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Structural Analysis of a Facile Lactonization System Facilitated by a "Trimethyl Lock"[1]

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A "trimethyl lock" was shown earlier to significantly facilitate the lactonization of compounds of type **1.** Our renewed interests in such facile cyclization systems stemmed from their potential applications in the preparation of redox-, esterase-, and phosphatase-sensitive prodrugs. Furthermore, such systems have also been used for the development of redox-sensitive protecting groups for amines and alcohols. In an effort to probe the general applicability of such systems being used as prodrug moieties and protecting groups, we studied the effects of the functional groups (X, **4**) attached to the side chain carboxyl group on the overall conformations of such systems using X-ray crystallography. Through analysis of the crystal structures of **4a–4d** with different functional groups attached to the side chain, we found that in all cases the side chain was folded back to bring the side chain carboxyl group within close proximity of the quinone oxygen, which is the potential attacking atom, and the X functional groups have minimal effect on the overall conformation of the system. In addition, severe strain was observed for **4a–4d,** which should be at least partially released upon cyclization. This would also help to explain the facile cyclization reaction brought about by the trimethyl lock.

INTRODUCTION

In the 1970s, reports of "trimethyl lock"-facilitated cyclization reactions generated much interest because the effect of the trimethyl lock was said to approach that of an enzyme in facilitating certain chemical reactions (*1–3*). In Scheme I, for example, the rate of lactonization for **1b** is about 10^5 times faster than that of **1a** (*1, 4, 5*). The situation is similar with the dihydroquinone system **1c** (*6*). The facilitation of other cyclization reactions by such a trimethyl lock system has also been observed (*3, 7–13*). The mechanism through which such a trimethyl lock and *gem*-dialkyl substitution facilitate certain cyclization reactions and its relevancy to

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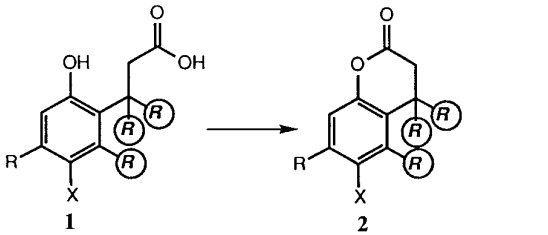

1

a, R = H, X = H
b, R = CH_3, X = H
c, R = CH_3, X = OH

2

a, R = H, X = H
b, R = CH_3, X = H
c, R = CH_3, X = OH

(Alkyl groups involved in the "trimethyl lock" highlighted in the circles)

SCHEME I

enzymatic reactions have been a subject of continued interest (*14*). However, we have a renewed interest in such facile cyclization systems because of their potential use in the preparation of redox- (*6*), esterase- (*15, 16*), and phosphatase-sensitive (*17*) prodrugs. Recently, we reported a novel redox-sensitive protecting group for amines and alcohols, utilizing this facile lactonization system **(1b)** (*18*). In broadening the application of the redox-sensitive facile cyclization systems **(4)** to the preparation of prodrugs and protecting groups of other amines and alcohols, we are concerned about the potential of the side chain functional group (X, **4**) to force conformational changes unfavorable for the facile cyclization. The fact that the quinone amides of aromatic amines (e.g., **4d**) readily undergo an undesirable spirocyclization to give **3** caused more concerns (*19*). Ideally, we would like to study the structural features of acids **1b–1c** and their derivatives to truly understand the conformational features of the facile cyclization systems. However, the phenolic acids **1b–1c** themselves, typically having a half-life of about 100 s in aqueous solution at room temperature (*6, 15, 16*), are too unstable to be studied using X-ray crystallography. In this study, we used the quinone acid **4a** and its derivatives **(4b–4d)** as models for their dihydroquinone counterparts **(1c, 5a–5c).** Such quinone acid derivatives **(4a–4d)** have all the salient features of their dihydroquinone counterparts **(1c, 5a–5c).** For this study, we purposely chose compounds with an ionizable side chain functional group **(4a),** an amide of a primary amine **(4b),** an amide of a secondary amine **(4c),** and an amide of an aromatic amine **(4d).** These selections represent commonly seen functional groups of different properties and sizes. For comparison purposes, we also studied the crystal structure of the lactone **(2c).** The structural analyses show that modifications of the carboxyl functional group have minimal effects on the overall conformation of the system, indicating that the prodrug and protecting group strategies are generally applicable to a variety of amines and alcohols. Furthermore, severe steric strain is observed with the quinone acid **(4a)** and its amide derivatives **(4b–4d),** which can be at least partially released upon lactonization. This would also help to explain in enthalpic terms the facile cyclization brought about by the trimethyl lock.

MATERIALS AND METHODS

The syntheses of the compounds of interest followed literature procedures (*18, 19*). The compounds were crystallized from ethyl acetate/hexane.

All X-ray experiments were carried out on a Rigaku AFC5R diffractometer with graphite monochromated CuKα radiation (λ = 1.5418 Å) using a rotating anode X-ray generator. The cell dimensions and crystal orientations were determined by the least-squares method using 25 centered reflections. The diffraction data were measured at room temperature (23°C) in the range of 2θ = 4.0 to 112.5° using the 2θ-ω scan technique. The weak reflections ($I < 10\sigma(I)$ were rescanned two times. The intensities of three representative reflections measured after every 150 reflections remained constant throughout data measurement. The diffraction data were corrected for Lorentz and polarization effects as well as absorption by an empirical method (*20*). The structures were solved by the direct method, and refined by the full-matrix least-squares method using all reflections. The function minimized was $\Sigma w(|\mathrm{Fo}| - |\mathrm{Fc}|)^2$ with $w = 4\mathrm{Fo}^2/\sigma^2(\mathrm{Fo}^2)$. Nonhydrogen atoms were refined with anisotropic thermal parameters. All hydrogens were located in the difference maps and were introduced into refinement with the isotropic thermal parameters. Atomic scattering factors were from the *International Tables for X-ray Crystallography* (1974, Vol. IV). The details of crystal data are listed in Table 1.

For compound **2c,** C3, C12, and C13 of the B-form were found to be disordered. Heavily disordered unknown solvent molecules were found in the crystal structure of compound **4a.** An attempt to build a reasonable disordered model using acetone and hexane molecules was not successful. The carbon atoms were assigned on the peak positions and refined those occupancy factors, while the positional and thermal parameters (B = 10 Å^2) were fixed. Those atoms are designed with an affix X.

RESULTS

The bond lengths (Å) and bond angles (degrees) for all five compounds **(2c, 4a–4d)** are illustrated in Figs. 1 and 2, respectively. For the convenience of comparison, the atoms of these four molecules are designated as illustrated in Fig. 1. These designations will be used throughout the text when comparing the angles, dihedral angles, and bond distances among these compounds.

Acid (*4a*)*, benzylamide* (*4b*)*, N-methyl-benzylamide* (*4c*)*, p-fluoroaniline amide* (*4d*). All four compounds showed very similar conformational features with regard to the quinone moiety and the side chain (Figs. 3b–3e). All compounds have bond lengths within the normal range regardless of the substitutions of the carbonyl group (Fig. 1). The side chains of all four compounds fold back to bring the side chain carbonyl carbon C(o) in close proximity to the quinone oxygen O(g), which is the potential attacking atom in the cyclization reaction. The distances between these two atoms range from 3.14 to 3.36 Å (Table 2). However, for the cyclization to occur after reduction (Scheme II), simple proximity of the atoms involved in the reaction is not sufficient. Also important is the relative directionality for the atoms involved in the reaction to approach each other during the reaction (*14, 21, 22*).

TABLE 1
Crystallographic Data and Physical Characteristics for Compounds **2c, 4a–4d**

	Lactone **(2c)**	Acid **(4a)**	Benzylamide **(4b)**	*N*-methylbenzyl amide **(4c)**	*P*-fluoroaniline amide **(4d)**
Molecular formula	$C_{13}H_{16}O_3$	$C_{13}H_{16}O_4$	$C_{20}H_{23}NO_3$	$C_{21}H_{25}NO_3$	$C_{19}H_{20}FNO_3$
Mol. wt.	220.27	236.27	325.41	339.43	329.37
Color	Colorless	Yellow	Yellow	Yellow	Yellow
Size (mm)	0.50 × 0.30 × 0.30	0.30 × 0.30 × 0.10	0.50 × 0.20 × 0.10	0.30 × 0.10 × 0.05	0.50 × 0.30 × 0.20
Space group	$P2_1/n$	$C2/c$	$P2_1/c$	$P2_1/a$	$P2_1/n$
a (Å)	9.697	26.194	11.450	11.470	9.620
b (Å)	13.935	9.839	16.720	15.084	12.020
c (Å)	17.675	13.675	9.584	11.660	29.547
α (degrees)	90	90	90	90	90
β (degrees)	95.68	117.222	102.24	109.933	90.181
γ (degrees)	90	90	90	90	90
V	2376.6	3133.7 Å^3	1793	1896.6	3416.6
Z	8	8	4	4	8
Density, Calcd. (g/cm^3)	1.231	1.001	1.205	1.189	1.281
Linear absorption coefficient (cm^{-1})	6.7	5.8	6.1	6.0	7.4
No. reflections measured	3518	2269	2610	2776	5112
Scan angle (degrees)	1.15 + 0.30 tan θ	1.68 + 0.30 tan θ	0.94 + 0.30 tan θ	1.13 + 0.30 tan θ	1.10 + 0.30 tan θ
Scan speed (degrees/min)	32	32	32	16	32
No. independent reflections	3294	2210	2470	2627	4781
R_{int}	0.019	0.009	0.059	0.040	0.017
Transmission factor	0.83–1.06	0.89–1.08	0.93–1.02	0.86–1.14	0.83–1.35
R factor	0.075	0.082	0.079	0.043	0.043
wR factor	0.089	0.089	0.092	0.068	0.059

Therefore, the relative positions of the attacking oxygen atom O(g) and the side chain carbonyl carbon C(o) are described in terms of angles C(a)–O(g)–C(o) and O(g)–C(o)–O(p), which are listed in Table 4.

It should be noted that the distances between methyl groups involved in the trimethyl-lock are about the same for these four compounds **(4a–4d)** when compared with the lactone **(2c)** (Table 2). However, the bond angles of the quinone systems are severely distorted from the ideal 120°, particularly on the side of the trimethyl-lock (Fig. 2). For example, the bond angle for C(k)–C(f)–C(e) is 125.7° for both the acid **4a** and the benzylamide **4b** and 125.2° for the *N*-methyl benzylamide **4c.** On the other hand, the bond angle for C(f)–C(e)–C(j) is 126.1° for the acid **4a,** 128.4° for the benzylamide **4b,** 128.3° for the *N*-methyl benzylamide **4c,** and 127.2° for the *p*-fluoroaniline amide **4d.**

One important feature of the open-chain compounds is the significant deviation of coplanarity of the quinone system in all four compounds **(4a–4d).** The folding back of the side chain pushes the quinone carbonyl adjacent to the side chain out of the plane of the quinone system as judged by the relevant dihedral angles (Table 3). For example, for the open-chain compounds **(4a–4d),** the dihedral angles

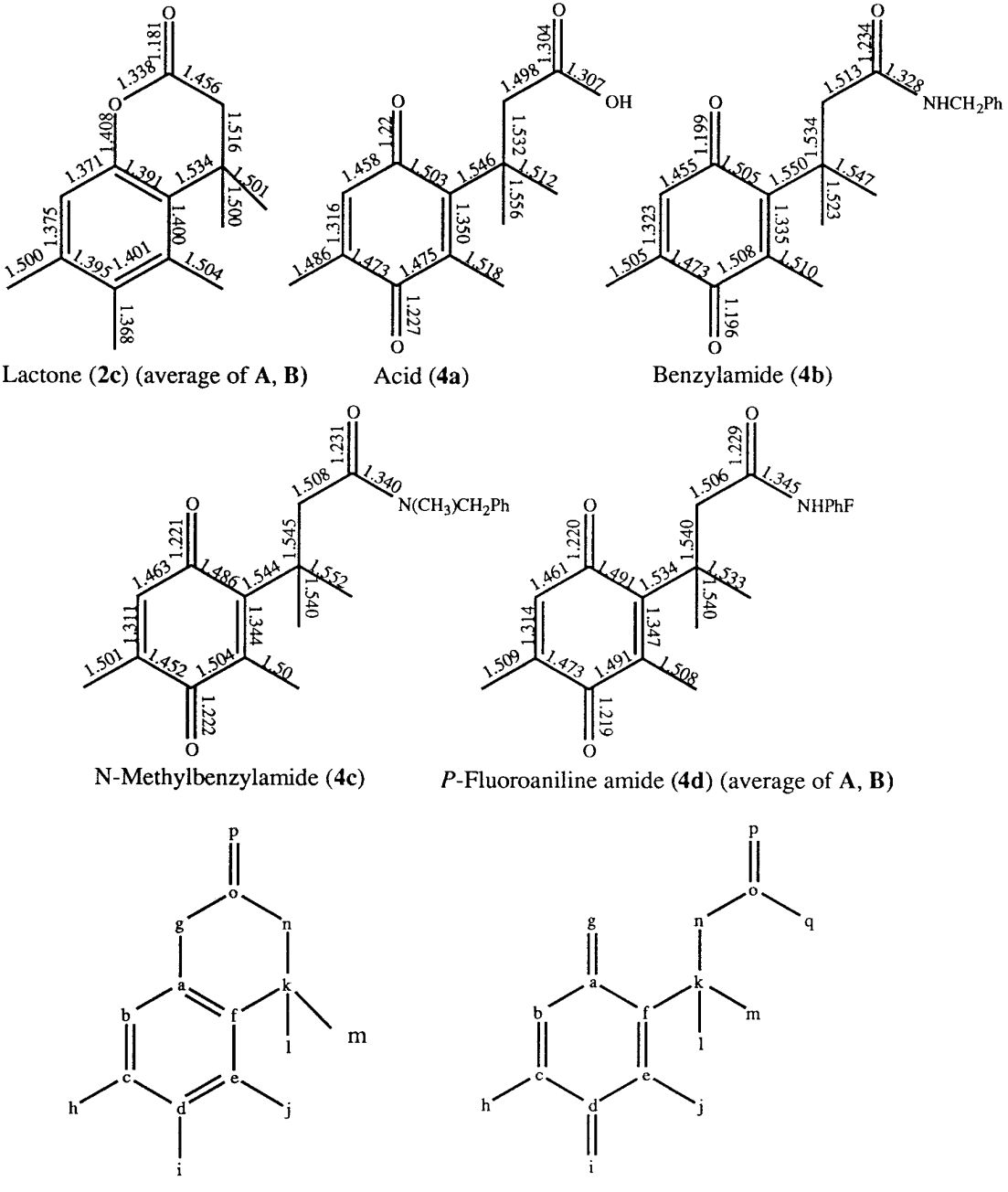

FIG. 1. Bond lengths (Å) for each compound and the designations for each atom of both the lactone **2c** and the open chain compounds **4a–4c.**