162. Contribution to the Problem of Nucleophilic Substitution Reactions at Small-Ring Carbon Atoms Occurring with Retention of Configuration

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Beitrag zum Problem der nucleophilen Substitutionsreaktionen am Kohlenstoffatom kleinerer Ringe mit Retention der Konfiguration. – *Zusammenfassung.* Mit Natriumiodid und mit Tetraäthylammoniumacetat in Aceton findet auch unter energischen Bedingungen keine nukleophile Substitution des Bromatoms in 4-*endo*-Brom-1,3,5,7-tetramethyl-*anti*-tricyclo[5.1.0.0^{3,5}]octane-2,6-dion (**10**) statt, obschon bei **10** – nach neueren Anschauungen – gute Voraussetzungen für eine solche Reaktion vorhanden sein sollten. Dies bestätigt die bekannte Trägheit von Dreiring-Kohlenstoffatomen gegenüber S_N2-Reaktionen und erhöht die Wahrscheinlichkeit, dass trotz der verwendeten Bedingungen die relativ schnellen Substitutionen der Bromatome in den Ketonen **6** und **7** durch Acetat unter Retention der Konfiguration nicht S_N2-Reaktionen sind. Ein Alternativmechanismus mit vorübergehender Öffnung des Dreirings wird für diese Umwandlungen in Betracht gezogen, und zwar **6** → **11** → **8** und **7** → **12** → **9**.

Inversion of configuration (**1** → **3**) is the generally expected stereospecificity of kinetically controlled bimolecular nucleophilic substitution (S_N2) reactions at saturated carbon atoms [1] [2]. Attention has recently been drawn to the circumstances under which S_N2 reactions may occur with *retention* of configuration (**1** → **5**) (compare [3]). Theoretical considerations, led to the proposal that angle strain¹) during the transition from a tetracoordinated to a pentacoordinated carbon atom might be an important point [4] [5]: While normally – according to the classical concept [2] – some factor [7] causes the nucleophile Y to attack the carbon atom in **1** *anti* to the leaving group X (see **2**), the new view proposes that compression of two bonds by incorporation of two ligands (*e.g.* A and B) in a small ring [4] and the consequent changes in the bonding situation [5] cause preferred attack by Y *syn* to X (see **4**). Very detailed model concepts for qualitative and quantitative treatment were elaborated, one requiring the species with the pentacoordinated carbon atom to be an intermediate [4], the other a transition state [5].

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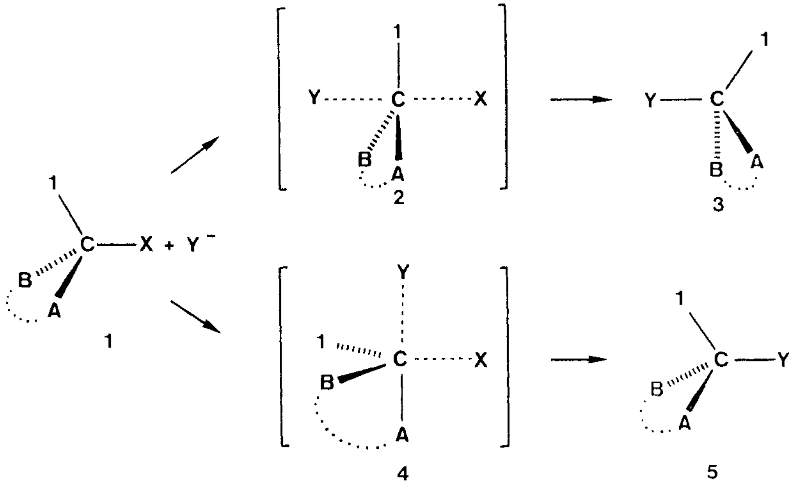
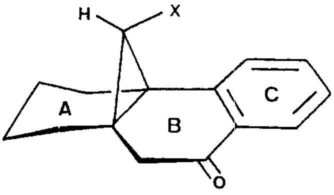
¹) The same strain argument had been applied earlier [6] to an interpretation of S_N reaction velocities.

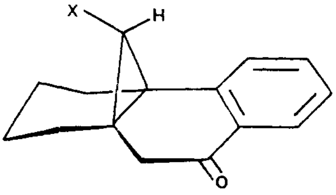


A reaction of a four-membered ring system, with retention of configuration under typical S_N2 conditions [8] seemed to afford an experimental confirmation of this view, but it soon was shown that these reactions occurred with inversion, the illusion of retention being attributable to a secondary thermodynamically controlled isomerization²) [9].

We now discuss what seems to be another confirmation of this proposal, a reaction carried out under S_N2 conditions on a three-membered ring system leading to retention of configuration [12]: The two cyclopropyl bromide derivatives **6** and **7** were converted with tetraethylammonium acetate in acetone to the acetates **8** and **9**, respectively [12]. Kinetic control was assured by the fact that the two stereoisomers gave stereoisomeric products and retention of configuration was established by two X-ray analyses.



6 X = Br
8 X = OAc



7 X = Br
9 X = OAc

We note that these substitutions are facile giving high yields at room temperature, whereas the previous (rather sparse) literature [1] [13] [14] on S_N2 reactions at cyclopropyl carbon atoms lead to the conclusion that such reactions are – at best – ex-

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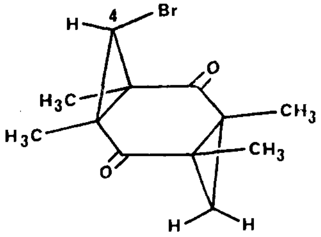
²) The well known [10] isomerizations by halogen exchange had previously been applied [11] to four-membered ring compounds.

tremely slow; in fact, even under energetic S_N2 conditions, cyclopropyl bromide and chloride were found to give no measurable reaction [13] [14][3]).

From previous work [18] we had at our disposal a cyclopropyl bromide derivative sufficiently similar to compound **6** to be suitable for a study of this discrepancy, namely 4-*endo*-bromo-1, 3, 5, 7-tetramethyl-*anti*-tricyclo[5.1.0.$0^{3,5}$]octane-2,6-dione (**10**). The two cyclopropyl bromides **6** and **10** do not differ much in intramolecular crowding, especially with respect to the approach of a nucleophile to the electrophilic carbon atom either *anti* to the bromine atom as proposed by the classical view [1] [2], or *anti* to one of the neighbouring ring carbon atoms as suggested by the newer proposals [4] [5]. Moreover, the two (electron-withdrawing) carbonyl groups flanking the three-membered ring make **10** – according to theory [5] – an even better substrate for a S_N2 reaction with retention than **6** or **7**.



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We treated **10** with tetraethylammonium acetate in acetone for 36 hours under reflux, and for 48 hours at 120° in a sealed tube. In both cases the educt **10** was recovered (92 and 97%). This was also the case after treatment of **10** with sodium iodide in refluxing acetone for 48 hours (98% of **10** recovered). Thus any nucleophilic substitution reaction on the cyclopropyl carbon atom C(4) of **10** would take place very slowly. This is in agreement with older work [13] [14], but in sharp contrast to the behaviour of **6** and **7** [12]. Furthermore, molecules with slight variations of the carbon skeleton of **6**/**7** have been found not to undergo substitution under the conditions applied to **6** and **7**: When the carbonyl group in ring B, the saturated ring A or the benzenoid ring C are missing, other or no reactions take place [19].

Therefore, we consider the possibility that the transformations **6** → **8** and **7** → **9** are not a result of direct substitution but rather due to elimination of HBr with subsequent addition of HOAc: Acetate anion could abstract a proton from the carbon atom in α-position to the carbonyl group, concomittantly introducing a double bond with (*Z*)-configuration into the carbonyl-bearing ring, breaking the propellane axis, and ejecting the bromide ion[4]). If part or all of these steps are stereospecific (possibly

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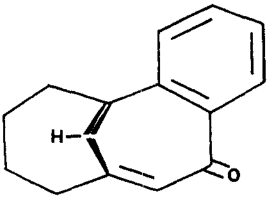
[3]) More extensive data are available on nucleophilic substitution reactions with cyclopropyl compounds under ion-promoting conditions which are almost always accompanied by opening of the three-membered ring to give allylic compounds [13] [15] [16]. The metal hydride dehalogenations at cyclopropyl carbon atoms [17] are not considered in this connection, since so far there is no evidence that they belong to the class of S_N2 reactions.

[4]) A remote analogy to this might be found in the Ag^+-promoted hydrolysis of 10,10-dibromo-[4.3.1]propellane [16]. A system similar to **6** or **7** has been subjected to basic methanolysis conditions, but no product was isolated [20].

concerted) then – whatever stereospecificity factor exists in transforming **6** into **11** (with (*Z*)-configuration of the second double bond in the carbonyl-bearing ring) – they would also operate to transform **7** into **12** (with the corresponding (*E*)-configuration). The intermediates **11** and **12** should be highly strained (compare [21])



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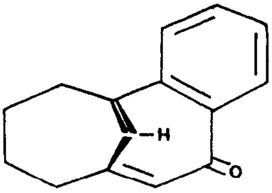

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reacting with the acetate ion rapidly and on the same side of the one-carbon atom bridge as the bromide ion leaves, followed by ring closure and protonation to reform the original ring system. In other words, both overall substitutions might not be of the S_N2 type, but could nevertheless follow second order kinetics (although higher order kinetics cannot be excluded), and would be stereospecific in the sense of retention of configuration[5]. Since the intermediate **12** is likely to be more strained than **11** (the (*E*)-configuration of one of the double bonds of **12** is part of the seven-membered ring consisting of trigonal carbon atoms only), the reaction mechanism considered here leads to the expectation that the substitution reaction **6** → **8** is faster than **7** → **9**.

Our preliminary rate measurements indicate that this is the case; furthermore, ^1H-NMR.-spectra of the reaction mixture with **7** show transient signals in the olefinic proton region, which so far have not been identified.

Although more evidence will be needed to confirm or contradict the above mechanism, we present it here as a possibility in order to suggest caution in using the results obtained [12] (compare footnote 31 in [5] and footnote ** in [9b]) with compounds **6** and **7** as a contribution to the understanding of S_N2 reactions at saturated carbon atoms occurring with retention of configuration. Since compound **10**, despite being a good substrate, has not undergone S_N2 reaction, the probability that such reactions on three-membered ring carbon atoms will be found has decreased; but still we cannot exclude the possibility that, if found, they will be accompanied by retention of configuration.

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Experimental Part

Analytical gas-liquid chromatography (GLC.) was carried out on an *Erba* Fractovap Model G 1 using an emulphor capillary column (23 m × 0.33 mm; 160–170°); injector temperature 180°.

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[5] A variant of this mechanism may be considered which makes use of the concept of a half-opened cyclopropane ring, as proposed in the solvolyses of norcarane derivatives [22].

The retention time at 160° column temperature for 4-*endo*-bromo-1,3,5,7-tetramethyl-*anti*-tricyclo[5.1.0.0^{3,5}]octane-2,6-dione (**10**) was 293 sec. – NMR.-spectra (60 MHz) were measured in deuteriochloroform.

*Treatment of 4-*endo*-bromo-1,3,5,7-tetramethyl-*anti*-tricyclo[5.1.0.0^{3,5}]octane-2,6-dione* (**10**) *with sodium iodide.* A solution of 90 mg (0.33 mmol) of **10** [18], m.p. 149°, in 2 ml of dry acetone containing 200 mg (1.32 mmol) of sodium iodide was heated for 2 days under reflux. No new product was observed when the reaction was followed by GLC. The solvent was evaporated, and the residue filtered through a short silica gel column with chloroform to yield 89 mg of educt **10**, identified by m.p., mixed m.p., GLC. and NMR.-spectrum.

*Treatment of 4-*endo*-bromo-1,3,5,7-tetramethyl-*anti*-tricyclo[5.1.0.0^{3,5}]octane-2,6-dione* (**10**) *with tetraethylammonium acetate.* a) A solution of 89 mg (0.33 mmol) of **10** [18], m.p. 149°, and 248 mg (1.32 mmol) of tetraethylammonium acetate [21] in 2 ml of dry acetone was heated for 36 h under reflux. The solvent was evaporated, and the residue filtered through a short silica gel column with chloroform/pentane 2:3 to yield 82 mg of educt **10**, identified by m.p., mixed m.p. and GLC.

b) A solution of 70 mg (0.26 mmol) of **10** [18], m.p. 149°, and 190 mg (1.01 mmol) of tetraethylammonium acetate [21] in 2 ml of dry acetone was heated at 120° for 48 h in an evacuated sealed tube. Work-up as above yielded 68 mg of educt **10**, identified by m.p., mixed m.p., GLC., IR.- and NMR.-spectra.

Comparison of the reaction velocities of *syn*- and *anti*-11-bromo-2,3-benzo-tricyclo[4.4.1.0]undecen-4-one (*6* and *7*) with tetraethylammonium acetate. – To separate solutions of 5 mg (0.017 mmol) of *syn*-bromide **6** and *anti*-bromide **7** in 0.9 ml hexadeuterioacetone was added 5 mg (0.026 mmol) tetraethylammonium acetate in 0.1 ml deuterioacetone. The ^{1}H-NMR.-spectra of the solutions were measured at 27° at a XL-100-instrument and the decrease in intensity of the singlet (δ wandering from ~1.8 to 1.9) due to acetate ion was followed. This decrease was about twice as fast in the solution containing **6** than in that containing **7**. In the case of **6** the rate of the intensity decrease of the singlet ($\delta = 3.70$) due to H—C(Br) was equal that of the acetate signal; the H—C(Br) signal of **7** ($\delta = 2.90$) partially overlaps with the signals due to the two hydrogen atoms on ring B ($\delta = 2.7$–2.93).

In the course of the reaction of **7** the ^{1}H-NMR.-spectrum showed rapid appearance of a singlet at $\delta = 5.65$ and a multiplet at $\delta = 6.2$–5.9, together up to an intensity of about 1 proton, both of which disappeared again towards the end of the reaction. In the reaction with **6** a very weak multiplet appeared in the same region, but only towards the end of the reaction. A transient yellow color was noticed during the reaction of **6** but not of that of **7**.

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