 6.5g(94%), m.p. 130°C; IR (Nujol), 2900, 2840, 1680, 1670, 1470, 1310, 1290, 1050, 730 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.4-1.6(d, 2H), 2.4(s, 3H), 3.3-3.5(m, 2H), 3.62(brs, 1H), 5.8-5.9(m, 2H), 7.3-7.5(m, 2H), 7.7-8(m, 2H); MS, m/e: 238(M^+, 50%), 173(50%), 118(20%), 89(32%), 66(100%).

Preparation of 1,12,13,14,15,15'-hexachlorotetracyclo [10.2.1.$0^{2,11}$.$0^{4,9}$] pentadeca-4,5,7,13-tetraene-3,10-dione (13)

A mixture of 1,4-naphthoquinone (5g, 31.6m mol) and hexachlorocyclopentadiene (8.64g, 31.6m mol) was heated at 160°C for 12h. After slow cooling to room temp. the solid was filtered and purified by silica gel column chromatography to furnish **13**, 8.18g(60%). m.p.135°C, IR(Nujol), 1685, 1600, 810cm^{-1}; ^{1}HNMR ($CDCl_3$) δ: 4.0(s, 2H), 7.6-8.1(m, 4H); MS, m/e; 430 (M^+, 13%), 395(16%), 359(11%), 313(8%), 272(87%), 167(100%) and 104(60%).

Preparation of 1,12,13,14,15,15'-hexachlorotetracyclo [10.2.1.$0^{2,11}$.$0^{4,9}$] pentadeca-2,4,5,7,13-pentaene-3,10-dione (14)

The air oxidation of **13** led to the compound **14** m.p.139°C; IR (Nujol): 2940, 1680, 1600, 1470, 1300, 740 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 7.6-7.8(m, 2H), 8.0-8.2(m, 2H); ^{13}C NMR ($CDCl_3$) δ: 179.19(s), 148.58(s), 137.96(s), 134.41(d), 131.94(d), 126.62(s), 81.82(s); MS m/e: 428(M^+, 5%), 398(100%), 358(78%), 302(20%), 265(50%), 195(25%), 132(20%).

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